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A Systematic Review of Antibiotic Resistance in Nontyphoidal *Salmonella* in South Asia (1997-2012)

By

Kevin Wayne Humphries Jr.
Master of Public Health

Hubert Department of Global Health

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Saad B. Omer, PHD, MPH, MBBS
Committee Chair

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Introduction: Nontyphoidal Salmonellosis (NTS) is a problem for the region of South Asia which is home to half the world's poor and contains the greatest number of malnourished children. Antibiotic resistance has made the disease burden caused by NTS more difficult to mitigate since many common NTS strains are no longer susceptible to a wide range of antibiotics.

Project Goal: This systematic review was conducted to understand the level of effectiveness of antibiotics against NTS strains in South Asia with a focus on the effectiveness of the WHO recommended antibiotic therapy: Floroquinolones and third generation cephalosporins followed by either ampicillin, amoxicillin, co-trimoxazole, or chloramphenicol if necessary.

Methods: A systematic review of literature of all human related *Salmonella* isolates from 1997-2012 was conducted using PubMed after the titles and abstracts were screened for material concerning antimicrobial resistance tests to antibiotics.

Results: Fifty-one percent of isolates (n=252) tested for nalidixic acid susceptibility were resistant and 31% (n=184) for ciprofloxacin. The other floroquinolones tested for NTS susceptibility in the studies under review were enrofloxacin, norfloxacin, and sparfloxacin (Table 2) and *Salmonella* pathogens showed resistance rates of 3% (n=2), 5% (n=7), and 6% (n=1) respectively. The third generation cephalosporins tested for NTS drug resistance yielded an average resistance of 37% (n=10) for cefpodoxime, 34% (n=37) for cefoperazone, 30% for cefotaxime (n=61), 18% (n=28) for ceftazidime, and 16% (n=53) for ceftriaxone. However, there was a wide range of variation among the studies. Among first line drugs chloramphenicol, NTS pathogens had the lowest amount of resistance to chloramphenicol 12% (n=70) compared to 38% (n=127) of amoxicillin, 38% (n=237) of ampicillin, and 32% of co-trimoxazole (n=110). The reviewed literature includes resistant isolates from vegetables, seafood, meat, eggs, humans, and even environmental water sources.

Conclusion: Resistant serovars were isolated from a wide variety of sources showing the need for stricter management of antibiotics for medical purposes and agricultural purposes to mitigate the NTS burden of disease; protect immunocompromised populations such as malnourished children, the elderly, and those living with HIV/AIDS; and to lift the economic burden caused by NTS.

A Systematic Review of Antibiotic Resistance in Nontyphoidal *Salmonella* in South Asia (1997-2012)

By

Kevin Wayne Humphries Jr.

B.S. in Biology
Georgia Institute of Technology
2010

Thesis Committee Chair: Saad B. Omer, PHD, MPH, MBBS

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Background

Bacterial resistance to antibiotics is a worldwide problem that plagues both low and high income countries (Radyowijati & Haak, 2003). Increase in international trade, travel, use of antibiotics in animal cultivation, transfer of resistant strains in hospitals through inadequate aseptic practices, and misuse of antibiotics are determinants of antimicrobial resistance (Radyowijati & Haak, 2003). Enteric pathogens cause a high global disease burden which especially affects the children and immunosuppressed of developing countries (Radyowijati & Haak, 2003). Decreased drug susceptibility is hindering the ability of current antibiotics to all*eviate this disease burden. Several enteric pathogens, such as Escherichia Coli, Kliebsella*, *Salmonella*, *Shigella*, and *Vibrio cholerae* have become resistant to almost all commonly available antibiotics (Kariuki, 2010). It is especially difficult to mitigate the spread of antibiotic resistance when antibiotics can be bought with a prescription (regardless of legality) from a variety of sources from hospitals and pharmacies to roadside stalls and hawkers (Radyowijati & Haak, 2003). Also, nontyphoidal *Salmonella* serovars sometimes associated with the use of antibiotics in animals used as human food (Nelson & Williams, 2007). However, being exposed to an antibiotic before salmonellosis onset can predispose a patient developing to a resistant *Salmonella* infection(Chimalizeni, Kawaza, & Molyneux, 2010a). A formal surveillance system for antibiotic resistance is absent in many low income countries (Kariuki 2010). Information regarding the prevalence of antimicrobial resistance in current bacterial pathogens is insufficient (Menezes et al., 2010). This is especially true in populous countries with unrestricted over-the-counter policies (Menezes, et al., 2010).

The annual incidence of (NTS) is 1.3 billion cases, of whom approximately three million die annually (Chimalizeni, Kawaza, & Molyneux, 2010b). In high income nations, the mortality to the disease is 2% but is 18-24% in low income countries where invasive infections are frequent (Chimalizeni, et al., 2010a). Since the 1990 global outbreak of the multidrug resistant strain S. Typhimurium DT104, the number of drug resistant Salmonella strains has spread around the world (Sanchez-Vargas, Abu-El-Haija, & Gomez-Duarte, 2011).

South Asia is home to half the world's poor (Bank, 2011) and malnutrition makes the children of the region especially vulnerable to infectious disease (Zaidi, Awasthi, & deSilva, 2004). The World Bank defines South Asia as the nations of Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka (Bank, 2011). In these countries, antibiotics are freely available over the counter and many customers self-medicate. Also, unskilled medical practitioners improperly prescribe drugs (Zaidi, et al., 2004). Drugs are sometimes of poor quality because of use beyond expiration date, improper storage conditions, or faulty manufacture, leads to less than inhibitory drug levels which causes increased resistance among microbes (Zaidi, et al., 2004).

This systematic review is intended to assess the prevalence of antibiotic resistance to NTS from the period of 1997-2012. This includes identifying serovars which cause the major burden of nontyphoidal salmonellosis, describing the level of drug resistance to prevalent serovars, and gauging present effectiveness of antibiotics against Nontyphoidal *Salmonella* (NTS) strains with a focus on antimicrobial therapy recommended by WHO. Finally, this review will make recommendations for strategies to control antimicrobial resistance in NTS.

An update of trends in NTS drug resistance will inform healthcare providers in Bangladesh so that proper measures can be taken to stock appropriate medication and better target inappropriate drug use. Also, this update can help inform public health officials and government bodies on the effectiveness of drug policy implementation and necessary strategies to enforce policy.

Literature Review

Antimicrobial resistance in NTS strains has been well documented globally. This literature review includes the documentation of NTS resistance over the past 15 years in South Asia. According to the classification system in use by the Centers for Disease Control and Prevention, Salmonella is classified as two species: *Salmonella enterica* and *Salmonella bungori. Salmonella enterica* but S. enterica subspecies I (also known as subspecies enterica) has 2,443 different serotypes and *Salmonella bungori* has 20 different serotypes. *S. enterica* is divided into six subspecies but S. enterica subspecies I, known as subspecies enterica, accounts for more than 99% of human cases of disease (Smith, 2005). Typhoid fever (or enteric fever) is caused by serotypes adapted to humans which are *S. enterica* serotypes *Typhi*, *Paratyphi A, Paratyphi B*, and *Paratyphi C* (Smith, 2005). NTS is more common than typhoid fever and globally the most common NTS strains are S. Enteritidis, S. Typhimurium, and S. Newport (Sanchez-Vargas, et al., 2011).

NTS infections can cause a range of symptoms that vary in severity including gastroenteritis, bacteremia, endovascular infection and focal infection. Infections are characterized by an incubation period of 6-12 hours, followed by nausea, vomiting, diarrhea (non-bloody). Other symptoms include fever, chills, abdominal pain, myalgia, arthralgias and headache (Sanchez-Vargas, et al., 2011). Diarrhea due to NTS is usually self-limiting but invasive infection occurs when NTS spreads past the gastrointestinal mucosa and infects sites which are normally sterile such as the bloodstream, the meninges, bone, and joint spaces (Crump et al., 2011). In high income countries, NTS is usually characterized by mild gastroenteritis which resolves in a few days without active treatment but in poorer crowded parts of the world NTS is more often linked to invasive disease (Chimalizeni, et al., 2010b).

Treatment with antibiotics is not the first line of recourse but is necessary in cases of invasive disease (Sanchez-Vargas, et al., 2011). Flouroquinolone is usually the first line of therapy and azithromycin, cephalosporins, trimethoprim-sulfamethoxazole, or ampicillin are alternatives (Sanchez-Vargas, et al., 2011). A third generation cephalosporin or intravenous fluoroquinolone is recommended in the case of bacteremia (Sanchez-Vargas, et al., 2011).

The World Health Organization found that S. Enteritidis is the most common serotype worldwide (65%), followed by S. Typhimurium (12%) and S. Newport (4%) according to Salmonella-Surveillance data, which is WHO's global surveillance system for foodborne disease(Sanchez-Vargas, et al., 2011). However, the prevalence in serotype varies by region.

The past thirty years has seen a worldwide increase of NTS which now seems to be on the decline (Chimalizeni et al. 2010). The increase was due to S. Typhimurium DT 104 which has spread rapidly throughout the world (Chimalizeni et al. 2010). Recently, it has been on the decline but there has been an increase in the prevalence of S. *Enteritidis*. This increase was followed by multidrug resistance (Chimalizeni et al. 2010). Resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracyclines (ACSSuT) is now widespread (Chimalizeni et al. 2010). NTS strains resistant to quinolones and third-generation cephalosporins have been identified in most parts of the world (Chimalizeni et al. 2010). However, antimicrobial resistance has been observed to fluctuate (Chimalizeni et al. 2010). Kenya, for example saw a fall in resistance from 69% in 1994-1997 to 11% in 2002-2004, in spite of the continued use of drugs to which NTS was resistant (Chimalizeni et al. 2010). NTS infections are the most frequent in the malaria season and heighten towards the end of rain seasons (Chimalizeni et al. 2010). NTS often co-occurs with cases of malaria in the blood because it causes the release of unbound iron which favors NTS bacteremia (Chimalizeni et al. 2010).

Concerning the disease burden in South Asia, a national surveillance study of India found S. *Typhimurium* to be the most common serovar isolated from humans (30%), *S. Worthington* (24%), *S. Welterveden* (11%), and *S. Bareilly* (11%) from the period of 2001 – 2005 (Y. Kumar, Sharma, Sehgal, & Kumar, 2009). *S. Worthington* was found to be in northern, central, and southern parts of India but not in eastern and western areas and was the most common isolate cultured from seafood (Y. Kumar, et al., 2009). S. *Typhimurium* showed a high frequency in poultry and humans simultaneously, implicating a possible transmission route from poultry to humans (Y. Kumar, et al., 2009).

Methods

All studies accessible through the PubMed database from 1997-2012 regarding antimicrobial resistance in South Asian countries in humans were reviewed. The search term below for antimicrobial resistance in India generated 145 items:

> ((resistan* OR susceptib* OR sensitiv* OR antibiogram[Title/Abstract]) AND salmonell*[Title/Abstract]) AND India[Title/Abstract] AND (Humans[Mesh] AND ("1997"[PDat] : "2012"[PDat]))

The exact same search term was used to look for studies of NTS in other nations by substituting the country for the word India.

All studies retrieved by this search were screened for subject matter that pertained to antibiotic resistance in NTS in either the title or abstract. Studies that were solely about typhoidal samonellosis in the title and abstract were excluded. These articles all describe the antibiotic susceptibility of NTS isolates from humans or from sources of possible human exposure to NTS such as poultry, the environment, and agricultural produce. Also, the study must fall within the 1997-2012 timeframe. Many studies were excluded during this step because they had no serotyping to differentiate NTS from typhoidal *Salmonella* strains, but simply tested all *Salmonella* serovars as one entity.

All studies included in the review isolates NTS from samples from either hospital patients, vegetables, meat, eggs, seafood, paan leaves or environmental water samples. The studies then tested these isolates for susceptibility to a wide range of antibiotics using standard clinical microbiological methods. The results of these antibiotic susceptibility tests were compiled in charts and analyzed.

Nations	No. of Search Results	No. Remaining after Title and Abstract Screening	No. Remaining after Full Article Screening
India	145	28	14
Bangladesh	29	1	0
Nepal	29	2	1
Maldives	0		
Sri Lanka	1	0	
Afghanistan	1	0	
Pakistan	39	3	2
Bhutan	1	1	1

Table 1: Results of PubMed Database search and screenings

The title, reference, summary, research question, sample, methodology, strengths, weaknesses, and main points relevant to the systematic review were catalogued for each of the 19 studies included in the review.

Results

Floroquinolones are most commonly used to treat *Salmonella* infections since they are comparatively inexpensive and absorb well orally (Drug-resistant salmonella, 2005). Third-generation cephalosporins, must be administered through injections, are often used in children with severe infections since quinolones are not recommended for those of young age(Drug-resistant salmonella, 2005). Alternatives are chloramphenicol, ampicillin, amoxicillin, and co-trimoxazole (trimethoprim-sulfamethoxazole) (Drug-resistant salmonella, 2005).

Nalidixic Acid (7 studies) and ciprofloxacin (15 studies) were the primary floroquinolones tested for NTS antimicrobial susceptibility. Fifty-one percent of isolates (n=252) tested for nalidixic acid susceptibility were resistant and 31% (n=184) of ciprofloxacin (see Table 3). Ofloxacin showed 50% (n=95) resistance in the study conducted in Pakistan (Jabeen et al., 2010) but 6% in Kolkata, India (6%, n=2). However, only 32 isolates from children with diarrhea reporting to a hospital were tested for ofloxacin susceptibility in India (Sinha, Pazhani, Sen, & Niyogi, 2006) compared to 261 isolates in Pakistan that sourced from microbiology centers in 50 major towns and cities of Pakistan (Jabeen, et al., 2010). The other floroquinolones tested for NTS susceptibility in the studies under review were enrofloxacin [3% resistant (n=2)], norfloxacin [5% resistant(n=7)], and sparfloxacin [6%(n=1)] (Table 2 in Appendix) and *Salmonella* pathogens showed resistance rates of 5% (n=7) and 6% (n=1) respectively (see Table 2 in Appendix).

The third generation cephalosporins tested for *Salmonella* drug susceptibility were cefpodoxime (37%, n=10), cefoperazone (34%, n=37), cefotaxime (30%,n=61), ceftazidime (18%,n=28), and ceftriaxone(16%,n=53). However, there was a wide range of variation in third generation cephalosporin resistance, for example *S. Worthington* isolates were 100% (n=9) resistance against cefotaxime, ceftriaxone, and ceftazidime (Table 2 in Appendix)(Kapoor et al., 2006) and strains such as *S. Bsilla, S. Teko*, and *S. Newport* showed no resistance to third generation cephalosporins.

The total percentages of isolates resistant to the first line drugs amoxicillin, ampicillin, chloramphenicol, and co-trimoxazole were 38% (n=127), 38% (n=237), 12% (n=70), and 32% (n=338) respectively. Overall, the resistance to first line drugs was 38% (n=127). Ampicillin in Pakistan fell from a peak of about 50% in 1992 to about 8% in 2006 (Jabeen, et al., 2010).

Discussion

Antibiotic resistance to floroquinolones and third generation cephalosporins is prevalent in the South Asian sites where data was available for the systematic review. These sites include x. Isolates came from samples of vegetables, seafood, meat, eggs, humans, and even environmental water sources (Table 2 in Appendix) showing that there is a wide range of NTS human exposure pathways.

Antimicrobial overuse is a key determinant of antibiotic resistance (Radyowijati & Haak, 2003). Nalidixic acid, ofloxacin, and ciprofloxacin had a collective resistance of 39% (n=533) compared to 4% (n=10) of enrofloxacin, norfloxacin, and sparfloxacin. This could indicate overuse of nalidixic acid, ofloxacin, and ciprofloxacin. In Pakistan, floroquinolone resistance increased from 23% to 51% from 2002-2006 (Jabeen, et al., 2010). Resistant strains were especially present in the imported carcasses to Bhutan from India; 95% (n=40) of *S. Enteritidis* were resistant to ciprofloxacin and 95% (n=40) were resistant to nalidixic acid.

Among third generation cephalosporins, ceftriaxone had the lowest overall percentage of resistant *NTS* isolates (16%, n=53) despite having the highest number of isolates (n=342). *S. Worthington* (70%, n=29) and *S. Agona* (90%, n=9) exhibited a high degree of resistance to ceftriaxone. More isolates are necessary to determine whether such a resistance level is common in these strains.

Among first line drugs, NTS pathogens had the highest susceptibility infectious diseases in South Asia to chloramphenicol (12%, n=70). Resistance to chloramphenicol fell from 26% in 1990 to 7% in 2006 in Pakistan according to a longitudinal study (Jabeen, et al., 2010). This could be due to a decline in the use of first line drugs in preference for use of floroquinolones and third generation cephalosporins (Jabeen, et al., 2010). In Pakistan, resistance against co-trimoxazole fluctuated from about 70% in 1994 to 30% to 1999 approximately 48% in 2006 and ampicillin fell from a peak of about 50% in 1992 to approximately 8% in in 2006 (Jabeen, et al., 2010).

The prevalence of resistant strains is alarming. Antibiotics must be regulated for medical and agricultural use. The systematic review shows that drug resistant NTS pathogens in India and Pakistan are present not only in sick humans, but also in the crops they consume, environment they live in, and even within exported seafood and poultry. The high degree of resistance in food imports from India could compromise global demand for Indian food products and be a detriment to the nation's burgeoning economy. India and Pakistan could also be at risk to other South Asian nations through food imports; Bhutan imported 1,300 metric tons valued at U.S. $2.4 million in 2005 most of which came from India (Ellerbroek et al., 2010).

Further research should include more data regarding NTS antimicrobial resistance from the nations of South Asia other than India and Pakistan. This should include a more extensive analysis into NTS strains vary in resistance profiles so that health providers can be prepared with an appropriate stock of effective medicines. Antimicrobial resistance can rise and fall dramatically (Jabeen, et al., 2010), and must be constantly monitored for the best medical preparedness and public health regulatory action.

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Appendix

Table 2: Antimicrobial resistance of Nontyphoidal *Salmonella* isolates against antimicrobial therapy drugs recommended by WHO

Region	Citation	Sampling	Time Frame	Serovar	no. of isolates	Amoxicillin	Ampicillin	Chloramphenicol	Co-trimoxazole	Cefpodoxime	Cefoperazone	Cefotaxime	Ceftazidime	Ceftriaxone	Ciprofloxacin	Enrofloxacin	Nalidixic Acid	Norfloxacin	Ofloxacin	Sparfloxacin
Nepal (Kathmandu)	(Kansakar, Baral, Malla, & Ghimire, 2011)	877 stool isolates from a hospital	2002-2004	Enteritidis	1									0%	0%					
North India (New Delhi)	(S. Kumar, Rizvi, & Berry, 2008)	blood isolates from a hospital	1999; 2002; 2005	Typhimurium	5	0%	100%	20%	0%	0%		0%		0%	0%	0%			0%	0%
				Senftenberg	3	0%	67%	33%	0%	33%		67%		33%	67%	0%			0%	0%
				Group E not Senftenberg	3	100%	67%	33%	0%	0%		33%		33%	0%	0%			0%	0%
				Other Salmonella groups	5	40%	20%	0%	40%	0%		0%		20%	0%	0%			0%	20%
North India (New Delhi)	(Kapoor, et al., 2006)	fecal samples of infants w/diarrhea in hospital	Oct 2001 to March 2001	Worthington	9		100%	78%				100%	100%	100%	33%			33%		
North India (Chandigarh)	(Taneja, Mohan, Khurana, & Sharma, 2004)	fecal samples patients at hospital	2000-2002	NTS	27	63%		37%	35%			48%			19%		59%			
North India (Bareilly & Kanpur)	(Singh et al., 2007)	974 vegetable samples from vegetable vendors	March 2004 to Sept 2004	Anatum	2		0%	0%	0%		0%	0%	0%	0%	0%		0%			
				Bsilla	1		0%	0%	0%		0%	0%	0%	0%	0%		0%			
				Mons	2		0%	0%	0%		100%	0%	0%	0%	0%		100%			
				Rottnest	1		0%	0%	0%		0%	0%	0%	0%	0%		100%			
				Saintpaul	14		14%	7%	7%		64%	50%	21%	0%	0%		100%			
				Weltevreden	5		0%	0%	0%		60%	20%	20%	0%	0%		80%			
				Teko	4		0%	0%	0%		0%	0%	0%	0%	0%		50%			

				Newport	2		0%	0%	0%		0%	0%	0%	0%	0%		100%			
				Virchow	4		0%	0%	75%		25%	25%	25%	0%	0%		100%			
North India (11 North Indian Cities)	(Singh et al., 2006)	776 water samples for Paan washing and 120 Paan samples	prior to 2005	Saintpaul	32		19%	0%	0%		53%	50%	0%	0%	0%		59%			
				Newport	1		100%	0%	0%		100%	100%	100%	0%	100%		100%			
				Virchow	3		100%	33%	0%		100%	0%	33%	33%	0%		33%			
				Teko	1		100%	0%	0%		100%	0%	100%	0%	0%		100%			
North India (New Delhi)	(Randhawa, Mehta, Das, Chugh, & Aneja, 2006)	blood culture from infant at hospital	prior to Nov 2006	Virchow	1		0%	0%	100%					0%	0%					
Northeastern India (Arunchal Pradesh, Assam, Meghalaya)	(Murugkar, Rahman, Kumar, & Bhattacharyya, 2005)	samples form livestock & humans with diarrhea	April 2003 to April 2004	Typhimurium	39	31%	41%	18%							10%	5%	15%	3%		
				Enteritidis	36	64%	64%	0%							8%	0%	14%	0%		
				Gallinarum	12	3%	3%	0.02							0.02	0.02	0.02	0.01		
				Bareilly	3	24%	27%	0							0.03	0	0.06	0		
East India (Kolkata)	(Sinha, et al., 2006)	68 isolates from infant feces at hospital	prior to 2006	Worthington	32		66%	13%	16%					63%	6%				6%	
South India (Coimbatore)	(Suresh, Hatha, Sreenivasan, Sangeetha, & Lashmanaperumalsamy, 2006)	492 eggshells, 492 egg content, 82 egg storing trays	June 1997 to May 1998	Enteritidis	40		100%								5%		43%			
				Cerro	4		100%								0%		0%			
				Molade	1		100%								100%		0%			
				Mbandaka	1		100%								100%		0%			
South India (Chennai)	(Karthikeyan, Thirunarayan, & Krishnan, 2011)	infant admitted to hospital	2009	Virchow	1		100%		0%				100%	100%	0%					
South India (Pondicherry,Bangalore, and Mangalore)	(Menezes, et al., 2010)	17 stool, 3 blood, & 1 cerebropsinal isolate from hospitals	2006-2008	Typhimurium	5		20%	20%		20%		20%	20%	20%	0%		20%			
				Agona	10		90%	60%		80%		90%	90%	90%	90%		30%			
				Enteritidis	3		0%	0%		0%		0%	0%	0%	33%		33%			
				Lexington	1		0%	0%		0%		0%	0%	0%	0%		0%			
				Seftenberg	1		0%	0%		0%		0%	0%	0%	100%		100%			
				Kirkee	1		0%	0%		0%		0%	0%	0%	0%		0%			

South India (Kochi)	(Parvathi, Vijayan, Murali, & Chandran, 2011)	isolates from water, shrimp, & crabs, brackish lagoons a mostly from freshwater conditions	2008-2009	Newport	60	25%	25%	15%							15%			5%		
Pakistan (Karachi)	(Hassan Ali, Farooqui, Khan, Khan, & Kazmi, 2010)	7 raw meat samples	prior to Oct 2009	Enteritidis	24	33%	33%												0%	
Pakistan (50 towns & cities Pakistan)	(Jabeen, et al., 2010)	primarily blood & stool isolates	2006	NTS	189		25%	7%	47%					5%	51%		54%		50%	
Imports from India	(Akiyama, Khan, Cheng, & Stefanova, 2011; Ellerbroek, et al., 2010)	isolates obtained from shrimp to U.S.	2001-2005	Saintpaul	13		0%	0%												
Imports from India	(Ponce, Khan, Cheng, Summage-West, & Cerniglia, 2008)	1 fish & 3 shrimp samples imported to U.S.	2003-2004	Weltevreden	4		0%	0%												
Bhutan	(Ellerbroek, et al., 2010)	skin samples from 400 poultry breasts	prior to Feb 2009	Enteritidis	42		19%	0%				0%	0%		95%		95%			
				Subsp. I rough form	2		50%	0%				0%	0%		100%		50%			
				Typhimurium	8		0%	0%				0%	0%		13%		13%			
Total no. of isolates resistant					1277	127	237	70	110	10	37	61	28	53	184	2	252	7	97	1
Total isolates tested					4298	330	619	571	338	37	109	202	155	342	602	75	497	144	261	16
Percentage of Resistant Isolates						38%	38%	12%	32%	27%	34%	30%	18%	16%	31%	3%	51%	5%	37%	6%
						First Line Drugs				3rd Generation Cephalosporins					Floroquinolones					
Total no. of isolates resistant						544.31				189.45					543					
Total isolates tested						1858				845					1595					
Percentage of Resistant Isolates						29%				22%					34%					

Table 3: NTS Resistance against all antibiotics used in studies of systematic review

	Amikacin	Amoxicillin	Amoxicillin/clavulanic acid	Ampicillin	Ampicillin + cloxacillin	Ampicillin sulbactam	Azithromyin	Bacictracin	Cefaclor	Cefazolin	Cefepime	Cefoxitin	Cefpodoxime	Cefoperazone	Cefotaxime	Ceftazidime	ceftriaxone	Cefuroxime	Cephalexin	Cephalothin	Chloramphenicol	Chlortetracycline	Ciprofloxacin	Colistin	Cotrimoxazole	Doxycycline
Antibiotics	Ak	Am	Ac	A	Ax	As	Az	B	Cr	Cz	Cpm	Cn	Cep	Cs	Ce	Ca	Ci	Cu	Cn	Ch	C	Ct	Cf	Cl	Co	D
No. Tested Resistant	19	127	32	237	7	16	28	60	5	9	9	3	10	37	61	28	53	16	39	50	70	36	184	11	110	68
Number Tested	130	327	48	619	72	25	48	60	24	21	22	21	37	109	202	155	342	37	175	132	571	96	602	124	338	124
Percentage Resistant	15%	39%	67%	38%	10%	64%	58%	100%	21%	43%	41%	14%	27%	34%	30%	18%	16%	43%	22%	38%	12%	38%	31%	9%	32%	55%

	Enrofloxacin	Erythomycin	Florfenicol	Furazolidone	Gentamicin	Imipenem	Kanamycin	Meropenem	Nalidixic Acid	Neomycin	Netilmicin	Nitrofurantoin	Norfloxacin	Ofloxacin	Penicillin-G	Piperacillin	Piperacillin/Tazobactam	Polymixin-B	Roxithromycin	Sparfloxacin	Streptomycin	Sulfisoxazole	Sulphamethoxazole	Tetracycline	Tobramycin	Trimethoprim
Antibiotics	Ef	E	Fl	Fr	G	I	K	M	Na	N	Nt	Nf	No	O	P	Pc	Pc/Tz	PB	R	Sf	S	Sx	Sm	T	To	Tr
No. Tested Resistant	2	30	0	56	57	6	108	1	252	56	2	54	7	97	60	8	0	46	6	1	5	0	48	130	60	41
Number Tested	75	52	52	108	361	72	322	58	497	118	16	135	144	261	60	21	22	46	24	16	141	54	124	323	97	283
Percentage Resistant	3%	58%	0%	52%	16%	8%	34%	2%	51%	47%	13%	40%	5%	37%	100%	38%	0%	100%	25%	6%	4%	0%	39%	40%	62%	14%

Table 4: Complete Resistance by Percentage against Drugs Azithromycin – Doxycycline

	# of isolates	Amikacin	Amoxicillin	Amoxicillin/clavulanic acid	Ampicillin	Ampicillin + cloxacillin	Ampicillin sulbactam	Azithromyin	Bacictracin	Cefaclor	Cefazolin	Cefepime	Cefoxitin	Cefpodoxime	Cefoperazone	Cefotaxime	Ceftazidime	ceftriaxone	Cefuroxime	Cephalexin	Cephalothin	Chloramphenicol	Chlortetracycline	Ciprofloxacin	Colistin	Cotrimoxazole	Doxycycline
Kansakar 2011		Ak	Am	Ac	A	Ax	As	Az	B	Cr	Cz	Cpm	Cxn	Cep	Cs	Ce	Ca	Ci	Cu	Cn	Ch	C	Ct	Cf	Cl	Co	D
Enteritidis	1																	0						0			
Enteritidis	1																	0%						0%			
Kumar 2008			Am		A	Ax	As	Az						Cep				Ci	Cu	Cn		Ch		Cf	Cl	Co	
Typhimurium	5		0		5		2	0						0		0		0	2	0		1		0		0	
Senftenberg	3		0		2		0	0						1		2		1	0	2		1		2		0	
Group E not Senftenberg	3		3		2		3	0						0		1		1	3	1		1		0		0	
Other Salmonella groups	5		2		1		2	0						0		0		1	1	0		0		0		2	
Total	16		5		10		7	0						1		3		3	6	3		3		2		2	
Typhimurium	5		0%		100%		40%	0%						0%		0%		0%	40%	0%		20%		0%		0%	
Senftenberg	3		0%		67%		0%	0%						33%		67%		33%	0%	67%		33%		67%		0%	
Group E not Senftenberg	3		100%		67%		100%	0%						0%		33%		33%	100%	33%		33%		0%		0%	
Other Salmonella groups	5		40%		20%		40%	0%						0%		0%		20%	20%	0%		0%		0%		40%	
Kapoor 2006		Ak		Ac																							
Worthington	9	8		9	9		9									9	9	9				7		3			
Worthington	9	89%		100%	100%		100%									100%	100%	100%				78%		33%			
Taneja 2004		Ak	Am[1]																			C		Cf		Co[2]	
NTS	27	1	15													13						10		5		9	
NTS	27	4%	63%													48%						37%		19%		35%	
Singh 2007		Ak		Ac	A	Ax									Cs	Ce	Ca	Ci			Ch	C		Cf	Cl	Co	D
Anatum	2	0		0	0	0									0	0	0	0			0	0		0	0	0	0
Bsilla	1	0		0	0	0									0	0	0	0			0	0		0	0	0	0
Mons	2	2		0	0	0									2	0	0	0			2	0		0	0	0	0
Rottnest	1	0		0	0	0									0	0	0	0			1	0		0	0	0	0
Saintpaul	14	4		1	2	2									9	7	3	0			9	1		0	4	1	3

Weltevreden	5	1		0	0	0									3	1	1	0			1	0		0	0	0	0
Teko	4	0		0	0	0									0	0	0	0			0	0		0	0	0	0
Newport	2	0		0	0	0									0	0	0	0			0	0		0	0	0	0
Virchow	4	0		0	0	0									1	1	1	0			3	0		0	2	3	1
Total	35	7		1	2	2									15	9	5	0			16	1		0	6	4	4
Anatum	2	0%		0%	0%	0%									0%	0%	0%	0%			0%	0%		0%	0%	0%	0%
Bsilla	1	0%		0%	0%	0%									0%	0%	0%	0%			0%	0%		0%	0%	0%	0%
Mons	2	100%		0%	0%	0%									100%	0%	0%	0%			100%	0%		0%	0%	0%	0%
Rottnest	1	0%		0%	0%	0%									0%	0%	0%	0%			100%	0%		0%	0%	0%	0%
Saintpaul	14	29%		7%	14%	14%									64%	50%	21%	0%			64%	7%		0%	29%	7%	21%
Weltevreden	5	20%		0%	0%	0%									60%	20%	20%	0%			20%	0%		0%	0%	0%	0%
Teko	4	0%		0%	0%	0%									0%	0%	0%	0%			0%	0%		0%	0%	0%	0%
Newport	2	0%		0%	0%	0%									0%	0%	0%	0%			0%	0%		0%	0%	0%	0%
Virchow	4	0%		0%	0%	0%									25%	25%	25%	0%			75%	0%		0%	50%	75%	25%
Singh 2006		Ak		Ac	A	Ax									Cs	Ce	Ca	Ci			Ch	C		Cf	Cl	Co	D
Saintpaul	32	2		0	6	0									17	16	0	0			20	0		0	2	0	16
Newport	1	0		1	1	1									1	1	1	0			1	0		1	0	0	1
Virchow	3	0		3	3	3									3	0	1	1			3	1		0	2	0	2
Teko	1	0		0	1	1									1	0	1	0			1	0		0	1	0	0
Total	37	2		4	11	5									22	17	3	1			25	1		1	5	0	19
Saintpaul	32	6%		0%	19%	0%									53%	50%	0%	0%			63%	0%		0%	6%	0%	50%
Newport	1	0%		100%	100%	100%									100%	100%	100%	0%			100%	0%		100%	0%	0%	100%
Virchow	3	0%		100%	100%	100%									100%	0%	33%	33%			100%	33%		0%	67%	0%	67%
Teko	1	0%		0%	100%	100%									100%	0%	100%	0%			100%	0%		0%	100%	0%	0%
Randhawa 2006		Ak			A													Ci				Ch		Cf		Co	
Virchow	1	0			0													0				0		0		1	
Virchow	1	0%			0%													0%				0%		0%		100%	
Murugkar 2005			Am		A															Cn		C	Ct	Cf			
Typhimurium (livestock)	29		8		13															5		5	18	2			12
Enteritidis (livestock)	25		15		14															5		0	9	2			8
Gallinarum (livestock)	12		7		9															4		8	6	1			5
Bareilly (livestock)	3		0		0															0		0	0	0			1
Total	69		30		36															14		13	33	5			26
Typhimurium (livestock)	###		28%		45%															17%		17%	62%	7%			41%
Enteritidis (livestock)	###		60%		56%															20%		0%	36%	8%			32%
Gallinarum (livestock)	###		58%		75%															33%		67%	50%	8%			42%

Bareilly (livestock)	###		0%		0%															0%		0%	0%	0%			33%
Typhimurium (humans)	10		4		3															2		2	1	2			3
Enteritidis (humans)	11		8		9															6		0	2	1			10
Total	21		12		12															8		2	3	3			13
Typhimurium (humans)	10		40%		30%															20%		20%	10%	20%			30%
Enteritidis (humans)	11		73%		82%															55%		0%	18%	9%			91%
Typhimurium (combined)	39		12		16															7		7	19	4			15
Enteritidis (combined)	36		23		23															11		0	11	3			18
Gallinarum	12		7		9															4		8	6	1			5
Bareilly	3		0		0															0		0	0	0			1
Total	75		42		48															22		15	36	8			39
Typhimurium	39		31%		41%															18%		18%	49%	10%			38%
Enteritidis	36		64%		64%															31%		0%	31%	8%			50%
Gallinarum	12		3%		3%															2%		0	0	0			0
Bareilly	3		24%		27%															18%		0	6%	0			0.3
Sinha 2006					A			Az										Ci				C		Cf		Co	
Worthington	32				21			28										20				4		2		5	
worthington	32				66%			88%										63%				13%		6%		16%	
Suresh 2006																											
Enteritidis	40				40																			2			
Cerro	4				4																			0			
Molade	1				1																			1			
Mbandaka	1				1																			1			
Total	46				46																			4			
Enteritidis	40				100%																			5%			
Cerro	4				100%																			0%			
Molade	1				100%																			100%			
Mbandaka	1				100%																			100%			
Karthikeyan 2011					A							Cf					Ca	Ci						Cf		Co	
Virchow	1				1							1					1	1						0		0	
Virchow	100%				100%							100%					100%	100%						0%		0%	
Menezes 2011		Ak		Ac	A						Cz	Cf	Cxn	Cep	Cs	Ce	Ca	Ci	Cu		Ch	C		Cf	Cl		
Typhimurium	5	0		1	1						1	0	1	1		1	1	1	1			1		0			
Agona	10	1		2	9						8	8	2	8		9	9	9	9			6		9			
Enteritidis	3	0		0	0						0	0	0	0		0	0	0	0			0		1			

Lexington	1	0		0	0						0	0	0	0		0	0	0	0			0		0			
Seftenberg	1	0		0	0						0	0	0	0		0	0	0	0			0		1			
Kirkee	1	0		0	0						0	0	0	0		0	0	0	0			0		0			
Total	21	1		3	10						9	8	3	9		10	10	10	10			7	0	11			
Typhimurium	5	0%		20%	20%						20%	0%	20%	20%		20%	20%	20%	20%			20%		0%			
Agona	10	10%		20%	90%						80%	80%	20%	80%		90%	90%	90%	90%			60%		90%			
Enteritidis	3	0%		0%	0%						0%	0%	0%	0%		0%	0%	0%	0%			0%		33%			
Lexington	1	0%		0%	0%						0%	0%	0%	0%		0%	0%	0%	0%			0%		0%			
Seftenberg	1	0%		0%	0%						0%	0%	0%	0%		0%	0%	0%	0%			0%		100%			
Kirkee	1	0%		0%	0%						0%	0%	0%	0%		0%	0%	0%	0%			0%		0%			
Parvathi 2011			Am		A				B											Cn	Ch	C		Cf			
Newport	60		15		15				60											9	9	9		9			
Newport	60		25%		25%				100%											15%	15%	15%		15%			
Hassan Ali			Am		A					Cr										Cn							D
Enteritidis	24		8		8					5										5							6
Enteritidis	24		33%		33%					21%										21%							25%
Jabeen 2011					A													Ci								Co	
NTS	189				47													9				13		96		89	
NTS	189				25%													5%				7%		51%		47%	
Aakiyama 2011					A																	C					
Saintpaul	13				0																	0					
Saintpaul	13				0%																	0%					
Ponce 2008					A																	C					
Weltevreden	4				0																	0					
Weltevreden	4				0%																	0%					
Ellerbroek 2010					A												Ca					C		Cf	Cl		
Enteritidis	42				8											0	0					0		40	0		
Subsp. I rough form	2				1											0	0					0		2	0		
Typhimurium	8				0											0	0					0		1	0		
Total	52				9											0	0					0		43	0		
Enteritidis	42				19%											0%	0%					0%		95%	0%		
Subsp. I rough form	2				50%											0%	0%					0%		100%	0%		
Typhimurium	8				0%											0%	0%					0%		13%	0%		

Table 5: Complete Resistance by Percentage against Drugs Azithromycin – Doxycycline

	# of isolates	Enrofloxacin	Erythomycin	Florfenicol	Furazolidone	Gentamicin	Imipenem	Kanamycin	Meropenem	Nalidixic Acid	Neomycin	Netilmicin	Nitrofurantoin	Norfloxacin	Ofloxacin	Penicillin-G	Piperacillin	Piperacillin/Tazobactam	Polymixin-B	Roxithromycin	Sparfloxacin	Streptomycin	Sulfisoxazole	Sulphamethoxazole	Tetracycline	Tobramycin	Trimethoprim
Kansakar 2011		Ef	E	Fl	Fr	G	I	K	M	Na	N	Nt	Nf	No	O	P	Pc	Pc/Tz	PB	R	Sf	S	Sx	Sm	T	To	Tr
Enteritidis	1																										
Enteritidis	1																										
Kumar 2008						G						N			O						Sf						
Typhimurium	5					0						0			0						0						
Senftenberg	3					2						1			0						0						
Group E not Senftenberg	3					1						1			0						0						
Other Salmonella groups	5					0						0			0						1						
Total	16					3						2			0						1						
Typhimurium	5	0%				0%						0%			0%						0%			0%			0%
Senftenberg	3	0%				67%						33%			0%						0%			0%			0%
Group E not Senftenberg	3	0%				33%						33%			0%						0%			0%			0%
Other Salmonella groups	5	0%				0%						0%			0%						20%			0%			0%
Kapoor 2006																											
Worthington	9				1	7								3													
Worthington	9				11%	78%								33%													
Taneja 2004					Fr[2]	G				Na																	
NTS	27				11	9				16																	
NTS	27				42%	33%				59%																	
Singh 2007					Fr	G	I	K		Na	N											S		Sm	T		Tr
Anatum	2				2	0	0	0		0	0											0		2	0		0

Bsilla	1				1	0	0	0		0	0											0		1	0		0
Mons	2				2	2	0	2		2	2											0		2	2		0
Rottnest	1				1	0	0	1		1	0											0		1	0		0
Saintpaul	14				8	6	2	14		14	5											0		12	8		2
Weltevreden	5				2	0	2	4		4	2											0		5	0		0
Teko	4				0	0	2	2		2	0											0		0	2		0
Newport	2				0	0	0	2		2	0											0		2	0		0
Virchow	4				4	0	0	0		4	0											0		4	2		2
Total	35				20	8	6	25		29	9											0		29	14		4
Anatum	2				100%	0%	0%	0%		0%	0%											0%		100%	0%		0%
Bsilla	1				100%	0%	0%	0%		0%	0%											0%		100%	0%		0%
Mons	2				100%	100%	0%	100%		100%	100%											0%		100%	100%		0%
Rottnest	1				100%	0%	0%	100%		100%	0%											0%		100%	0%		0%
Saintpaul	14				57%	43%	14%	100%		100%	36%											0%		86%	57%		14%
Weltevreden	5				40%	0%	40%	80%		80%	40%											0%		100%	0%		0%
Teko	4				0%	0%	50%	50%		50%	0%											0%		0%	50%		0%
Newport	2				0%	0%	0%	100%		100%	0%											0%		100%	0%		0%
Virchow	4				100%	0%	0%	0%		100%	0%											0%		100%	50%		50%
Singh 2006					Fr	G	I	K		Na	N											S		Sm	T		Tr
Saintpaul	32				19	0	0	20		19	0											3		14	1		0
Newport	1				1	1	0	1		1	1											0		1	1		1
Virchow	3				3	2	0	3		1	0											0		3	3		3
Teko	1				1	0	0	1		1	0											1		1	1		1
Total	37				24	3	0	25	0	22	1											4	0	19	6	0	5
Saintpaul	32				59%	0%	0%	63%		59%	0%											9%	0%	44%	3%	0%	0%
Newport	1				100%	100%	0%	100%		100%	100%											0%	0%	100%	100%	0%	100%
Virchow	3				100%	67%	0%	100%		33%	0%											0%	0%	100%	100%	0%	100%
Teko	1				100%	0%	0%	100%		100%	0%											100%	0%	100%	100%	0%	100%
Randhawa 2006						G																					
Virchow	1					0																					
Virchow	1					0%																					
Murugkar 2005		Ef						K		Na			Nf	No											T		Tr
Typhimurium (livestock)	29	0				1		12		4			10	0											17		4

Enteritidis (livestock)	25	0				0		8		3			14	0											12		2
Gallinarum (livestock)	12	0				0		5		7			10	0											11		1
Bareilly (livestock)	3	0				0		1		0			0	0											0		0
Total	69	0				1		26		14			34	0											40		7
Typhimurium (livestock)	###	0%				3%		41%		14%			34%	0%											59%		14%
Enteritidis (livestock)	###	0%				0%		32%		12%			56%	0%											48%		8%
Gallinarum (livestock)	###	0%				0%		42%		58%			83%	0%											92%		8%
Bareilly (livestock)	###	0%				0%		33%		0%			0%	0%											0%		0%
Typhimurium (humans)	10	2				1		1		2			2	1											0		2
Enteritidis (humans)	11	0				3		2		2			7	0											1		0
Total	21	2				4		3		4			9	1											1		2
Typhimurium (humans)	10	20%				10%		10%		20%			20%	10%											0%		20%
Enteritidis (humans)	11	0%				27%		18%		18%			64%	0%											9%		0%
Typhimurium (combined)	39	2				2		13		6			12	1											17		6
Enteritidis (combined)	36	0				3		10		5			21	0											13		2
Gallinarum	12	0				0		5		7			10	0											11		1
Bareilly	3	0				0		1		0			0	0											0		0
Total	75	2				5		29		18			43	1											41		9
Typhimurium	39	5%				5%		33%		15%			31%	3%											44%		15%
Enteritidis	36	0%				8%		28%		14%			58%	0%											36%		6%
Gallinarum	12	0				0		0		0			0	0											0		0
Bareilly	3	0				0.1		0.1		0.1			0.2	0											0		0
Sinha 2006						G									O												
Worthington	32					21									2												
worthington	32					66%									6%												
Suresh 2006								K			N														T		
Enteritidis	40							15		17	40								40						40		
Cerro	4							2		0	4								4						4		
Molade	1							0		0	1								1						1		
Mbandaka	1							0		0	1								1						1		
Total	46							17		17	46								46						46		
Enteritidis	40							38%		43%	100%								100%						100%		

Cerro	4							50%		0%	100%								100%						100%		
Molade	1							0%		0%	100%								100%						100%		
Mbandaka	1							0%		0%	100%								100%						100%		
Karthikeyan 2011																		Pc/Tz							T		
Virchow	1																	0							0		
Virchow	100%																	0%							0%		
Menezes 2011									M	Na							P	Pc/Tz									
Typhimurium	5								0	1							1	0									
Agona	10								1	3							7	0									
Enteritidis	3								0	1							0	0									
Lexington	1								0	0							0	0									
Seftenberg	1								0	1							0	0									
Kirkee	1								0	0							0	0									
Total	21								1	6							8	0									
Typhimurium	5								0%	20%							20%	0%									
Agona	10								10%	30%							70%	0%									
Enteritidis	3								0%	33%							0%	0%									
Lexington	1								0%	0%							0%	0%									
Seftenberg	1								0%	100%							0%	0%									
Kirkee	1								0%	0%							0%	0%									
Parvathi 2011			E			G		K		Na			Nf	No		PG									T	To	Tr
Newport	60		30			0		12					11	3		60									14	60	19
Newport	60		50%			0%		20%					18%	5%		100%									23%	100%	32%
Hassan Ali															O					Ro							Tr
Enteritidis	24														0					6							4
Enteritidis	24														0%					25%							17%
Jabeen 2011										Na					O												
NTS	189									102					95												
NTS	189									54%					50%												
Aakiyama 2011						G		K														S	Su		T		
Saintpaul	13					0		0														0	0		0		
Saintpaul	13					0%		0%														0%	0%		0%		
Ponce 2008						G		K														S	Su		T		
Weltevreden	4					1		0														1	0		1		

Weltevreden	4					25%		0%														25%	0%		25%		
Ellerbroek 2010				F		G		K		Na												S		Sm	T		Tr
Enteritidis	42			0		0		0		40												0		0	8		0
Subsp. I rough form	2			0		0		0		1												0		0	0		0
Typhimurium	8			0		0		0		1												0		0	0		0
Total	52			0		0		0		42												0		0	8		0
Enteritidis	42			0%		0%		0%		95%												0%		0%	19%		0%
Subsp. I rough form	2			0%		0%		0%		50%												0%		0%	0%		0%
Typhimurium	8			0%		0%		0%		13%												0%		0%	0%		0%