

PREVALENCE OF CLASS 1 INTEGRONS IN CLINICAL ISOLATES
OF NON-TYPHOIDAL *SALMONELLA ENTERICA* CIRCULATED
IN ARMENIA

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A total of 182 non-typhoid *Salmonella enterica* (NTS) isolates recovered from patients between 1996 and 2014 were included in the current study focused on class 1 integron detection and its association with multidrug resistance (MDR) phenotype. A high prevalence of isolates displaying MDR and penta-resistance (resistance to ampicillin, chloramphenicol, streptomycin, sulfonamide, tetracycline) phenotypes of clinical significance was revealed. Serotype-specific prevalence of antimicrobial resistance as well as class 1 integrons and inserted variable segments was detected in isolates. The results indicated the limitations of current antimicrobial therapy to control infections caused by MDR isolates of NTS, especially belonging to serotype Typhimurium.

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Keywords: non-typhoid *Salmonella*, multidrug resistance, *S. ser. Typhimurium*, *S. ser. Enteritidis*, class 1 integron.

Introduction. Non-typhoid *Salmonella* (NTS) infection is one of the most frequent foodborne diseases that cause morbidity and mortality worldwide [1]. Clinical manifestation of human salmonellosis usually is self-limiting gastroenteritis, characterized by abdominal pain, diarrhea, fever, nausea and vomiting. Although salmonellosis symptoms last less than 10 days the disease could be severe for high-risk groups such as infants, the elderly or immunocompromised persons [2, 3]. In more severe cases, treatment of salmonellosis includes electrolyte replacement, rehydration, and antimicrobial (AM) therapy. Current recommendations for AM therapy of salmonellosis include third-generation cephalosporins in children, and fluoroquinolones as a therapeutic alternative for infections resistant to third-generation cepheems in adults [2]. However, increasing prevalence and widespread dissemination of resistance to these AMs as well as of multidrug-resistance (MDR) among NTS isolates complicated treatment of salmonellosis [4, 5]. It was shown that integrons play an important role in the acquisition of resistance to AMs and development of MDR among NTS [6–10]. Integrons are known as genetic structures able to incorporate antimicrobial resistance genes by capturing the exogenous gene cassettes (or integron cassettes) via site-specific recombination and promote their functional expression [7–12]. Integrons are generally characterized by the presence

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of core features located on the 5' end of an integron: an integrase gene (*intI*), a proximal primary recombination site (*attI*), and a constitutive cassette promoter (Pc) [7, 9, 10, 12]. The 3'-conserved segment (3'-CS) of integrons consists of fused genes (*qacEΔ1/sulI*) encoding resistance to disinfectants and sulfonamides [9, 11], *orf5* of unknown function, and the remnants of genes (*tniΔ*) encoding transposition functions [7, 9]. The 5' and 3'-conserved segments of integron are separated by a variable segment (VS), wherein different cassette arrays can be integrated. Gene cassettes are self-mobilizable simple structures, usually formed by an open reading frame (ORF) restricted by a cassette-associated recombination site (*attC*) [9, 10, 13]. Gene cassettes may exist freely as circular DNA or incorporated to the *attI* site of the integron via integrase mediated recombination between *attI* and *attC* sites [9, 12]. The gene cassettes are capable of carrying genes that confer resistance to different classes of antimicrobials, such as aminoglycosides, chloramphenicols, inhibitors of folate pathway, tetracyclines, β-lactams as well as to antiseptics and disinfectants [9, 11]. The number of gene cassettes within the integron may vary, however, they are not a mandatory part of the integrons. Several classes of integrons described up to now but the widespread type of integron prevailing in clinical isolates of the *Salmonella* is the class 1 integrons [8, 14]. Integrons are not mobile elements but being carried on plasmids or located within a transposon they can be transmitted from one bacterium to another [9].

According to the National Centre for Disease Control and Prevention of Armenia, the number of confirmed cases of salmonellosis has been variable over the past decade [15]. The incidence of salmonellosis in Armenia has increased from 2016 to 2019 with children under 6 years of age comprising at least 50% of patients. A total of 793 cases of salmonellosis were registered in 2019 making the disease the leading foodborne bacterial infection in Armenia. *S. ser. Enteritidis* and *S. ser. Typhimurium* are the most common serovars among the human *S. enterica* isolates circulated in Armenia. The tendency towards the MDR phenotype among the clinical NTS isolates circulated in Armenia between 1996 and 2016 was reported [16]. The association of MDR phenotype with class 1 integrons in clinical isolates of NTS collected in 2011 was shown [17]. However, there is a lack of information regarding the prevalence of class 1 integrons in the clinical isolates belonging to the most common serovars of NTS in Armenia. Thus, the aim of this study was to explore the presence and prevalence of class 1 integrons as well as the association of class 1 integrons and MDR phenotype in the human isolates of NTS circulated in Armenia.

Materials and Methods.

Isolates of NTS. The study included a total of 182 non-typhoidal *Salmonella enterica* subsp. *enterica* isolates recovered from fecal samples of patients with salmonellosis admitted to the “Nork” Clinical Hospital of Infectious Diseases (MH, Armenia) over the period from 1996 to 2014. All these isolates were confirmed to be non-typhoidal *S. enterica* by standard biochemical tests: fermentation of glucose, negative urease reaction, lysine decarboxylase, negative indole test, H₂S production, and fermentation of galactitol (dulcitol). Serotypes of *Salmonella* isolates were determined in accordance with the White-Kauffmann-Le Minor scheme [18] with the use of commercially available polyvalent antisera for flagellar (H) and lipopolysaccharide (O) antigens. The study protocol was approved by the Ethics

Committee of the Institute of Molecular Biology NAS RA (IORG number 0003427, Assurance number FWA00015042 and IRB number 00004079). The patients were enrolled in the 2014 study after providing a written informed consent.

Antimicrobial Susceptibility Testing. Susceptibility to antimicrobials was tested by standard disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute [19]. The following disks with AMs (“Liofilchem®” s.r.l, Italy) were used: ampicillin (10 µg), amoxicillin + clavulanic acid (20 µg / 10 µg), azithromycin (15 µg), ceftazidime (30 µg), ceftriaxone (30 µg), chloramphenicol (30 µg), ciprofloxacin (5 µg), gentamicin (10 µg), nalidixic acid (30 µg), streptomycin (10 µg), sulfonamide (300 µg), tetracycline (30 µg) and trimethoprim-sulfamethoxazole (1.25 µg / 23.75 µg). Muller-Hinton agar (“Liofilchem®”, Italy) was used for bacterial growing. Bacterial inoculum was adapted to be equal to a 0.5 McFarland standard (corresponding to $1.5 \cdot 10^8$ CFU/mL). *Escherichia coli* ATCC 25922 strain was used as quality control. The results were interpreted according to the CLSI guidelines [19]. Isolates that were resistant to at least three different classes of tested AM agents were identified as MDR.

DNA Extraction. Template DNA of isolates for PCR-amplification was extracted with the use of the FastDNA® Kit (“Qbiogene Inc.”), according to the guidelines of the manufacturer.

PCR-identification of Class 1 Integrins: All isolates were tested for the presence of class 1 integrase-specific *intI1* gene, variable segment of integrons, and 3'-conserved segment. Primer sets, mix composition, and conditions used for PCR amplification were as described previously (Tab. 1) [20]. The PCR products were visualized by ethidium bromide staining after gel electrophoresis in 2% agarose (DNA Ladder: GenScript, M1060, 2000 b.p.).

Table 1

Primers, target genes, and expected amplicon sizes for detection of class 1 integrins

Primer	Target gene	Sequence of nucleotides* (5'-3')	PCR product, b.p.	Annealing temperature, °C
Int-1U	<i>intI1</i>	GTTCGGTCAAGGTTCTG	923	64
Int-1D		GCCAACTTTCAGCACATG		
In-F	variable segment	GGCATACAAGCAGCAAGC	variable length	52
In-B		AAGCAGACTTGACCTGAT		
qacEΔ1-F	3'-conservative segment	ATCGCAATAGTTGGCGAAGT	800	56
Sul1-B		GCAAGGCGGAAACCCGCGCC		

* Oligonucleotide supplier: Integrated DNA Technologies, BVBA (Belgium).

Statistical Analyses. *P* value (two-tailed) from Fisher's exact test was calculated using the on-line [GraphPad QuickCalcs](#) resource (accessed July 2020) to evaluate statistical differences between the compared groups. *P* values less than 0.05 were considered to be significant.

Results and Discussion. A total of 182 NTS isolates recovered from fecal samples of patients with salmonellosis over the period from 1996 to 2014 were studied. Among these isolates, the two serotypes were predominant, Typhimurium

(112 isolates, 62%) and Enteritidis (39 isolates, 21%), while the prevalence of all other NTS serotypes was lower (31 isolates, 17%).

All clinical isolates were tested for susceptibility towards 13 AMs belonging to 9 different classes. The results indicated that only 3.85% (7 out of 182) of isolates were sensitive to all AMs tested, whereas 75.8% (138/182) of isolates were resistant to 3 or more classes of AMs (Tab. 2), i.e. displayed the MDR phenotype, which is of great concern. Moreover, 20.88% (38/182) of tested isolates exhibited resistance at least to ampicillin, chloramphenicol, streptomycin, sulfonamide, tetracycline (ACSSuT), a penta-resistance profile typical for *S. ser. Typhimurium* phage type DT104 [21]. It was reported that in *S. Typhimurium* DT104 strains genes encoding for the ACSSuT resistance are located within MDR region of the chromosomal *Salmonella* Genomic Island 1 (SGI1) [21, 22]. The hazard is the possibility of transferring the SGI1 clonally and horizontally to other serotypes, which is of great concern.

Table 2

Number of classes of antimicrobials to which clinical NTS isolates displayed resistance

Number of classes of AMs	Total isolates		Serotype of <i>Salmonella enterica</i>					
			Typhimurium		Enteritidis		other	
	N=182	%	N=112	%	N=38	%	N=32	%
0 (sensitive)	7	3.85	0	0	6	16	1	3.1
1	20	11	6	5.4	14	37	0	0
2	17	9.34	8	7.1	5	13	4	12.5
3 (MDR)	17	9.34	12	11	4	10.5	1	3.1
4 (MDR)	34	18.7	25	22.3	4	10.5	5	15.6
5 (MDR)	27	14.8	18	16	1	2.6	8	25
6 (MDR)	17	9.34	10	9	2	5.3	5	1.6
7 (MDR)	34	18.7	25	22.3	2	5.3	7	22
8 (MDR)	5	2.75	4	3.6	0	0	1	3.1
9 (MDR)	3	1.65	3	2.7	0	0	0	0
Total MDR	138	75.82	98	87.5	13	34.2	27	84.4
ACSSuT*	38	20.88	30	26.79	0	0	8	25

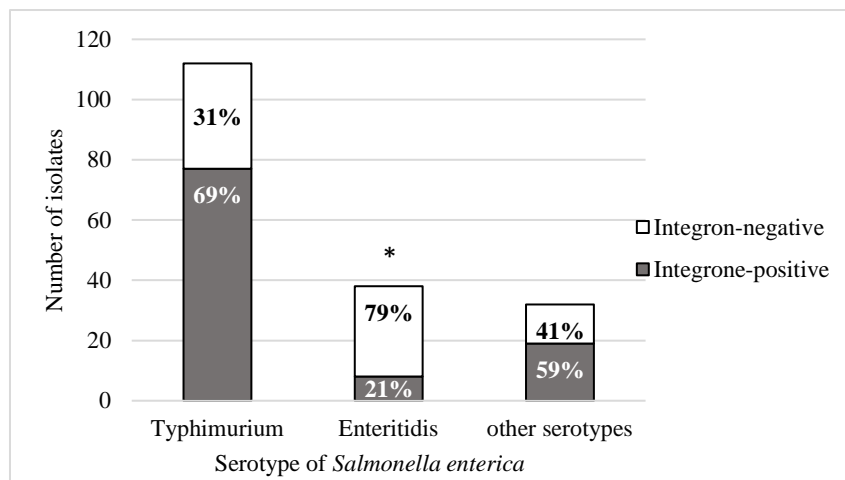
* AM resistance profile: ampicillin (A), chloramphenicol (C), streptomycin (S), sulfonamide (Su) and tetracycline (T).

Since, *S. ser. Enteritidis* and *S. ser. Typhimurium* were the most common serovars among the human *S. enterica* isolates in this study, it was actual to explore AM resistance phenotypes within these serovars apart. Notably, 16% (6/38) of the *S. ser. Enteritidis* isolates were susceptible to all tested AMs, while we did not detect *S. ser. Typhimurium* isolates showing susceptibility to all these AMs. Although the MDR phenotype could be found in all NTS serotypes investigated, the results indicated the higher prevalence of MDR isolates among *S. ser. Typhimurium* compared to *S. ser. Enteritidis* (87.5% and 34.2%, respectively; $P=0.0001$). The most common phenotypes for *S. ser. Typhimurium* isolates were resistance to 4 and 7 classes of AMs (22.3%); whereas, for *S. ser. Enteritidis* isolates the most common was resistance to 1 class of AMs 37% (14/38), in particular to nalidixic acid

(quinolone). It should also be noted that 79% (30/38) of the isolates displaying at least ACSSuT phenotype belonged to *S. ser. Typhimurium*, while in *S. ser. Enteritidis* isolates this phenotype was not detected ($P=0.0019$). Thus, the higher prevalence of resistance to AMs as well as MDR and ACSSuT phenotypes was identified in isolates belonging to serotype Typhimurium compared to isolates belonging to serotype Enteritidis.

PCR-testing for the identification of class 1 integron revealed that 53.85% of isolates in this study (98 out of 182) were positive for *intI1* gene and 3'-conserved segment with the expected size of PCR-products (923 b.p. and 800 b.p., correspondingly), as well as generated VS amplicons. Of note, *intI1* gene was also detected in six isolates (3.3%) that were negative for 3'-conserved segment. In addition, VS was detected in four isolates (11,11%) that were negative for *intI1* gene and 3'-conserved segment. Thus, the results indicated that 57.14% (104 out of 182) of clinical isolates of NTS were positive for class 1 integrons.

The following distribution of integron-positive isolates among the most common serotypes was revealed (see Figure): 69% (77/112) of *S. ser. Typhimurium*, followed by 21% (8/38) of *S. ser. Enteritidis*, while other serotypes of *Salmonella* made up 59% (19/32).



* Statistically significant differences between *S. Enteritidis* isolates and isolates belonged to other serotypes of NTS, two-tailed Fisher's exact test, $P<0.05$.

Distribution of integron-positive isolates among NTS isolates.

The results indicated the lower prevalence of integron-positive isolates among the isolates belonging to *S. ser. Enteritidis* compare to isolates of *S. ser. Typhimurium* ($P<0.0001$) and isolates belonging to other serotypes of *Salmonella* ($P=0.0014$).

The most common size of VS was 1500 b.p. (61.5%, 64/104), which was mainly identified in *S. ser. Typhimurium* (55 isolates), while it was rare in *S. ser. Enteritidis* (1 isolate). It should be noted that 37.5% (24/64) of isolates with embedded amplicon of 1500 b.p. displayed ACSSuT phenotype. The second most common size of VS was 1000 b.p. (24%, 25/104) with the following serotype distribution: 12 *S. ser. Typhimurium*, 5 *S. ser. Enteritidis*, and 8 isolates belonging

to other serotypes of *Salmonella*. All VSs with other sizes (from 200 b.p. to 2000 b.p.) were detected with lower prevalence. Interestingly, in 14 isolates VS was represented by amplicons of different sizes in combination. The most common was combination of 2000 b.p. and 1500 b.p. amplicons, which was detected in 7 isolates and all these isolates belonged to *S. ser. Typhimurium*. The combination of 1500 b.p. and 200 b.p. amplicons was identified in 2 isolates (*S. ser. Typhimurium* and *S. ser. Arizonae*). All other combinations of VS amplicons were encountered as singletons: 1) 2000 b.p., 1500 b.p., 400 b.p. and 200 b.p. amplicons detected in *S. ser. Typhimurium* isolate; 2) 2000 b.p. and 600 b.p. amplicons detected in *S. ser. Typhimurium*; 3) 2000 b.p., 1500 b.p. and 1000 b.p. amplicons identified in *S. ser. Typhimurium*; 4) 800 b.p., 400 b.p. and 200 b.p. amplicons found in *S. ser. Enteritidis*, 5) 1000 b.p., 800 b.p., and 700 b.p. amplicons detected in isolate belonging to other NTS serotype. Thus, the results indicated the serotype-specific distribution of VS amplicons in integron-positive isolates with the predominance of 1500 b.p. and 2000 b.p. amplicons in *S. ser. Typhimurium* isolates.

Table 3

Resistance to AMs in clinical NTS isolates depending on the presence of class 1 integrons

Classes of AMs*	Number of NTS isolates			Number of <i>S. ser. Typhimurium</i> isolates		
	integron-positive	integron-negative	<i>P</i> **	integron-positive	integron-negative	<i>P</i> **
0 ^a	0	7	0.0023	0	0	NS
1	4	16	0.0005	2	4	NS
2	5	12	0.02	3	5	NS
3	3	14	0.0007	3	9	0.0013
4	25	9	0.0357	20	5	NS
5	17	10	NS	11	7	NS
6	14	3	0.0377	9	1	NS
7	30	5	0.0001	24	2	0.003
8	3	2	NS	2	2	NS
9	3	0	NS	3	0	NS
ACSSuT ^b	32	6	0.0002	26	4	0.02

* - Number of classes of AMs to which clinical isolate displayed resistance;

** - *P* values less than 0.05 were considered to be significant;

^a - susceptible to all AMs tested;

^b - resistance to ampicillin, chloramphenicol, streptomycin, sulfonamide, tetracycline.

NS - not significant;

Link between integron carriage and antimicrobial resistance (AMR) phenotypes was then analyzed. The results indicated that 68.84% of MDR (95 out of 138) isolates in this study was integron-positive, whereas in non-MDR isolates the prevalence of integron-positive isolates was lower, 20.45% (9/44, $P < 0.0001$). It should be noted that susceptibility to all tested AMs was detected only in integron-negative isolates ($P < 0.0023$, Tab. 3) and all of them, except one, belonged to the serotype *S. ser. Enteritidis*. Resistance to 1–3 classes of AMs was higher in integron-negative isolates, whereas resistance to 4, 6, and 7 classes of AMs was higher in

integron-positive isolates. Among integron-positive isolates, the most common phenotype was resistance to 7 classes of AMs that was detected in 30 isolates, of which 24 isolates also displayed ACSSuT phenotype. It should be noted that ACSSuT phenotype was significantly higher detected in integron-positive isolates as compared with integron-negative isolates ($P=0.0002$). In contrast, the most common phenotype in integron-negative isolates was resistance to only one AM (nalidixic acid).

Comparative analysis of AM resistance phenotypes depending on integron carriage, which was performed within NTS serovars apart, revealed some differences for *S. ser. Typhimurium* (Tab. 3). It should be noted that the higher prevalence of MDR phenotype was revealed in integron-positive *S. ser. Typhimurium* isolates compared with integron-negative isolates (93.5% and 74.3%, respectively; $P=0.01$). In addition, the penta-resistance phenotype (ACSSuT) was significantly higher in integron-positive *S. ser. Typhimurium* isolates compared to integron-negative ($P=0.02$).

Conclusion. The high prevalence of MDR and penta-resistance (ACSSuT) phenotypes was revealed among NTS isolates recovered from patients between 1996 and 2014, which is of great concern. The high frequency of class 1 integron carriage was observed in human NTS isolates, which is of clinical significance. Strong association between the MDR and the presence of class 1 integrons was detected. Serotype-specific prevalence of AM resistance as well as class 1 integrons and inserted variable segments was revealed in clinical NTS isolates. The results indicated the limitations of current AM therapy to control infections caused by MDR isolates of NTS, especially belonging to serotype Typhimurium.

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Մ. Կ. ՉԱԽԱՐՅԱՆ

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 ՀԱՅԱՍՏԱՆՈՒՄ ՇՐՋԱՆԱՌՎՈՂ ՈՉ ՏԻՖՈԻԴՆ ՍԱԼՄՈՆԵԼԱՆԵՐԻ
 ԿԼԻՆԻԿԱԿԱՆ ԻԶՈԼԱՏՆԵՐՈՒՄ

Աշխատանքում հետազոտել են 1996–2014 թթ. ընթացքում ոչ տիֆային սալմոնելայի (ՈՏՍ) 182 կլինիկական իզոլյատներ՝ 1-ին դասի ինտեգրոնները պարզելու և նրանց կապը բազմադեղակայունության (ԲԴԿ) ֆենոտիպի հետ: Բացահայտվել է կլինիկական նշանակություն ունեցող բազմակայունության և պենտաակայունության (կայունություն ամպիցիլինի, քլորամֆենիկոլի, ստրեպտոմիցինի, սուլֆոնամիդի, տետրացիկլինի նկատմամբ) ֆենոտիպեր ցուցաբերող ՈՏՍ իզոլյատների բարձր տարածվածություն: Հայտնաբերվել են շճատիպին հատուկ կայունության տարածվածություն հակամանրէային դեղամիջոցների նկատմամբ, ինչպես նաև 1-ին դասի ինտեգրոնները և ներդրված փոփոխական հատվածները: Արդյունքները վկայում են ՈՏՍ իզոլյատներով հարուցված վարակների հակամանրէային թերապիայի կիրառմամբ վերահսկման սահմանափակումները, հատկապես *Typhimurium* շճատիպին պատկանող իզոլյատների դեպքում:

M. K. ZACHARYAN

РАСПРОСТРАНЕННОСТЬ ИНТЕГРОНОВ ПЕРВОГО КЛАССА
 В КЛИНИЧЕСКИХ ИЗОЛЯТАХ НЕТИФОИДНЫХ САЛЬМОНЕЛЛ,
 ЦИРКУЛИРУЮЩИХ В АРМЕНИИ

В работе исследовано 182 клинических изолята нетифоидных сальмонелл (НТС), выделенных у пациентов за период 1996–2014 гг. с целью выявления интегронов 1-го класса и их ассоциированности с фенотипом множественной лекарственной устойчивости (МЛУ). Выявлена высокая распространенность изолятов с клинически значимыми фенотипами МЛУ и пентарезистентности (устойчивости к ампициллину, хлорамфениколу, стрептомицину, сульфонамиду, тетрациклину). Обнаружена серотип-специфическая распространенность устойчивости к антимикробным препаратам, а также интегронов 1-го класса и встроенных вариабельных сегментов. Результаты свидетельствуют об ограниченных возможностях антимикробной терапии при контроле над инфекциями, вызванными МЛУ-изолятами НТС, особенно принадлежащими к серотипу *Typhimurium*.