

A Epizootiological Study of Salmonella Infection on Piggery: II. A Study on Drug Resistance and R Plasmids in *Salmonella*

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養豚場에 있어서 *Salmonella* 感染症의 疫學的인 研究 : II. *Salmonella* 屬菌의 藥劑耐性 및 傳達性 R plasmid

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抄 錄 : 1984년 5월부터 1985년 5월까지 大邱, 慶北, 慶南 및 忠南地域 7個 養豚場의 仔豚 및 成豚의 糞便 및 養豚場의 糞, 下水, 飼料, 推肥, 쥐 등 7,440例와 大邱市 屠畜場의 屠畜豚 腸間膜淋巴節 및 直腸內容物 555例로부터 分離한 319株의 *Salmonella*屬菌을 대상으로 抗菌劑에 대한 耐性 및 傳達性 R plasmid의 分布狀況을 調査하였던 바 그 結果는 다음과 같다.

1. 供試菌 319株 中 250株(78.4%)가 ampicillin(An), chloramphenicol(Cm), gentamicin(Gm), kanamycin(Km), nalidixic acid(Na), rifampicin(Rf), streptomycin(Sm), sulfadimethoxine(Su), 또는 tetracycline(Tc)에 耐性を 나타내었으며, 藥劑別로는 Su(74.9%), Sm(53.0%) 및 Tc(28.5%)에 높은 耐성이 認定되었다.
2. 耐性菌 250株의 傳達性 R plasmid 保有率은 51.2%(128株)였으며, 藥劑別로는 Am경우 100%, Tc 92.3% 및 Cm 75.0% 순으로 保有率이 높았다.
3. 耐性菌 250株의 耐性樣相은 SmSu(91株), Su(59株) 및 TcSmSu(50株)耐性型이 대부분이었고 R plasmid 傳達後의 耐性樣相은 TcSmSu(40株) 및 TcSu(28株) 耐性型이 많았다.
4. 養豚場別 耐性菌 出現頻度는 48.0~93.6%로 多樣하였고, 傳達性 R plasmid 保有率은 0~77.8%로 耐性菌 出現頻도와 一致되지 않았다.
5. 供試菌 319株 中 各各 2株는 Rf 및 Gm에 대해 耐성을 나타내었고, 耐性菌 250株 中 73.2%(183株)가 多劑耐성이었으므로 *Salmonella*의 多劑耐性化 傾向이 있었다.
6. 耐性菌 250株 中 R plasmid 傳達後 5株는 TcAmCmSmSu耐性型, 1株는 TcAmKmSmSu耐性型임이 확인되었다.

Introduction

Antimicrobial drugs have successfully been used

for the treatment and prevention of bacterial infections in human and veterinary medicine. The widespread use of antibiotics, particularly as feed additives for

growth promotion of domestic animals, has increased antibiotic resistance of bacteria year after year in many countries(Blackburn *et al.*, 1948; Saxena *et al.*, 1984; Ryder *et al.*, 1980; Terakado *et al.*, 1980).

The antibiotic resistance have found to be mediated by conjugative R plasmids, which has been considered to be a major cause in the spread of multiple drug resistance among members of enterobacteriaceae and many other organisms(Ishiguro *et al.*, 1980; Datta *et al.*, 1971).

In recent years, most of *Salmonella* strains isolated from domestic animals were resistant to antibiotics such as tetracycline, streptomycin and sulfadimethoxine. The prevalence of antibiotic resistance in *Salmonella* isolates, especially when mediated by R plasmids, causes a serious problems not only on animals hygiene but also on public health(Ryder *et al.*, 1980; Terakado *et al.*, 1980).

An increased incidence of antibiotic resistant strains of *Salmonella* has been reported in domestic animals throughout the world(Saxena *et al.*, 1984; Ishiguro *et al.*, 1979; Grant *et al.*, 1976; Kashiwazaki *et al.*, 1974). However, there have been few studies on the antibiotic resistance patterns and on the distribution of the R plasmids among *Salmonella* isolated from pigs in Korea(Nakaoka *et al.*, 1985; Yoon *et al.*, 1981; Tak *et al.*, 1979).

We described the serovars of *Salmonella* strains isolated from pigs(Choi *et al.*, 1986). This paper deals with the incidence of antibiotic resistance and of R plasmids in the *Salmonella* isolates from pigs.

Materials and Methods

Bacterial strains: A total of 319 *Salmonella* isolates were examined for the assay of drug resistance. They were isolated from various samples on 7 piggeries in Taegu, Gyeongbuk, Gyeongnam and Chungnam, and a slaughter house in Taegu during the period from May, 1984 to May, 1985. The serovars of all the *Salmonella* strains were described in a previous report (Choi *et al.*, 1986).

Antibiotic susceptibility test: Antibiotic susceptibility test of *Salmonella* isolates was performed by the agar dilution method(Steers *et al.*, 1959)

using 9 kinds of antibiotics(Sigma chemical Co.). The antibiotics and their concentrations were as follows; 25 μ g/ml of ampicillin(Am), chloramphenicol(Cm), kanamycin(Km), nalidixic acid(Na), rifampicin(Rf) and tetracycline(Tc); 12.5 μ g/ml of gentamicin(Gm) and streptomycin(Sm); 200 μ g/ml of sulfadimethoxine(Su).

Heart infusion agar(Difco) was used for the test, except in the test with Su in which Mueller-Hinton agar was used. An isolate was recorded as resistant if its growth was not inhibited by these concentrations of the drugs.

Detection of R plasmids: This was performed by the method described by Ishiguro *et al.*(1980). Each resistant *Salmonella* isolate(donor) and the *Escherichia coli* recipient strain was cultivated in brain heart infusion(Difco) at 37°C for 18 hours. Broth (2ml) in a test tube was inoculated with 0.2ml of each donor broth culture and an equal amount of the recipient culture. The mixture was incubated at 37°C for 18 hours. A loopful of the mixed culture was streaked on a selective agar plate containing Na(50 μ g/ml) and one of the drugs to which the donor was resistant. Concentrations of the drugs added to the selective media were the same as those used in antibiotic susceptibility tests. The selective media were incubated overnight at 37°C and the transferred resistance marker was determined by observing growth on each selective medium. No growth of donor and recipient strain on each selective media was confirmed.

Results

The antibiotic resistance of the 319 *Salmonella* isolates examined are shown in Table 1. of these, 250 isolates(78.4%) were resistant to one or more antibiotics such as Su, Sm, Tc, Km, Am, Cm, Gm and Rf.

Of the 319 *Salmonella* isolates, 239(74.9%) were resistant to Su, 167(52.4%) to Sm, 91(28.5%) to Tc, 14(4.4%) to Km, 11(3.4%) to Am, 8(2.5%) to Cm and 2(0.6%) to Gm and Rf, respectively. However, all were sensitive to Na.

Transferred drug resistance from *Salmonella* isolates to *E. coli* ML 1410 is also shown in Table 1. Of the

Table 1. Frequency and Transferability of Drug Resistance for 319 *Salmonella* sp. Isolated.

Antimicrobial drugs	No. of resistance strains	No. of strain transferred resistance
Sulfadimethoxine(Su)	239(74.9%)	117(48.9%)
Streptomycin(Sm)	167(52.4%)	71(42.5%)
Tetracycline(Tc)	91(28.5%)	84(92.3%)
Kanamycin(Km)	14(4.4%)	1(7.1%)
Ampicillin(Am)	11(3.4%)	11(100 %)
Chloramphenicol(Cm)	8(2.5%)	6(75.0%)
Gentamicin(Gm)	2(0.6%)	1(50.0%)
Rifampicin(Rf)	2(0.6%)	0
Nalidixic acid(Na)	0	0

250 resistant *Salmonella* isolates, 128(51.2%) harbored conjugative R plasmides. Transfer frequencies of conjugative R plasmids on each selective drug were shown most frequently to Am(100%), followed by Tc(92.3%), Cm(75.0%), Gm(50.0%), Su(48.9%), Sm(42.5%) and Km(7.1%).

The drug resistance patterns and transferred drug resistance of *Salmonella* isolates were given in Table 2. The drug resistance patterns of 250 resistant strains were distributed from one to six fold pattern, and Sm, Su resistance patterns(91 strains), Su patterns (59 strains) and TcSmSu patterns(50 strains) were

Table 2. Resistance Patterns and Transferable Drug Resistance for *Salmonella* Isolates

Resistance patterns	No. of strains	No. of strains with transferable resistance	Resistance patterns transferred
Tc Am Cm Km Sm Su	3	3	Tc Am Cm Sm Su
Tc Am Cm Km Sm	1	1	Tc Am Cm Km Sm
Tc Am Cm Sm Su	2	2	Tc Am Cm Sm Su
Tc Km Gm Sm Su	2	1	Tc Gm Sm Su
		1	Tc Sm Su
Tc Am Sm Su	3	1	Tc Am Sm Su
		1	Tc Am Su
		1	Am Sm
Tc Cm Sm Su	2	1	Tc Sm Su
		1	Sm Su
Tc Tm Sm Su	2	2	Tc Sm Su
Tc Rf Sm Su	1	1	Sm Su
Tc Am Su	2	2	Tc Am Su
Tc Km Su	2	2	Tc Su
Tc Sm Su	50	36	Tc Sm Su
		12	Tc Su
		1	Tc
Km Sm Su	3		—
Rf Sm Su	1		—
Tc Km	1	1	Tc
Tc Sm	1	1	Tc Sm
Tc Su	16	14	Tc Su
Sm Su	91	16	Sm Su
		1	Sm
		1	Su
Tc	3	3	Tc
Sm	5	2	Sm
Su	59	20	Su
Total	250 (78.4%)	128 (51.2%)	

Abbreviation: See Table 1

Table 3. Drug Resistance and R Plasmids in *Salmonella* Isolated from Various Pig Farms

Resistance to	Farms								Total
	A	B	C	D	E	F	G	H	
Su	39*	22	69	7	13	8	24	52	239
Sm	7	17	62	3	14	8	13	43	167
Tc	8	14	20		14		12	23	91
Km		1	13						14
Am	1	1	3		1		3	2	11
Cm		3	3					2	8
Gm			2						2
Rf	2								2
Na									0
Sensitive	5	25	5	7	3	1	13	10	69
Total no. of strains tested	47	48	78	14	21	9	38	64	319
No. of resistant strains	42 (89.4)	23 (48.0)	73 (93.6)	7 (50.0)	13 (85.7)	8 (88.9)	25 (65.8)	54 (84.3)	250 (78.4)
No. of R ⁺ strains	17 (40.5)	15 (65.2)	33 (45.2)	2 (28.6)	14 (77.8)	0 (0.0)	15 (60.0)	12 (59.3)	128 (51.2)

Abbreviation : See Table 1

A, B, D : The farm in Taegu.

E : The farm in Gyeongnam.

G : Several farms in Gyeongbuk & Taegu.

Figures in parentheses are percentages.

* : Number of strains.

C : The farm in Gyeongbuk.

F : The farm in Chungnam.

H : Slaughter house in Taegu.

found most frequently in the total 20 resistance patterns detected in this experiment. Most (73.2%) of *Salmonella* strains were multiple resistant, indicating the multiple resistant strains were more than single resistant strains. The most common resistant patterns of transferred R plasmids were TcSmSu (40 strains) and TcSu (28 strains).

The incidence of drug resistance and R plasmids in *Salmonella* isolated from various samples on 7 piggeries and a slaughter house were shown in Table 3. Among different pig farms, the incidence of drug resistance was higher in A (89.4%), C (93.6%), E (87.5%) and F (88.9%) farms than in B (48.0%) and D (50.0%) farms.

Only two *Salmonella* strains isolated from A and C farms were resistant to Rf and Gm, respectively. Of the 14 resistant strains to Km, 13 were isolated from C farm and *Salmonella* strains isolated from D and F farms were resistant to only Sm and Su.

The transfer frequencies of conjugative R plasmids were higher in E farm (77.8%), but all strains

isolated from F farm were not transmitted to recipient *E. coli* ML 1410.

Discussion

The extensive use of various antibiotics for preventive, therapeutic and nutritive purposes in domestic animals has increased the resistance of enterobacteriaceae to these drugs. Most of the drug resistance of enterobacteriaceae carried conjugative R plasmids and resistance might be transferred among bacterial genera or from strains colonizing animals to man (Makino *et al.*, 1981; Mitsuhashi *et al.*, 1967).

In recent years, an increased incidence of drug resistant strains of *Salmonella* has been reported in domestic animals in Japan and other parts of the world (Blackburn *et al.*, 1984; Ishiguro *et al.*, 1980). In Korea, Tak *et al.* (1979) reported that 18 (78.8%) of 23 *Salmonella* strains isolated from pigs slaughtered were resistant to one or more antibiotics, such as Am, Sm, Tc, Km and Cm. The present finding of a higher incidence (78.4%) of antibiotic resistance in

Salmonella strains is generally in agreement with the report of other works (Terakado *et al.*, 1980; Tak *et al.*, 1979; Sojka *et al.*, 1977).

In many part of the world, most of *Salmonella* strains isolated from swine were resistant to antibiotics such as Tc, Sm and Su (Blackburn *et al.*, 1984; Ishiguro *et al.*, 1980; Terakado *et al.*, 1980; Neu *et al.*, 1975) and the result is similar with ours. This may have been due to their use as feed additives for promotion of growth or may have been due to R plasmid carrying Sm and Tc resistance from the other enterobacterial strains.

In Japan, since the legislative control of the use of antibiotics in animal feed was established in 1976, decreasing tendency of drug resistance was observed in piggeries (Ishiguro *et al.*, 1980, 1979). This may indicated that the legislative control was effective on reduction of drug resistance. Therefore, it is necessary to the legislative control of the use of antibiotics as feed additives in Korea.

One interesting finding is the low rate of strains resistant to Cm in *Salmonella* isolated from domestic animals in Korea and is a contrast to the reports of other workers who noted the high rates of Cm resistant strains in recent years (Blackburn *et al.*, 1984; Ishiguro *et al.*, 1980; Sato *et al.*, 1977; Neu *et al.*, 1975). This may be due to the infrequency of therapeutic use of Cm in these piggeries, as compared with that in many part of the world.

In Korea, *Salmonella* strains isolated from domestic animals were not found resistant to Gm until now. However, two *Salmonella* strains were resistant to Gm in this experiments. The cause of the appearance of *Salmonella* strains resistant to Gm is not clear, but we suppose that it may be few studies on the drug resistance of *Salmonella* from domestic animals in Korea.

In the present study, 128 (51.2%) of the 250 resistant strains harbored conjugative R plasmids. These findings agree with the results of other investigators (Ishiguro *et al.*, 1980; Terakado *et al.*, 1980). The high incidence of these resistant *Salmonella* strains carried conjugative R plasmids, suggesting that R plasmids might play a major role in the emergence of drug resistant *Salmonella* strains. Fortunately, the

emergence of the strains was infrequent when compared with that of *E. coli* from the same one (Seol *et al.*, 1984; Makino *et al.*, 1981; Tak & Chung, 1976).

Resistance to Rf was not transferred to *E. coli* recipient by conjugation, suggesting that the resistance is not mediated by R plasmids but is probably of chromosomal origin.

The emergence of multiple drug resistant *Salmonella* strains has been widely recognized and become one of the most serious problems in human and veterinary medicine. Terakado *et al.* (1980) reported that high incidence of multiple drug resistance was observed in the *Salmonella* and most common resistant patterns were TcSmSu, Su and SmSu.

In the present study, 73.2% of 250 resistant strains showed a multiple resistance to antibiotics tested and SmSu, Su and TcSmSu were found most frequently in the total 20 resistance patterns. These findings suggest the excessive use of antibiotics in the treatment of animal diseases and large scale administration of feed additives in piggeries could be responsible for spread of multiple drug resistance among *Salmonella* strains from these animals. Furthermore, it may concern with that all swine feed with dairy products containing Tc alone excreted multiply resistant *E. coli* strains (Seol *et al.*, 1984; Datta *et al.*, 1971; Mitsuhashi *et al.*, 1967).

Isolation of conjugative R plasmid conferring five fold resistance pattern markers from *Salmonella* strains of animal origin have not been found in Korea. In the experiments, we indicated that R plasmids conferring five fold pattern resistance markers (TcAmCmSmSu and TcAmKmSmSu) were isolated from C pig farms. This finding may indicate the tendency of multiple drug resistance in Korea, as many part of the world (Makino *et al.*, 1981; Timoney, 1978; Grant *et al.*, 1976).

Terakado *et al.* (1980) reported that Tc-resistant strains of *Salmonella* transferred resistance (multiple or single) more frequently than did strains with resistance patterns that did not include resistance to Tc and the result is similar with ours.

Comparisons by region provided in Table 3 indicated a higher incidence of resistant strains in A (88.4%),

C(93.6%), E(85.7%) and F(88.9%) farms and a lower frequency in B(48.0%) and D(50.0%) farms. This may be a reflection of the difference in the frequency of the use of antibiotics among piggeries.

In the experiments, 2 and 14 resistant strains to Gm and Km, respectively, were isolated from C pig farms. This farm was contaminated heavily with *Salmonella*, as compared with that in other farms, so that it may reflect the greater use of Km and Gm for treatment of *Salmonella* infection. To prevent the spread of drug resistant *Salmonella*, more improved prevention and treatment of these infection are required. The transfer frequency of conjugative R plasmids was higher in E farm(77.8%) than in other farms, it seems that this difference is concerned with properties of R plasmids.

From these results, it is necessary to assay the incompatibility group and genetic properties of R plasmids derived from the present *Salmonella* strains on an epidemiological viewpoint.

Conclusions

This paper deals with the incidence of antibiotic resistance and of R plasmids in 319 *Salmonella* strains isolated from various samples on 7 piggeries in Taegu, Gyeongbuk, Gyeongnam and Chungnam and a slaughter house in Taegu during the period from May, 1984 to May, 1985.

The results were summarized as follows:

1. Of the 319 strains examined, 250(78.4%) were resistant to one or more antibiotics such as ampicillin(Am), chloramphenicol(Cm), gentamicin(Gm), kanamycin(Km), sulfadimethoxine(Su), streptomycin(Sm), rifampicin(Rf) and tetracycline(Tc), and higher resistant to Su(74.9%), Sm(53.0%) and Tc(28.5%). Only two *Salmonella* strains isolated from A and C farms were resistant to Rf and Gm, respectively.

2. Of the 250 resistant *Salmonella* strains, 128 (51.2%) harbored conjugative R plasmids and the transfer frequency of Am(100%), Tc(92.3%) and Cm(75.0%) resistance was higher than that of the other drug. The most common resistance patterns were SmSu, Su and TcSmSu. However, the most common pattern transferred was TcSmSu and TcSu.

3. Among various pig farms, the incidence of drug resistance was higher in A(89.4%), C(93.6%), E(85.7%) and F(88.9%) farms than in B(48.0%) and D(50.0%) farms. The transfer frequency of conjugative R plasmids was higher in E farm(77.8%), but all strains isolated from F farm was not transmitted.

4. R plasmids conferring five fold pattern resistance markers(TcAmCmSmSu and TcAmKmSmSu) were originated at C pig farm. This was initial report on the isolation of this patterns in Korea.

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