Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1971, **45**, 85-93

An Eleven-Year Study of Drug Resistance in *Salmonella* in the Netherlands*

A. MANTEN [1], P. A. M. GUINÉE [2], E. H. KAMPELMACHER [3] & C. E. VOOGD [4]

From 1959 to 1969 a total of 123 070 strains of salmonellae, representing nearly all the strains that have been isolated from animals and man, were collected in the Netherlands and tested for antibiotic resistance.

In the course of the study, only a few strains of S. typhi *and* S. paratyphi *B were found to be resistant to chloramphenicol, ampicillin, or tetracycline.*

From 1959 to 1966 there was a sharp increase in the prevalence of tetracycline resistance in both the human and the animal strains of S. typhimurium *and* S. panama *; subsequently, however, the prevalence declined. During 1966–70 approximately one-third of the tetracycline-resistant human and animal strains of* S. typhimurium *were also resistant to ampicillin. This type of multiple resistance was only occasionally encountered in the other serotypes. In contrast to resistance to tetracycline and ampicillin, the incidence of* S. typhimurium *resistant to chloramphenicol remained low during the whole period of observation. In all other serotypes drug resistance remained at a low level.*

It is shown in this study that the greatly increased use of broad-spectrum antibiotics for medical and veterinary purposes and for animal feeding over the last decade in the Netherlands has not led to the development of serious drug resistance from the medical point of view. An important factor involved in the low incidence of resistance to chloramphenicol may be that R-factors in salmonellae usually lose this resistance determinant rapidly.

In the Netherlands the annual mortality figures for all forms of salmonellosis decreased from 0.84 (per 100 000 inhabitants) in 1961 to 0.25 in 1969.

Over the last two decades in most of the economically developed countries, tens to hundreds of tons of antibiotics have been used annually for medical and veterinary purposes, and in foodstuffs and food preservatives. One of the hazards involved in this practice is that it may lead to the development of resistance in medically important bacteria. The discovery of extrachromosomal elements carrying drug resistance in bacteria has added a new dimension to the whole problem.

In the Netherlands, the potential hazards for public health of antibiotic-resistant salmonellae have been recognized since 1955, and in 1958 a programme was started to screen all the strains of *Salmonella* isolated in that country for resistance to tetracycline and chloramphenicol. After 1966, resistance to ampicillin was also tested. It was relatively easy to establish the programme on a nation-wide basis, since it has always been the practice to send all *Salmonella* strains isolated to the National Institute of Public Health, Utrecht, for typing.

The majority of the strains received by the National Salmonella Centre of our Institute are from human patients or from animals such as cattle, pigs, and poultry. A fairly large proportion (20–30%) are, however, from other sources, such as laboratory and wild animals, slaughterhouses, meat-, bone-, and fish-meal, egg products, and sewage. The latter strains will not be dealt with in this paper. A more or less complete account of all the strains examined

* From the National Institute of Public Health, Utrecht, The Netherlands.

[1] Head, Laboratory of Chemotherapy.

[2] Head, National Salmonella Centre.

[3] Head, Laboratory for Zoonoses.

[4] Research Officer, Laboratory of Chemotherapy.

between 1959 and 1968 is to be found in a series of publications by Manten et al. (1961a, 1961b, 1962, 1964, 1966) and by Voogd et al. (1968, 1970).

DEFINITION OF DRUG RESISTANCE AND METHOD OF ESTABLISHING RESISTANCE PATTERNS

In vitro the genus *Salmonella* is usually fairly uniformly susceptible to tetracycline, chloramphenicol, and ampicillin. In our laboratory, the vast majority of species and strains of drug-sensitive bacteria, when cultivated on antibiotic-supplemented slants of 5% sheep blood agar (pH 7.2–7.4), had minimum inhibitory concentration (MIC) values varying from 2 to 5 μg of tetracycline per ml, 5 to 10 μg of chloramphenicol per ml, and 2 to 5 μg of ampicillin per ml.

To detect resistant strains each strain was transferred to agar slants containing 25 μg of tetracycline per ml, 50 μg chloramphenicol per ml, or 25 μg of ampicillin per ml, amounts roughly corresponding to 10 times the normal MICs for *Salmonella*. In order to exclude any possibility of contamination with resistant bacteria of other species, the bacteria grown on one or more of the slants were identified again. If the same *Salmonella* serotype was found, the degree of resistance was determined by tube-dilution assays on 5% sheep blood agar slants using dilute suspensions of the organism in saline as inoculum. If the MIC at retesting appeared to be at least 10 times the normal value the strain was regarded as resistant.

RESULTS

During the period of observation (1959–69) altogether 123 070 strains of *Salmonella* were tested. They may be grouped into those of human origin (76 337 strains, or 62.0%), those obtained from slaughtered animals and poultry (28 936 strains, or 23.5%), and those from various other sources (17 797 strains, or 14.5%). The latter group will not be dealt with in any detail, since their relation to human health is generally more remote than that of the human and animal strains.

Among the human strains, *S. typhimurium* has been the prevailing serotype over the whole period of observation. The second most frequently encountered type was *S. panama*. These two serotypes have consequently been studied in great detail, as have *S. typhi* and *S. paratyphi* B, since the latter are the most dangerous serotypes in human salmonellosis.

The animal strains were isolated from cattle, pigs, and poultry. In the strains obtained from cattle, *S. dublin* was always the most prevalent type. In these animals *S. typhimurium* was also frequently found. The latter organism was predominant in pigs and poultry.

Salmonella typhi and *Salmonella paratyphi* B

Over the whole period of observation only a few strains of *S. typhi* and *S. paratyphi* B were found to be resistant to any of the three antibiotics examined.

It is shown in Table 1 that of the 610 strains of *S. typhi* examined only 3 (0.5%) were found to be resistant to chloramphenicol, the main drug used in the treatment of typhoid fever. Two of these strains were also resistant to tetracycline. Ampicillin resistance was encountered in only 1 strain, and resistance to tetracycline in 10 strains. Among the 1 295 isolates of *S. paratyphi* B, 18 (1.4%) were resistant to chloramphenicol. Most of them (15) were also resistant to tetracycline. The chloramphenicol-resistant strains were found mainly in 1959, a year in which the incidence of human infections was also relatively high. In the 10 years after 1959, only 4 chloramphenicol-resistant strains were found. The number of tetracycline- and ampicillin-resistant strains was also low between 1959 and 1969.

Table 1. *S. typhi* and *S. paratyphi* B: resistance to tetracycline (T), chloramphenicol (C), and ampicillin (A) during 1959–69

Organism	No. of strains examined	No. of strains resistant to:						
		T	C	A	T+C	T+A	C+A	T+C+A
S. typhi	610	7	1	0	2	1	0	0
S. paratyphi B	1 295	15	3	1	15	3	0	0

Salmonella typhimurium

The patterns of drug resistance among strains of *S. typhimurium* varied in type. The strains that occurred most frequently were those resistant to tetracycline alone or to tetracycline and ampicillin. This was true of both the human and the animal strains. In contrast, chloramphenicol-resistant strains were found in only relatively small numbers. Because of an outbreak of salmonellosis in calves in 1968,

Table 2. *Salmonella typhimurium*: resistance to tetracycline (T), cloramphenicol (C), and ampicillin (A) among human and animal strains

Year	Human strains								Animal strains							
	No. of strains examined	Percentage of strains resistant to:							No. of strains examined	Percentage of strains resistant to:						
		T	C	A	T+C	T+A	C+A	T+C+A		T	C	A	T+C	T+A	C+A	T+C+A
1959	5 417	2.2	0.6	—	0.4	—	—	—	135	5.8	6.7	—	4.4	—	—	—
1960	3 253	1.3	0.4	—	0.2	—	—	—	365	4.4	0.6	—	0.6	—	—	—
1961	5 027	6.7	0.9	—	0.2	—	—	—	501	9.2	0.1	—	0.0	—	—	—
1962	4 359	24.4	0.9	—	0.5	—	—	—	541	19.0	2.0	—	0.4	—	—	—
1963	3 513	33.0	1.6	—	1.0	—	—	—	840	29.5	0.7	—	0.5	—	—	—
1964	2 830	30.5	0.6	—	0.2	—	—	—	1 037	20.0	0.6	—	0.4	—	—	—
1965	2 441	38.4	0.7	—	0.6	—	—	—	1 035	35.7	0.5	—	0.5	—	—	—
1966	3 346	40.4	1.1	22.7	0.1	18.4	0.1	0.7	1 276	32.2	0.6	9.8	0.1	9.1	0.0	0.5
1967	3 880	21.7	0.7	11.1	0.3	7.3	0.1	0.2	943	22.0	0.7	10.8	0.3	5.6	0.1	0.1
1968	3 155	17.1	0.9	4.6	0.1	2.5	0.2	0.2	1 030	18.0	6.8	3.3	6.5	1.8	0.0	0.1
1969	4 469	32.5	0.4	9.7	0.1	6.6	0.1	0.1	764	37.1	1.9	11.1	1.6	6.7	0.4	0.2

caused by a strain resistant to both chloramphenicol and tetracycline, the figure for that year is exceptional. Strains resistant to tetracycline, chloramphenicol, and ampicillin were also found, but usually only in small numbers (Table 2).

From 1959 to 1963 there was a continuous increase in the number of tetracycline-resistant strains of *S. typhimurium* among those of both human and animal origin (see Fig. 1). In 1966, 40.4% and 32.2% of human and animal strains, respectively, of *S. typhmurium* were tetracycline-resistant. After this the proportions of tetracycline-resistant strains showed large fluctuations.

Fig. 1 also shows that changes in the proportions of human and animal strains of *S. typhimurium* resistant to tetracycline follow a parallel course. This similarity probably demonstrates the close epidemiological relationship of animal and human strains of the serotype in question.

In contrast to the findings with tetracycline, the incidence of chloramphenicol resistance remained very low in the human strains over the whole period of the survey. In 1963, it reached a peak of 1.62% and in 1969 it was no more than 0.42%. The frequency of ampicillin resistance, however, was at first rather high (22.7% in 1966), but it subsequently decreased (Fig. 2.)

More or less the same trends occurred in the strains of *S. typhimurium* isolated from animals. It is interesting that resistance to ampicillin in the animal strains varied in a similar way to tetracycline resistance, although ampicillin had not been used in animal medicines or in animal foodstuffs in the Netherlands at that time.

Salmonella panama

The total number of strains of *S. panama*, as well as the number of tetracycline-resistant strains, increased considerably between 1963 and 1965. In 1964 and 1965, the incidence of this type of resistance among the human strains reached levels of 42.6% and 43.0%, respectively (Table 3). Maximum tetracycline resistance appeared later than the peak in the number of strains isolated from human patients.

The incidence of ampicillin resistance in *S. panama* has always been low, in contrast to the position with *S. typhimurium* between 1966 and 1969. The incidence of chloramphenicol-resistance also remained low.

Other serotypes

A third serotype found among the human strains was *S. stanley*. Especially in the period from 1961 to

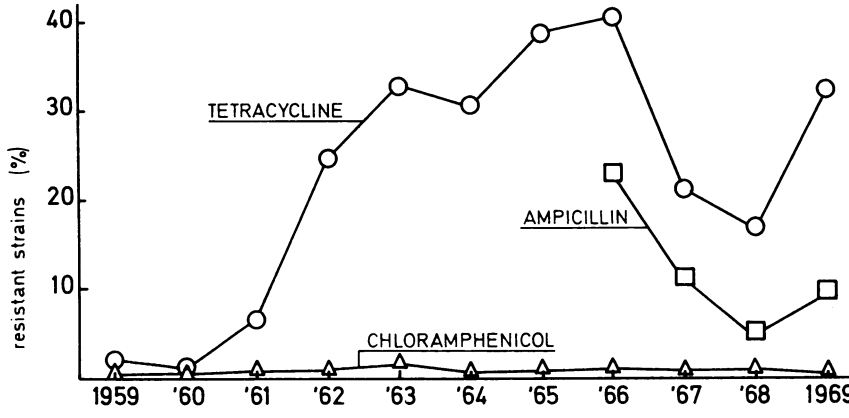

Fig. 1. Increase in proportion of tetracycline-resistant strains of *Salmonella typhimurium* between 1959 and 1969.

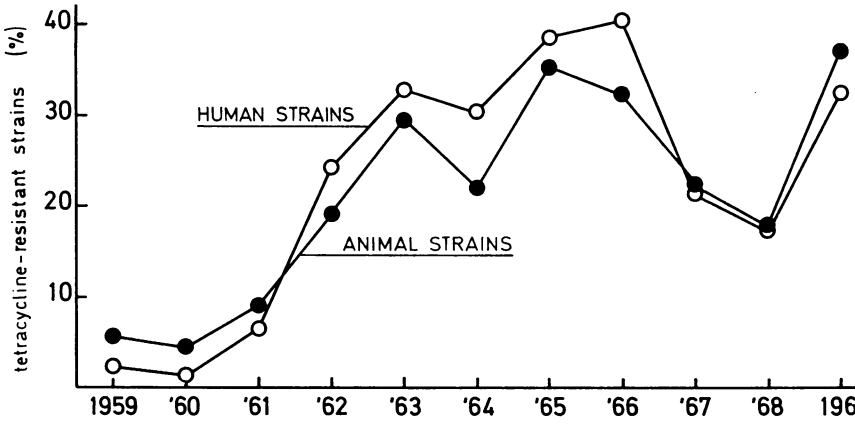

Fig. 2. Resistance to tetracycline, ampicillin, and chloramphenicol among human strains of *Salmonella typhimurium* between 1959 and 1969.

1964, it caused many disease outbreaks in the Netherlands. This organism occurred only sporadically in animals.

Of the 76 337 human strains typed in the National Salmonella Centre during 1959–69, 7 685 (1%) were *S. stanley*. Only 218 of them (2.9%) were found to be resistant to any of the drugs used in this investigation.

In the Netherlands, and also in other countries, *S. dublin* is the main cause of salmonellosis in cattle. This serotype also occasionally causes infection in other animals and in man. Only 268, or 2.6%, of the total number of 10 342 strains found, were resistant to the antibiotics tested.

It is clear from the above figures that *S. stanley* and *S. dublin* did not readily become resistant. In this respect they appear to differ from *S. typhimurium* and *S. panama*.

Table 4 shows that the many other serotypes obtained from man and animals also showed only a low tendency to become resistant to antibiotics. They fall in the same group as *S. stanley* and *S. dublin*.

Table 3. *Salmonella panama*: resistance to tetracycline (T), chloramphenicol (C), and ampicillin (A) among human and animal strains

Year	Human strains								Animal strains							
	No. of strains examined	Percentage of strains resistant to:							No. of strains examined	Percentage of strains resistant to:						
		T	C	A	T+C	T+A	C+A	T+C+A		T	C	A	T+C	T+A	C+A	T+C+A
1959	10	—	0.0	—	0.0	—	—	—	3	0.0	0.0	—	0.0	—	—	—
1960	42	0.0	0.0	—	0.0	—	—	—	0	0.0	0.0	—	0.0	—	—	—
1961	771	0.7	0.5	—	0.0	—	—	—	12	0.0	0.0	—	0.0	—	—	—
1962	592	2.7	1.8	—	0.2	—	—	—	36	5.6	0.0	—	0.0	—	—	—
1963	1 365	22.1	2.5	—	0.9	—	—	—	72	27.8	0.0	—	0.0	—	—	—
1964	1 374	42.6	2.2	—	1.6	—	—	—	156	44.9	1.3	—	1.3	—	—	—
1965	725	43.0	0.5	—	0.5	—	—	—	130	46.9	0.0	—	0.0	—	—	—
1966	685	25.4	3.2	2.0	1.4	0.7	0.3	0.3	73	19.2	0.0	0.0	0.0	0.0	0.0	0.0
1967	536	23.7	0.7	1.7	0.0	0.7	0.0	0.2	71	19.7	0.0	4.2	0.0	1.4	0.0	0.0
1968	585	24.1	0.7	1.7	0.0	0.2	0.0	0.5	78	28.2	0.0	0.0	0.0	0.0	1.3	0.0
1969	861	43.8	2.0	3.8	0.4	0.2	0.9	0.2	33	9.1	0.0	0.0	0.0	0.0	0.0	0.0

Table 4. Other *Salmonella* serotypes: resistance to tetracycline (T), chloramphenicol (C), and ampicillin (A) among human and animal strains

Year	Human strains								Animal strains							
	No. of strains examined	Percentage of strains resistant to:							No. of strains examined	Percentage of strains resistant to:						
		T	C	A	T+C	T+A	C+A	T+C+A		T	C	A	T+C	T+A	C+A	T+C+A
1959	3 513	1.2	0.8	—	0.3	—	—	—	1 463	1.1	0.2	—	0.1	—	—	—
1960	2 342	1.5	0.6	—	0.4	—	—	—	1 669	0.7	0.0	—	0.1	—	—	—
1961	3 522	2.3	0.4	—	0.1	—	—	—	1 125	1.3	0.0	—	0.0	—	—	—
1962	3 056	2.4	0.5	—	0.3	—	—	—	1 200	1.4	0.0	—	0.0	—	—	—
1963	2 919	1.8	0.5	—	0.2	—	—	—	1 092	1.8	0.0	—	0.0	—	—	—
1964	2 384	3.2	0.4	—	0.3	—	—	—	1 847	6.1	0.3	—	0.1	—	—	—
1965	1 197	3.3	0.4	—	0.3	—	—	—	2 103	2.9	0.1	—	0.0	—	—	—
1966	1 830	2.9	0.4	1.7	0.1	1.1	0.0	0.1	1 999	1.8	0.1	0.9	0.1	0.8	0.0	0.0
1967	1 506	3.7	0.3	1.4	0.0	0.5	0.1	0.1	2 397	4.5	0.1	0.9	0.0	0.2	0.0	0.0
1968	1 231	3.7	0.3	1.0	0.1	0.2	0.2	0.0	1 549	4.5	0.1	1.5	0.1	0.1	0.3	0.1
1969	1 778	4.0	0.6	2.4	0.1	0.4	0.1	0.2	2 311	3.4	0.0	0.6	0.1	0.2	0.1	0.0

Of the total of 25 278 strains of human origin collected in the period from 1959 to 1969, 625 (2.5%) were resistant to tetracycline and 129 (0.51%) were resistant to chloramphenicol; 109 (1.7%) of 6 345 strains were resistant to ampicillin. Of 18 755 animal strains the corresponding figures were 547 (2.9%) for tetracycline and 24 (0.13%) for chloramphenicol; 80 (0.97%) of 8 256 strains were resistant to ampicillin.

DISCUSSION

Salmonellosis in man is usually a self-limiting disease that is confined to the intestines, though infants and elderly people may succumb during the acute phase of the infection. *S. typhimurium* is the prevailing species incriminated in this type of enteritis, but a great many other serotypes may be involved as well. For example, in the Netherlands *S. panama* and *S. stanley* have been responsible for many disease outbreaks in the human population during the past decade.

Among the salmonellae, *S. typhi* and *S. paratyphi* B stand out because of their high pathogenicity and host-specificity to man. In typhoid and paratyphoid fever the disease agents enter the intestines, and then penetrate their walls, leading to generalized systemic infections. Occasionally, other *Salmonella* types may also enter the blood and tissues and cause serious disease, but in healthy adults this occurs but rarely.

In all cases of generalized systemic salmonellosis in man, chloramphenicol is the therapeutic agent of first choice (Woodward et al., 1952; Geddes, 1964; Sleet et al., 1964; Dawking & Hornick, 1967). Its high activity in typhoid fever and similar diseases is probably due to its excellent penetration into tissues and cells harbouring the bacteria (Showacre et al., 1961). A second important antibiotic is ampicillin, which up to now has been the only agent suitable for the treatment of human carriers of *Salmonella* (Christie, 1964; Whitby, 1964; Münnich et al., 1964; Simon & Miller, 1966). The tetracyclines, notwithstanding their high *in vitro* activity on salmonellae, are practically devoid of any therapeutic action in typhoid fever as well as in salmonelloses of all other kinds. The same applies to streptomycin, gentamicin, paromomycin, the polymyxins, nalidixic acid,[1] and the sulfonamides (Woodward et al., 1952; Dawkins & Hornick, 1967). Treatment of human salmonellosis of the self-limiting type with antibiotics, as has recently been done in an epidemic caused by *S. typhimurium*, may lead to prolongation of the carrier state and thus increase the opportunity of spread of infection and of resistant bacteria (Aserkoff & Bennett, 1969). Consequently, the treatment of *Salmonella* enteritis with antibiotics, including chloramphenicol and ampicillin, in previously healthy subjects appears, in general, not to be justified.

Seen in this light, the sharp increase of tetracycline resistance in *S. typhimurium* and *S. panama* observed from 1960 to 1966 in the Netherlands, as well as similar findings in other countries (Ramsey & Edwards, 1961; McWorther et al., 1963; Yurack, 1964; Anderson & Datta. 1965; Chabbert & Baudens, 1966; Lebek, 1967; Hofmann et al., 1967; Schroeder et al., 1968), would not appear to be of much significance for public health. It is obvious, however, that the situation with respect to ampicillin resistance and especially chloramphenicol resistance must be further analysed.

The incidence of ampicillin resistance in the human strains of *S. typhimurium* (the only serotype in which resistance to this antibiotic appeared frequently) dropped from 22.7% in 1966 to 4.6% in 1968 and then rose to 9.7% in 1969. It is improbable that these fairly large variations were due to differences in the annual therapeutic use of ampicillin in the Netherlands.

As shown in Fig. 2, the changes in resistance to tetracycline and to ampicillin from year to year run more or less parallel, since a fairly constant proportion of the tetracycline-resistant strains was also resistant to ampicillin. The same was true for the animal strains of *S. typhimurium* (Table 2). The use of tetracyclines in human and veterinary medicine has probably led to the emergence of R-factors carrying determinants for resistance to both tetracycline and ampicillin, and the use of tetracyclines in animal husbandry may have contributed to such an effect.

It is certain that the relatively high incidence of ampicillin resistance in the human strains of *S. typhimurium* observed in some years cannot be associated with the use of ampicillin in veterinary medicine or as a supplement in animal foodstuffs, since up to 1970 in the Netherlands it had not been used in these fields. The tetracyclines, on the other hand, have found wide application both in veterinary medicine and, in amounts usually not exceeding 10 ppm, in

[1] 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid.

animal foodstuffs. It has been found in animals that oral administration of the tetracyclines, even in small quantities, may lead to a multiplication of R-factors in *Escherichia coli* (Smith & Halls, 1966; Walton, 1966; Bulling et al., 1968). Furthermore, R-factors with determinants for more than one drug may become prominent in this way and, under certain conditions, be transferred *en bloc* to other Enterobacteriaceae, including *S. typhimurium*. It may be presumed, therefore, that the use of tetracycline in animal foodstuffs has also contributed to the incidence of ampicillin resistance in the latter organism, though the part it has played is probably small.

It has been said already that chloramphenicol is the only reliable drug for the treatment of typhoid and paratyphoid fevers. Resistance of the causative agents of these diseases to chloramphenicol would create a major problem in treatment. As shown in Table 1, chloramphenicol resistance was found only rarely in *S. typhi* and in *S. paratyphi* B between 1960 and 1969. In the former pathogen, it occurred in only 3 strains of a total of 610. In 1959, during disease outbreaks due to *S. paratyphi* B, 14 (3.5%) of 401 strains were resistant to chloramphenicol. In the following 10 years, only 4 chloramphenicol-resistant strains (out of a total of 894) were found. Drug resistance in typhoid and paratyphoid fever has thus not really been a problem in the Netherlands so far.

Also in the majority of strains of *S. typhimurium* and the other serotypes isolated, the incidence of resistance to chloramphenicol was low and remained so throughout the period of observation. In 1963, among the human strains of *S. typhimurium*, the incidence of chloramphenicol resistance was at its highest level of 1.62%, whereas in 1969 it was no more than 0.42%. The figures for other salmonellae were similar.

Chloramphenicol is not used as a supplement in animal foodstuffs. However, the drug is fairly extensively used in veterinary practice. The question therefore arises as to why the incidence of resistance to chloramphenicol among animal and human strains of salmonellae remained at such a low level, at least in the Netherlands, whereas the figures for tetracycline resistance increased so considerably in both groups of strains. At least two factors were involved. From 1959 to 1969 the use of the tetracyclines in both human and veterinary medicine increased in the Netherlands, and following a partial raising of the governmental regulations on the addition of antibiotics to animal foodstuffs in 1959, the use of oxytetracycline and chlortetracycline also increased. Although the exact figures for the annual national consumption of chloramphenicol and the tetracyclines are not known to us, there is no doubt that the former antibiotic has always been used on a much smaller scale than the tetracyclines.

A more important factor involved in the low incidence of chloramphenicol resistance is the spontaneous loss of this type of resistance which frequently occurs in *Salmonella*. In contrast, tetracycline resistance is retained much longer. The phenomenon underlying the disappearance of resistance in Enterobacteriaceae is the segregation of resistance determinants in R-factors. In species of *Salmonella* the rate of this segregation has been found to be usually high (and especially so in chloramphenicol resistance) as compared with that in *E. coli*, for instance (Lebek, 1963; Watanabe et al., 1964).

If the use of antibiotics for non-medical purposes were to lead to a significant increase in the rate of mortality from human salmonellosis, this would be a strong argument against such use. Table 5 shows the annual rates of mortality from all forms of salmonellosis, including typhoid and paratyphoid

Table 5. Annual mortality from salmonellosis (all forms) in the Netherlands, 1959–69 *

Year	Mortality per 100 000 inhabitants
1959	0.63
1960	0.41
1961	0.84
1962	0.60
1963	0.39
1964	0.32
1965	0.28
1966	0.35
1967	0.30
1968	0.32
1969	0.25

* Data kindly supplied by Dr H. Bijkerk, Inspector of Communicable Diseases, the Netherlands.

fever, during the period 1959–69. In the Netherlands, the annual mortality rate decreased from 0.84 (per 100 000 inhabitants) in 1961 to 0.25 in 1969.

It appears from the above analysis that the veterinary and non-medical use of antibiotics in the Netherlands, has not so far led to any significant emergence of drug resistance in *Salmonella* (including *S. typhi* and *S. paratyphi* B).

RÉSUMÉ

ÉTUDE, POURSUIVIE PENDANT 11 ANNÉES, DE LA PHARMACORÉSISTANCE DE *SALMONELLA*, AUX PAYS-BAS

De 1959 à 1969, on a recherché la résistance aux antibiotiques de 123 070 souches de *Salmonella*, soit la quasi-totalité des souches isolées chez l'homme et chez l'animal aux Pays-Bas.

Durant cette période, seules quelques rares souches (respectivement 0,5 et 1,4%) de *S. typhi* et de *S. paratyphi* B ont fait preuve d'une résistance au chloramphénicol. Le nombre de ces sérotypes résistants à l'ampicilline et à la tétracycline était également très faible.

De 1959 à 1966, la proportion des souches, d'origine humaine ou animale, de *S. typhimurium* (le sérotype le plus fréquemment rencontré aux Pays-Bas) et de *S. panama* résistantes à la tétracycline s'est fortement accrue. En ce qui regarde les souches humaines de *S. typhimurium*, elle est passée de 2,2% en 1959 à 40,4% en 1966. Elle s'est cependant abaissée par la suite. Pendant les quatre dernières années de l'étude, un tiers environ des souches de *S. typhimurium*, humaines et animales, résistantes à la tétracycline l'étaient également à l'ampicilline. Ce type de résistance multiple n'a été trouvé qu'occasionnellement chez les autres sérotypes. Contrastant avec la résistance à la tétracycline et à l'ampicilline, la résistance de *S. typhimurium* au chloramphénicol ne s'est manifestée que chez un petit nombre de souches: 1,62% des souches humaines en 1963, 0,42% en 1969. Chez tous les autres sérotypes, la pharmacorésistance est restée peu fréquente.

Le chloramphénicol est le médicament le plus utilisé pour traiter les salmonelloses. Il ressort de la présente étude que l'usage croissant des antibiotiques à large spectre en médecine humaine et vétérinaire, en élevage et en agriculture aux Pays-Bas pendant la dernière décennie n'a pas entraîné l'apparition d'une pharmacorésistance gênante du point de vue thérapeutique.

Aux Pays-Bas, le taux annuel de la morbidité par salmonellose (toutes formes) a décru de 0,84 pour 100 000 en 1961 à 0,25 pour 100 000 en 1969.

REFERENCES

Anderson, E. S. & Datta, N. (1965), *Lancet*, **1**, 407

Aserkoff, B. & Bennett, J. V. (1969) *N. Engl. J. Med.*, **281**, 636

Bulling, E., Scholz, M. & Malla, D. S. (1968) *Berl. Münch. tierärztl. Wschr.*, **81**, 151

Chabbert, Y. A. & Baudens, J. G. (1966) In: Hobby, G. L., ed., *Antimicrobial agents and chemotherapy–1965*, Ann Arbor, Michigan, American Society for Microbiology

Christie, A. B. (1964) In: Brumfitt, W. & Williams, J. D., ed., *International Conference on Therapy with the New Penicillins*, London, Fellowship of Postgraduate Medicine

Dawkins, A. T. & Hornick, R. B. (1967) In: Hobby, G. L., ed., *Antimicrobial agents and chemotherapy—1966*, Ann Arbor, Michigan, American Society for Microbiology

Geddes, A. M. & McMurdoch, J. (1964) In: Brumfitt, W. & Williams, J. D., ed., *International Conference on Therapy with the New Penicillins*, London, Fellowship of Postgraduate Medicine

Hofmann, S., Knothe, J. & Wiedemann, B. (1967) *Zbl. Bakt., I. Abt. Orig.*, **245**, 449

Lebek, G. (1963) *Zbl. Bakt. I. Abt., Orig.*, **188**, 494

Lebek, G. (1967) *Path. et Microbiol. (Basel)*, **30**, 1015

Manten, A., Guinée, P. A. M. & Kampelmacher, E. H. (1966) *Zbl. Bakt., I. Abt. Orig.*, **200**, 13

Manten, A., Kampelmacher, E. H. & Guinée, P. A. M. (1961a) *Antonie v. Leeuwenhoek*, **27**, 103

Manten, A., Kampelmacher, E. H. & Guinée, P. A. M. (1961b) *Antonie v. Leeuwenhoek*, **27**, 461

Manten, A., Kampelmacher, E. H. & Guinée, P. A. M. (1962) *Antonie v. Leeuwenhoek*, **28**, 428

Manten, A., Kampelmacher, E. H. & Guinée, P. A. M. (1964) *Antonie v. Leeuwenhoek*, **30**, 10

McWorther, A. C., Murrell, M. C. & Edwards, P. R. (1963) *Appl. Microbiol.*, **11**, 368

Münnich, D., Uri, J. & Valu, G. (1964) *Chemotherapia*, **8**, 226

Ramsey, C. H. & Edwards, P. R. (1961) *Appl. Microbiol.*, **9**, 389

Schroeder, S. A., Terry, P. M. & Bennett, J. V. (1968) *J. Amer. med. Ass.*, **205**, 903

Showacre, J. L., Hopps, H. E., du Buy, H. G., Smadel, J. E., Bernheim, B. C., Danauskas, J. X. & Jackson, E. B. (1961) *J. Immunol.*, **87**, 153

Simon, H. J. & Miller, R. C. (1966) *N. Engl. J. Med.*, **274**, 807

Sleet, R. A., Sangster, G. & McMurdoch, J. (1964) *Brit. med. J.*, **1**, 148

Smith, H. W. & Halls, A. (1966) *Brit. med. J.*, **1**, 266

Voogd, C. E., Guinée, P. A. M., Manten, A. & Kampelmacher, E. H. (1968) *Antonie v. Leeuwenhoek*, **34**, 357

Voogd, C. E., Guinée, P. A. M., Manten, A. & Valkenburg, J. J. (1970) *Antonie v. Leeuwenhoek*, **36**, 297

Walton, J. R. (1966) *Lancet*, **2**, 1300

Watanabe, T., Ogata, C. & Sato, S. (1964) *J. Bact.*, **88**, 922

Whitby, J. M. F. (1964) *Lancet*, **2**, 71

Woodward, T. E., Smadel, J. E., Parker, R. T. & Wisseman, C. L., Jr (1952) *Ann. N.Y. Acad. Sci.*, **55**, 1043

Yurack, J. A. (1964) *Canad. J. Microbiol.*, **10**, 521