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Characterization of resistance plasmids and carried phages in an epidemic clone of multi-resistant *Salmonella typhimurium* in India

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SUMMARY

Hospital outbreaks of severe gastroenteritis caused by multi-resistant *Salmonella typhimurium* have occurred in a number of cities throughout India since 1977. The strains involved belong to phage types 66 or 122, or are untypable; the latter are derived from types 66 or 122 by acquisition of one or more of a number of temperate bacteriophages. Types 66 and 122 are closely related and react with the same phages of the *S. typhimurium* typing scheme.

A plasmid belonging to compatibility group $F_I me$ encoding resistance to ampicillin, chloramphenicol, kanamycin, streptomycin, sulphonamides, spectinomycin, tetracyclines, gentamicin and trimethoprim (R-type ACKSSuSpTGTm) is present in all of the multi-resistant strains. Several other plasmids have been identified including an SSu resistance determinant, a group I_2 transfer factor and an R factor coding for resistance to kanamycin, streptomycin and sulphonamides which is compatible with plasmids of all the standard compatibility groups. These plasmids are only present in a proportion of the strains examined.

Examination of strains from other sources has identified a paediatric hospital outbreak in Saudi Arabia and a number of sporadic infections in Great Britain which have been caused by the same organisms. These studies show that, despite differences in phage type and plasmid content, this group of strains belongs to a single clone which has become widespread in India with some extension to other countries.

INTRODUCTION

In recent years multiply antibiotic-resistant salmonellae have caused severe outbreaks of enteritis in paediatric units in many countries of the developing world. The serotypes responsible include *Salmonella typhimurium* phage type 193 and *S. saintpaul* in South America (WHO, 1974), *S. typhimurium* phage type 208 in the Middle East (Anderson *et al.* 1977*a*) and *S. wien* in North Africa (McConnell *et al.* 1979).

Since 1971 a number of hospitals in widely separated parts of India have reported salmonella outbreaks with unusual clinico-epidemiological features. Several serotypes have been implicated; *S. anatum* and *S. newport* in New Delhi,

S. alachua in Calcutta and *S. weltevreden* in Southern India (Ahuja *et al.* 1979). Also a marked increase in the incidence of multiple drug resistance has been observed in *S. anatum*, *S. bareilly* and *S. typhimurium* (Agarwal *et al.* 1980). In these outbreaks nosocomial spread of infection was important and in one hospital necessitated closing the paediatric unit. In all the outbreaks most of the patients were neonates, although older children and some adults were also affected. The most common clinical presentation was enteritis, with the exception of the *S. newport* outbreak where septicaemia was particularly prevalent. In two *S. typhimurium* outbreaks mortality was high, suggesting that these strains might have enhanced virulence.

Between 1977 and 1980 the Division of Enteric Pathogens studied multi-resistant *S. typhimurium* from outbreaks in seven hospitals in India; from Ludhiana and New Delhi in the north, Bombay and Poona in the west and Trivandrum and Bangalore in the south (Diarrhoeal Diseases Control Programme, 1979; Rowe *et al.* 1980). The epidemic clone involved belonged to phage types 66 or 122 or a related group of untypable strains. This paper describes the genetic characterization of these strains with reference to the antibiotic resistance plasmids and temperate phages present.

In addition, the culture collection of the Division of Enteric Pathogens was searched for multi-resistant *S. typhimurium* which might be related to the Indian clone. This selection process identified two sources of such strains; an outbreak of salmonellosis in a paediatric unit in Saudi Arabia, and sporadic infections in Great Britain in patients recently returned from Asia or East Africa.

MATERIALS AND METHODS

Bacterial strains and plasmids

One hundred and ninety-one *S. typhimurium* strains from India were phage typed and tested for antimicrobial resistance in the Division of Enteric Pathogens.

S. typhimurium from other areas were selected from approximately 8000 or more strains examined in this laboratory each year on the basis of their antimicrobial resistance pattern (= R-type) and phage type. Strains resistant to ampicillin, chloramphenicol, kanamycin, streptomycin, sulphonamides, spectinomycin, tetracyclines, gentamicin and trimethoprim (R-type ACKSSuSpTGTm) and belonging to phage types 66, 122 or untypable were included in this study. These comprised strains from an outbreak of gastroenteritis in a paediatric unit in Saudi Arabia and sporadic infections isolated in Great Britain, mainly from patients infected abroad.

Resistances were transferred into *Escherichia coli* K12 *lac*$^+$*nal*^{r} (DEP Ref. 14R525) and thence to *S. typhimurium* phage type 36 (DEP Ref. 42R500). Where no direct transfer was detected, two standard transfer factors, Δ of compatibility group I_1 and X of group F_{II}, were used to test for mobilization (Anderson & Threlfall, 1974).

Representative plasmids of known compatibility groups were transferred to

E. coli K12 *lac*$^{-}$*str*^{r} (DEP Ref. 1R716). These included representatives of the compatibility groups: B, C, D, F_I, F_{II}, F_{IV}, H, I_1, I_2, J, K, M, N, P, W, X (Jacob *et al.* 1977); MP10 and F_I*me* (Anderson *et al.* 1977*a*). Additionally, two plasmids, TP201 and TP202, which are compatible with plasmids of all the groups listed above, were included. These were identified in strains of *Shigella sonnei* isolated in Venezuela in 1973 (Vargas *et al.*, in preparation).

Phage typing

S. typhimurium strains were phage-typed by the method of Callow (1959). Those strains which did not react with the typing phages of the definitive typing scheme (Anderson *et al.* 1977*b*) were tested with an ancillary set of phages which is being developed in this laboratory in order to subdivide untypable strains.

Detection of lysogenic bacteriophages

Temperate phages were isolated as described by Callow (1959). Single plaque lines were then spotted on strains of *S. typhimurium* phage type 36 which is sensitive to all the phages of the typing scheme, and on Indian strains of phage types 66, 122 and representative untypable strains from related outbreaks.

Resistance testing and plasmid characterization

All strains were tested by a strip diffusion method for resistance to ampicillin (A), chloramphenicol (C), kanamycin (K), streptomycin (S), tetracycline (T) and gentamicin (G); resistance to sulphonamides (Su), spectinomycin (Sp), trimethoprim (Tm), furazolidone (Fu) and nalidixic acid (Nx) was tested in plate spot tests (Anderson & Threlfall, 1974). Plasmids were assigned to compatibility groups using the methods of Grindley *et al.* (1972) and Anderson & Threlfall (1974). Plasmids belonging to group F_I*me* were identified by the criteria described by Anderson *et al.* (1977*a*).

Labelling of transfer factors by transposition

A number of strains carried transfer factors which did not have any antibiotic resistance markers. In order to determine the compatibility group of such plasmids they were 'marked' with ampicillin resistance by transposition. The transfer factors were transferred from the wild strain to an *E. coli* K12 strain carrying TnA (Hedges & Jacob, 1974) on the chromosome (DEP Ref. 52R494). The progeny were then tested for transfer of ampicillin resistance to a further host strain and the stable association of the resistance with the transfer factor was confirmed. Testing for incompatibility could then be undertaken in the usual way.

RESULTS

Phage typing

One hundred and ninety-one *S. typhimurium* strains isolated from paediatric outbreaks in India between 1978 and 1980 were examined. Of these, 187 (96·4%) belonged to phage types 66 or 122 or were untypable (Table 1). Two strains were phage type 193 and one each of types 3 and 10.

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Table 1. *Multi-resistant* S. typhimurium *from India*, 1978–1980

Source	Date received	Total	Phage type*	No.	Drug resistance spectrum†	No.
Ludhiana	Dec. 1978	33	U	27	ACKSSuSpTGTm	29
	June 1979		122	4	ACKSSuSpT	1
	Dec. 1979		66	1	ACKSSuSpTm	1
			3	1	Sensitive	2
Delhi	June 1979	8	U	8	ACKSSuSpTGTm	8
Bombay	June 1978	84	122	37	ACKSSuSpTGTm	77
Hospital 1	Sept. 1978		U	23	ACKSSuSpTGTmFu	2
	Aug. 1979		66	21	ACKSSuSpGTm	2
			193	2	CKSSuTG	1
			10	1	CKSSuGTm	1
					Sensitive	1
Bombay	Jan. 1979	11	66	4	ACKSSuSpTGTm	9
Hospital 2			122	4	ACKSSuSpGTm	1
			U	3	ACKSSuSpT	1
Poona	Feb. 1980	10	U	10	ACKSSuSpTGTmFu	8
					ACKSSuSpTGTm	1
					Sensitive	1
Bangalore	July 1980	33	122	17	ACKSSuSpTGTm	30
			U	15	ACKSSuSpGTm	1
			66	1	AKSSuSpGTm	1
					KSSu	1
Trivandrum	Feb. 1979	12	U	10	ACKSSuSpTGTm	11
			66	1	ASSu	1
			122	1		
Total		191	U	96	ACKSSuSpTGTm	165
			122	63	ACKSSuSpTGTmFu	10
			66	28	ACKSSuSpGTm	4
			193	2	ACKSSuSpT	2
			10	1	ACKSSuSpTm	1
			3	1	AKSSuSpGTm	1
					CKSSuTG	1
					CKSSuGTm	1
					ASSu	1
					KSSu	1
					Sensitive	4

* U, untypable.

† *Drug resistance symbols*. A, ampicillin, C, chloramphenicol, K, kanamycin, S, streptomycin, Su, sulphonamides, Sp, spectinomycin, T, tetracyclines, G, gentamicin, Tm, trimethoprim, Fu, furazolidone.

Phage types 66 and 122 are closely related. They are sensitive to the same phages in the definitive typing scheme but fewer plaques are seen on type 122 than on type 66 (Table 2). Strains of both types 66 and 122 carry two phages. One phage, when introduced into *S. typhimurium* type 36, confers resistance to five phages of the typing scheme changing the phage type to type 2. The second phage converts type 36 to type 125. When both phages are present together in type 36 the phage type is changed to type 3 (Table 2). Furthermore, the second phage converts type 10 to type 66. Strains of both type 3 and type 10 have been isolated during the relevant outbreaks.

Table 2. *Phage types of* S. typhimurium *from India and plasmid or phage-determined derivatives*

Phages in routine test dilution	Type							
	2	3	10	66	122	125	NC10	36
1	–	–	–	–	–	+++	++	CL
2	CL	+++	–	–	–	SCL	SCL	CL
3	CL	CL	–	–	–	SCL	++	CL
4	CL	CL	–	–	–	SCL	SCL	CL
5	CL	CL	–	–	–	SCL	SCL	CL
6	CL	CL	–	–	–	+++	SCL	CL
7	–	–	–	–	–	SCL	SCL	CL
8	–	–	–	–	–	SCL	–	CL
10	CL	CL	CL	SCL	+	SCL	++	CL
11	CL	CL	CL	SCL	+	SCL	SCL	CL
12	CL	–	CL	–	–	–	–	SCL
13	CL	–	CL	–	–	–	–	CL
14	CL	CL	–	–	–	OL	CL	CL
15	CL	CL	–	–	–	OL	OL	CL
16	CL	CL	SCL	SCL	+	OL	CL	CL
17	CL	CL	–	–	–	SCL	SCL	CL
18	–	–	–	–	–	CL	–	CL
19	CL	CL	–	–	–	OL	++	CL
20	CL	CL	CL	SCL	++	SCL	+	CL
21	CL	CL	–	–	–	SCL	CL	CL
22	CL	SCL	CL	OL	+++	SCL	++	CL
23	CL	CL	CL	OL	+++	CL	+++	CL
24	CL	CL	–	–	–	SCL	SCL	CL
25	CL	CL	+	+	–	SCL	++	CL
26	CL	+++	+	+	–	SCL	++	SCL
27	CL	CL	–	–	–	OL	+	CL
28	+	+	–	–	–	OL	OL	CL
29	CL	CL	CL	OL	OL	CL	CL	CL
32	CL	+++	SCL	OL	–	OL	+	CL
35	CL	CL	–	+	–	CL	OL	CL
Source	Type 36 +phage	Wild strain				Type 36 +phage	Type 36 $+F_1me$	Standard strain

Key: CL, confluent lysis; SCL, semi-confluent lysis; OL, opaque lysis; + > ++ > +++, increasing numbers of discrete plaques.

While type 122 strains occasionally give rise to colonies of type 66, the latter is stable. This suggests that type 122 might carry a temperate phage or a plasmid, either of which renders the strain less susceptible to the typing phages concerned. The isolation of such a factor from type 122 has not been demonstrated.

The two strains belonging to phage type 193 carry a temperate phage which confers resistance to the phages of the definitive scheme. This phage corresponds to that found in other strains of type 193 isolated in the Far East (Frost *et al.* 1976). These type 193 strains differ from those which predominate in Great Britain whose phage type is determined by the phage restriction encoded by the resistance plasmids present (Threlfall *et al.* 1978).

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Table 3. *Subdivision of untypable* S. typhimurium

Source	Untypable subtypes u1	u3	u4	u5	u6	u7	u8	u9	Total
Ludhiana	4	4	6	2	11	—	—	—	27
Delhi	8	—	—	—	—	—	—	—	8
Bombay 1	—	—	12	6	5	—	—	—	23
Bombay 2	1	1	—	—	—	1	—	—	3
Poona	—	—	3	7	—	—	—	—	10
Bangalore	—	—	11	—	—	—	1	3	15
Trivandrum	—	—	7	—	3	—	—	—	10
Total	13	5	39	15	19	1	1	3	96

Table 4. *Presence of temperate bacteriophages in untypable strains*

Phage type	Phages 1993′*	1997′*	2449a′	2449b′	3939′	476′	267′	3427′
u1	+	+	+	+	−	−	−	−
u3	+	+	+	−	−	−	−	−
u4	+	+	−	−	+	+	−	−
u5	+	+	−	−	+	+	−	−
u8	+	+	−	−	+	+	−	−
u6	+	+	−	−	−	+	−	−
u7	+	+	−	−	−	−	+	−
u9	+	+	−	−	−	−	−	+

* Phages 1993′ and 1997′ are present in all strains of types 66 and 122 and related untypable strains.

The 96 untypable strains can be differentiated by their reactions with the phages of the ancillary typing scheme. Seven patterns were identified in strains isolated in 1978 and 1979, and a further two in the most recently isolated batch of strains from Bangalore. Strains identified as subtype u2 reverted to types 66 or 122 on storage and were therefore not available for detailed study. Table 3 shows the distribution of the remaining eight subtypes.

Representative strains of each subtype were tested for the presence of temperate phages. Each strain yielded at least three phages including the two, 1993′ and 1997′, present in types 66 and 122. Eight different phages were identified; their distribution is shown in Table 4. Subtypes u1 and u3 have a phage in common (2449a′) as do types u4, u5, u6 and u8 (476′). Within each of these two groups further differentiation is determined by a second phage (2449b′ and 3939′ respectively). No difference in phage content has been demonstrated between subtypes u4, u5 and u8. The phages present in u7 and u9 are unique to the subtype concerned.

All of the untypable strains examined in detail have proved to be unstable and a number have changed phage type during the course of the study. For example, three strains originally assigned to subtype u4 changed to u6 while 12 strains

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changed from u6 to type 122. These changes were due to the loss of a temperate phage, 3939′ and 476′ respectively.

Resistance to antibiotics

One hundred and eighty-seven of 191 strains (97·9%) were antibiotic resistant. Of these, 165 (86·4%) were resistant to ampicillin, chloramphenicol, kanamycin, streptomycin, spectinomycin, sulphonamides, tetracyclines, gentamicin and trimethoprim, R-type ACKSSuSpTGTm. A further ten strains were also resistant to furazolidone (Fu). The remaining 12 strains had one or more resistances fewer than the above spectrum (Table 1).

All drug-resistant strains were tested for resistance transfer to *E. coli* K12. Only 66 transferred their resistances directly, 15 transferring the complete resistance spectrum other than resistance to furazolidone and the remaining 51 transferring only SSu. Resistances other than Fu in the remaining 121 strains (74·1% of resistant strains) could be mobilized by either of the two standard transfer factors Δ and X (Anderson & Threlfall, 1974).

The plasmids identified were characterized according to their transferability and compatibility group (Table 5). There was no detectable difference in plasmid content between successive batches of strains from the same hospital. The plasmids are described below according to their compatibility groups.

$F_I$me plasmids

Of the 187 drug-resistant strains, 186 carried a non-autotransferring plasmid belonging to compatibility group F_I*me* conferring resistance to the complete spectrum of resistance (that is, R-type ACKSSuSpTGTm) excepting furazolidone, which was not transferred, either directly or by mobilization. Twelve strains were resistant to less than nine drugs; of these, eleven carried an F_I*me* plasmid coding for resistance to all the drugs represented.

The F_I*me* plasmid could be mobilized by the standard transfer factor X which belongs to compatibility group F_{II}, or by the KSSu R factor which was present in 16 strains. In *S. typhimurium* type 36 the F_I*me* plasmid confers resistance to a number of the typing phages. The resulting phage restriction pattern is designated NC10 (Anderson *et al.* 1977*a*).

SSu resistance determinants and group I_2 transfer factors

A non-autotransferring SSu resistance determinant was detected in 158 strains (84·5%). This could be mobilized by the standard transfer factors Δ and X.

In addition, 63 of these strains carried a transfer factor which transferred the SSu determinant in a Class 2 association, that is, the resistance determinant and transfer factor remained independent in the recipient strain (Anderson & Threlfall, 1974). Five of these transfer factors were labelled with ampicillin resistance by transposition using TnA (Hedges & Jacob, 1974), and shown to belong to compatibility group I_2.

Table 5. *Drug resistance transfer and mobilization*

		Autotransferring strains						Non-autotransferring strains			
			Plasmids identified						Plasmids identified		
Source	Total resistant strains	No.	KSSu R factor	I_2 transfer factor	ACKSSuSpTGTm F_1me (n)*	SSu determinant	Other determinants	No.	ACKSSuSpTGTm F_1me (n)*	SSu determinant	Other determinants
Ludhiana	31	7	2	6	7	7	AKSuGTm 1 SuTm 1	24	24	22	—
Delhi	8	1	1	—	1	1	AKSuGTm 1	7	7	6	—
Bombay 1	83	19	7	12	19	18	AKSuGTm 1 CKTG 1	64	64	45	SSuSpTTm 1
Bombay 2	11	7	1	6	7	6	—	4	4	4	—
Poona	9	6	—	6	6	6	—	3	3	1	—
Trivandrum	12	0	—	—	—	—	—	12	11	10	ASSu 1
Bangalore	33	26	5	33	26	25	—	7	7	7	—
Total	187	66	16	63	66	63	5	121	120	95	2

* Some plasmids encode fewer than nine resistances.

KSSu R factor

Sixteen strains, isolated in Bangalore, Bombay, Delhi or Ludhiana, carried an autotransferring plasmid conferring resistance to KSSu.

One of these plasmids, designated TP269, isolated from a strain of *S. typhimurium* type 66 isolated in Bombay, transferred to *E. coli* K 12 at a frequency approaching unity and was able to mobilize the F_Ime plasmid as already described. It did not promote the propagation of plasmid-specific phages including $\mu 2$ and fd (for F-like plasmids), If1 (I-like) or IKe (N), although it did inhibit the fertility of the F factor. When transferred to *S. typhimurium* phage type 36 no restriction of typing phages was observed. TP269 was compatible with representatives of all the compatibility groups listed previously. It was therefore tested for compatibility against other as yet unclassified plasmids isolated in this laboratory. TP269, and the other KSSu R factors, were found to be incompatible with two plasmids, TP201 and TP202, identified in *Sh. sonnei* isolated in Venezuela in 1973 (Vargas *et al.*, in preparation).

Other resistance determinants

Five strains with autotransferring plasmids and two strains with mobilizable resistances carried other resistance determinants in addition to those described above.

One strain was resistant only to ASSu; the resistances were carried on a plasmid mobilizable by Δ or X. The remaining resistance determinants were in strains resistant to ACKSSuSpTGTm and included three plasmids conferring resistance to AKSuGTm and one of each of the following combinations: CKTG, SuTm and SSuSpTTm.

Related strains from other countries

1. *Saudi Arabia.* In February 1980 we received multi-resistant *S. typhimurium* isolated during an outbreak of gastroenteritis in a paediatric ward in a hospital in Riyadh, Saudi Arabia.

Eight strains were examined; six belonged to phage type 122 and carried a non-autotransferring F_Ime plasmid coding for resistance to ACKSSuSpTGTm and an SSu resistance determinant. These strains were indistinguishable in their phage and plasmid content from the *S. typhimurium* strains isolated in India described above. The remaining two strains were untypable. One belonged to the Indian subtype u5 and carried an F_Ime plasmid and SSu determinant. The other strain reacted with two phages of the ancillary typing scheme, a pattern associated with F_Ime-carrying strains from the Middle East. This strain carried a non-autotransferring F_Ime plasmid and two resistance determinants, coding for resistance to AK and SSu respectively. This combination of plasmids was also identified in *S. typhimurium* belonging to phage type 208 or related untypable strains isolated in Israel, Iran and Turkey (Anderson *et al.* 1977*a*). The carried phages in these two strains have similar properties to those identified in untypable strains from India and Turkey respectively.

Table 6. '*Indian*' S. typhimurium *isolated in Great Britain*

Phage type	No.	R-type	No.	Source of infection	No.
Untypable	10	ACKSSuSpTGTm	10	India	6
				Philippines	1
				Saudi Arabia	1
				Zambia	1
				Not specified	1
Untypable	2	ACKSSuSpTGTmFu	2	Family outbreak	5
122	3	ACKSSuSpTGTmFu	3		
NC*	2	ACKSSuSpTGTm	2	India	2
193	1	ACKSSuSpTGTm	1	Philippines	1
66	1	ACKSSuSpTGTm	1	India	1
Total	19		19	India	9
				Philippines	2
				Other	8

*NC, reacts with one phage of the typing scheme but does not conform to a designated type.

2. S. typhimurium *isolated in Great Britain*. Characterization of the plasmids carried by *S. typhimurium* strains resistant to ACKSSuSpTGTm and belonging to types 66, 122 or related types in Great Britain between 1978 and 1980 identified 19 strains which appeared to belong to the Indian clone (Table 6). All of these carried a non-autotransferring $F_I me$ plasmid and an SSu resistance determinant; one strain also carried a group I_2 transfer factor. Twelve strains were untypable and carried temperate phages indistinguishable from those in the strains isolated in India. Three strains belonged to phage type 122 and one each to types 66 and 193. Two strains exhibited a phage typing pattern which does not conform to a designated phage type (= NC). These strains react with only one phage of the typing scheme and carry a temperate phage which determines this restriction pattern.

Of the 19 strains, nine were from patients infected in India or of Indian origin, two were acquired in the Philippines and three elsewhere abroad. The remaining five strains were from a family outbreak in which contact with Asians was subsequently established.

DISCUSSION

The *S. typhimurium* strains from India described in this study were isolated over a three-year period during outbreaks of enteritis in widely separated parts of the country. These outbreaks had several features in common. They were all hospital outbreaks involving young children, particularly neonates; the majority of patients had severe enteritis, and there were a number of septicaemias and fatalities. The strains were multi-resistant, and three phage types predominated, namely 66, 122 and a related untypable. The observed differences in phage type have been shown to result from the presence of a number of carried phages. Similarly a common pool of plasmids has been identified in these epidemic strains, namely a non-autotransferring $F_I me$ plasmid, an SSu resistance determinant, a

group I_2 transfer factor and an R factor coding for resistance to KSSu. However, some strains did not carry all four plasmids, although the F_I*me* plasmid was present in all but one strain.

Strains with these characteristic plasmids and phages have subsequently been identified among sporadic infections in Great Britain. The majority of these infections are known to have originated in India and there has been only one example of spread within the community. The identification of a related outbreak in Saudi Arabia indicates that this clone may be prevalent over a wider area than that represented in the present study. The F_I*me* plasmids, first characterized in strains of *S. typhimurium* phage type 208 from the Middle East (Anderson *et al.* 1977*a*) have now also been identified in salmonellae from Africa and South East Asia. In all cases the plasmid codes for resistance to a large number of antibacterial agents, so use of any drug will select for the complete resistance spectrum. These plasmids are unusual in that the majority of examples characterized are transfer defective. Non-autotransferring F_I*me* plasmids predominated among those from *S. typhimurium* isolated in the Middle East and have been shown to be deletion mutants of the autotransferring plasmid (Willshaw, Smith & Anderson, 1978). Those from India are of similar size, *ca.* 90×10^6 daltons, to the non-autotransferring Middle Eastern plasmids (G. A. Willshaw, unpublished observations). The group I_2 transfer factor, identified in 26 per cent of the Indian strains, was not found in the *S. typhimurium* phage type 208 strains in the Middle East. However, a group I_2 plasmid, conferring resistance to ampicillin, was identified in some of the *S. wien* isolated in North Africa and Europe (McConnell *et al.* 1979). These observations indicate that the F_I*me* and I_2 plasmids have both spread in different strains of salmonella.

Although variations in plasmid and temperate phage content have occurred, the strains from different outbreaks are clearly related. These studies have demonstrated the epidemic spread in South East Asia of a multi-resistant clone of *S. typhimurium*, an important characteristic of which is the presence of an F_I*me* plasmid. As in other similar examples, the presence of this plasmid seems to be associated with particularly severe infections.

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