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Salmonellosis in Indonesia: phage type distribution of *Salmonella typhi**

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SUMMARY

The distribution of phage types was studied among 577 strains of *Salmonella typhi* from Indonesia. Chemotype, colicinogeny, and tetrathionate reductase activity were also studied for most of these strains. The current phage type formula for Java was determined to be: A, D2, D6, E1a, E2, M1, and 46, but two other large groups of strains were also found, I+IV and degraded Vi+ strains. Significant differences in *S. typhi* strain distributions were noted between two localities on Java with respect to phage type and tetrathionate reductase activity. Comparisons were made with past phage typing studies in Jakarta as well as with more recent studies in other parts of south-east Asia. Phage types A, D1, D2, and E1 persisted at a rather steady level in Jakarta for 28 years. Evidence was found for

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epidemiological links to European and Asian areas. Antibiotic resistance among these Indonesian *S. typhi* strains was rare.

INTRODUCTION

Typhoid fever is a major public health problem of developing countries. It is also increasing elsewhere in places such as France and the United States, possibly associated with travel from Asia, the Middle East, Africa, and South America (Vieu, Diverneau & Binette, 1976; Rice, Baine & Gangarosa, 1977). Since Cragie & Yen (1938) described specific adaptation of certain bacteriophages to *S. typhi* strains of different origins, their phage-typing method has evolved into a major tool for epidemiological study of the sources of typhoid fever (Anderson & Williams, 1956). It is also an important method to demonstrate the spread of typhoid fever throughout the world (Felix, 1955; Nicolle, 1962*a*, *b*; Anderson & Nicolle, 1973). Erber & DeMoor (1954) observed that in the tropics, where typhoid fever is endemic, phage typing has special value to help trace specific outbreaks in epidemiological studies. The recent application of computer techniques has greatly facilitated such epidemiologic studies (Vieu *et al.* 1973).

Distribution of *S. typhi* phage types in certain areas of Indonesia has been reported previously (Lie Kian Joe, 1949; Lie Kian Joe, 1950; Erber & DeMoor, 1954; Felix, 1955; Gan-Oei Siok Yauw & Lie Kian Joe, 1960). The present study was designed to update information regarding *S. typhi* phage type distribution on Java and to assess the variation within Java as well as over other parts of south-east Asia.

MATERIALS AND METHODS

This study was based on 577 strains of *S. typhi* isolated from human sources during the period September 1973 through July 1975. Most were from blood culture of acute cases of enteric fever, but two strains were isolated from stools of carriers in Jakarta. There were 232 strains from the Jakarta area, these coming from four hospitals drawing patients from the northern, western, and central (2) areas of Jakarta. An additional 108 strains came from a hospital in suburban Cilandak that received patients from the suburban–rural area on the south side of Jakarta. The remaining 237 strains were obtained from the Yogyakarta area in central Java.

A modification of the standard method of phage-typing (Cragie & Yen, 1938; Cragie & Felix, 1947) was used as described by Nicolle (1961). There were 96 Vi phages used in this study as distributed by Dr E. S. Anderson from the International Centre for Enteric Phage Typing (ICEPT). A complementary phage typing system was used to subdivide phage type A strains (Nicolle, Pavlatou & Diverneau, 1953).

Several other complementary differentiating tests were done on these strains in addition to phage typing. All strains were examined for chemotype, i.e. acid production from xylose in peptone water with bromthymol blue, 24 h at 37 °C. Chemotype I was xylose positive while chemotype II was negative. The

colicinogeny of the *S. typhi* strains against *Escherichia coli* K-12 was also studied (Nicolle & Prunet, 1964). Additionally, most strains were tested for their ability to reduce tetrathionate (TTR test) (Nicolle & LeMinor, 1965).

In collating the variety of data collected during this study, a computer data bank was formed from which phage type frequencies were determined (Vieu *et al.* 1973).

The frequency of *S. typhi* phage types at various localities and for different times were compared using the χ^2 test, considering the data as a $2 \times R$ table. Individual pair comparisons of specific phage types or TTR types were examined using a test for the significance of difference between two sample proportions. In this case a conservative acceptance level was adopted ($P < 0{\cdot}001$), since the overall protection level (probability that any of the obtained differences were due to chance) for all possible tests made at the 0·001 significance level was approximately 0·02 for this study. Protection level was calculated as $1-(1-\alpha)^{\kappa}$ where α = significance level and κ = number of possible comparisons (Ferguson, 1966).

When using the hypothesis testing format to establish the fact that two groups of phage types of TTR types did not differ significantly, it was necessary to allow for a very liberal acceptance level 'α' (e.g. $P > 0{\cdot}25$), thus reducing β error (probability that a real difference is not detected) to a reasonable amount.

RESULTS

There were 16 phage types found among the 577 strains of *S. typhi* in this study. Additionally, I+IV, degraded Vi+ and Vi negative strains were present. The largest single group, 25%, consisted of strains designated I+IV, those resistant to Vi_{II} typing phages but reacting with I and IV unadapted Vi phages. The distribution of these 19 groups in Jakarta, Cilandak, and Yogyakarta appears in Table 1.

A comparison of phage type distribution was made between Jakarta and its suburb, Cilandak, phage type 53 being omitted from this analysis, since it was the cause of a focal outbreak that was the subject of intense case finding efforts that might have biased the result. The distribution of phage types was not significantly different between these two areas ($P > 0{\cdot}30$). Therefore, in all subsequent analyses, results from these areas were grouped together as the Jakarta area.

Phage type distributions were then compared for two diverse geographic areas of Java, Jakarta at the western end and centrally located Yogyakarta (Table 2). The five predominant types were the same for each locality. These were I+IV, D2, A, degraded Vi+ strains and E1a in decreasing order of prevalence. Vi negative strains were sixth most common in Jakarta and seventh in Yogyakarta. In Jakarta 6·2% of strains were phage type M1, while only 0·4% of this type was found in Yogyakarta ($P < 0{\cdot}001$). Phage type E2 was 6·8% of Yogyakarta strains with only 0·4% being found in Jakarta ($P < 0{\cdot}001$). The remaining distributional differences were composed of small numbers of strains.

During this study 11 strains of *S. typhi* were isolated that were resistant to chloramphenicol, streptomycin, sulpha drugs, and tetracycline (CSSuT). Ten of

Table 1. *Phage type distribution of* Salmonella typhi *strains isolated from human sources on Java*, 1973–5

Phage type/group	Jakarta	Cilandak	Yogyakarta*
I+IV	64	32	48
Degraded Vi+	18	15	20
Vi negative	23	4	9
A	25	12	40
C2	1	—	—
D1	3	—	1
D2	40	12	54
D6	9	4	15
E1a	20	9	18
E1b	2	1	—
E2	—	1	16
G1	—	—	2
G3	1	—	—
J1	2	—	—
M1	14	7	1
25	—	—	4
42	—	—	2
46	10	1	7
53	—	10†	—
Strains examined	232	108	237

* 1974–75. † A focal outbreak.

Table 2. *Comparative distribution of* Salmonella typhi *phage types from diverse geographic areas on Java*, 1974–5

Phage type/group	Jakarta area, 253 strains (%)	Yogyakarta, 237 strains (%)
I+IV	32	20
Degraded Vi+	11	8·4
Vi negative	6·3	3·8
A	8·7	17
C2	*R*	
D1	0·8	*R*
D2	14	23
D6	4·0	6·3
E1a	9·1	7·6
E1b	1·2	
E2	*R*	6·8
G1		0·8
G3	*R*	
J1	0·8	
M1	5·1	*R*
25		1·7
42		0·8
46	3·2	3·0
53	4·0*	

R = < 0·5%. * Focal outbreak. Blank space, type not found.

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Table 3. *Tetrathionate reductase (TTR) tests on* 394 *strains of* Salmonella typhi *collected from humans* 1973–5

Phage type	TTR negative (±)	Strains tested
I+IV	2	144
Degraded Vi+	13 (1)	53
Vi negative	3	36
D2	1 (1)	106
D6	2	28
E2	1	17
53	10	10
Totals	31 (2)	394

these were from a focal outbreak in Cilandak (Sanborn *et al.* 1975) and were phage type 53, the only members of this phage type found. The other was from an isolated case in central Jakarta and was a I+IV strain.

Sub-types of phage type A found in this study were Tananarive-25, Chamblee-7, Dakar-2, and non-typable strains-3 for the Jakarta area while there were 31, 5, 1, and 3 respectively for the Yogyakarta area. Thus, there were no appreciable distributional differences.

There were 509 *S. typhi* strains examined for chemotype. The majority, 403, were chemotype I, xylose positive. Ratios of chemotypes I and II from the three areas, Jakarta, Cilandak, and Yogyakarta, were not significantly different. Chemotype I predominated among I+IV, degraded Vi+, and Vi negative strains as well as among all phage types except for C2, D6, M1, and 42. Among strains of these phage types the chemotype I to II ratios were 0:1, 1:3, 1:10, and 0:2 respectively. Again, there were no significant differences between the three geographic areas.

There were 394 *S. typhi* strains tested for tetrathionate reductase activity, and 31 were negative with two plus–minus reactions. These were distributed among phage types as shown in Table 3. Jakarta yielded 5 TTR negative strains, Cilandak 23 (1±) and Yogyakarta 3 (1±). Of the Cilandak strains, 10 were from the focal outbreak of phage type 53.

The proportions of TTR negative strains in Jakarta and Cilandak were not significantly different, whether including the phage type 53 strains ($P > 006$) or excluding these ($P > 0{\cdot}44$). However, comparing the Jakarta–Cilandak distribution to that of Yogyakarta revealed a highly significant difference ($P < 0{\cdot}001$).

Colicinogeny was tested on 572 strains, and all were negative.

The present Jakarta phage type distribution as compared with that of earlier studies is shown in Table 4 (Felix, 1955; Gan-Oei Siok Yauw & Lie Kian Joe, 1960; Lie Kian Joe, 1949). Phage types A, D1, D2, E1, and the rare E2 were found in all these studies. The same was true for degraded Vi+ and Vi negative strains.

Phage type M (M1) was common in our study at 6·2% where it had been about 2·4% in the previous studies ($P < 0{\cdot}001$). A significant decrease was seen in the amount of phage type D6, dropping from a major position at approximately 24 to 28% over three previous studies down to 3·8% in the present study ($P < 0{\cdot}001$). Phage type B1 was not found in Jakarta, where it had been as frequent as 8% of

Table 4. *Historical comparison of* Salmonella typhi *phage type distribution in Jakarta, Indonesia*

	1973–5		1955–60*		1950–2†		1947–8‡	
Phage types Jakarta 1973–5	Rank	%	Rank	%	Rank	%	Rank	%
I+IV	1	28·2		§		§		§
D2	2	15·3	2	22·5	3	13·4	2	21·4
A	3	10·4	3	14·0	2	14·5	3	20·4
Degraded Vi+	4	9·7	5	6·8	9	3·5		
E1 (E1a)	5	9·4	6	5·3	4	10·7	4	12·6
Vi negative	6	7·9	8	3·6	10	2·1	8	1·8
M (M1)	7	6·2	11	0·7	8	3·6	10	0·7
D6	8	3·8	1	24·4	1	28·0	1	27·4
46	9	3·2		—		—		—
53	10	2·9		—		—		—
D1	11	0·9	14	0·5	11	1·3	9	1·4
J (J1)	12	0·6				*R*		
C2	13	*R*						
E2	14	*R*	10	1·4	12	1·0	11	*R*
G (G3)	15	*R*						
Other phage types found, 1947–60								
Non-typable			4	8·7	5	8·6	7	3·2
E3			7	4·8		—		—
25			9	2·4	7	4·7	6	3·9
E4			9	1·7		—		—
B1			12	0·7	6	8·0	5	6·7
D10			13	0·7		—		—
D9			15	0·5		—		—
36			16	0·5		—		—
D7			17	*R*		—		—
29			18	*R*		—		—
40			19	*R*		—		—
N							12	*R*
Strains examined	340		414		910		285	

Blank space, not found; —, phage not available; *R*, < 0·5%.
* Adapted from Gan-Oei Siok Yauw & Lie Kian Joe (1960).
† Adapted from Felix (1955).
‡ Adapted from Lie Kian Joe (1949).
§ Designation not in use.

strains in previous reports. Phage type 25 also was not found in Jakarta, but a few of these strains were found in Yogyakarta.

Current distributions of *S. typhi* phage types were compared for Java and the Indochina peninsula (Nicolle *et al.* 1975). The results are shown in Table 5. Major strain types common to the two areas were I+IV, degraded Vi positive, and E1. Analysis of the distributions of the following phage types showed highly significant differences ($P < 0{\cdot}001$) between the two areas: D2, D6, 46, E2, A, Vi negative, M1, and G1. Some phage types (E10, N, 37, T, 29, B2, and E9), common on the Indochina peninsula, were not found in this study.

Table 5. *Comparative distribution of* Salmonella typhi *phage types in southeast Asian areas*

	Java 1973–5		Indochina Peninsula*† 1948–73		Philippines‡ 1954–9		Philippines‡ 1969–72	
Phage types Java 1973–5	Rank	%	Rank	%	Rank	%	Rank	%
I+IV	1	25·0	1	28·3			5	2·1(?)
D2	2	18·4	6	4·6	4	0·8		
A	3	13·3	3	8·7	1	68·3	2	33·7
Degrades Vi+	4	9·2	2	10·8			3	4·3
E1	5	8·7	5	7·0	5	0·8	6	2·1
Vi negative	6	6·2	8	3·4				
D6	7	4·9	16	1·2				
M1	8	3·8	4	8·7				
46	9	3·1	29	*R*			7	1·1
E2	10	2·9	35	*R*	2	23·6	4	4·3
53	11	1·7		§				
25	12	0·7	28	*R*				
D1	13	0·6	18	*R*	6	0·8		
J1	14	*R*	14	1·5				
G1	15	*R*	9	2·8				
42	16	*R*						
G3	17	*R*	44	*R*				
C2	18	*R*	30	*R*				
Other phage types found in south east Asia								
E10			7	3·8				
N			10	2·7	7	0·8		
37			11	2·4				
T			12	2·0				
29			13	1·5				
B2			15	1·2				
E9			17	1·2				
J3			19	0·9				
M2			20	0·9				
E3			21	0·8				
B1			26	*R*			1	55·0
C1			34	*R*	3	4·9		
Strains examined	577		4514		124		282	

Blank space, Phage type not found; *R*, < 0·5%; (?), 'Non-typable', presumed I+IV.
* Cambodia, Laos, Thailand, Vietnam.
† Adapted from Nicolle *et al.* (1975).
‡ Adapted from Basaca-Sevilla *et al.* (1974).
§ Not found in this collection but reported by others from Thailand.

Distribution of phage types from Java was compared with that of the Philippines (Basaca-Sevilla *et al.* 1974). Type B1 was most frequent in the Philippines but not found in Java, and type A was much more prevalent in the Philippines than in Indonesia (Table 5).

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DISCUSSION

The 577 strains reported here comprised a sample comparable to previous studies, only that by Felix (1955) being substantially larger. Numbers of strains collected from Jakarta and Yogyakarta were generally proportionate to the populations in those areas. Jakarta strains provided a good cross-section of the community, coming from five hospitals serving four areas of the city. Similarly, Yogyakarta strains came from the major hospital there as well as from clinics in suburban areas surrounding the city.

The present basic phage type formula for Java appears to be A, D2, D6, E1a, E2, M1, and 46, plus I+IV and degraded Vi+ strains. This pattern is similar to that reported by Felix (1955) and also by Lie Kian Joe (1949), except for the lack of types B1, E3, and E4; the lower frequency of D1 and 25; and the addition of the newer type 46. Thus, phage types A, D1, D2, D6, E1, E2, and M have maintained endemic presence in Jakarta for at least 28 years.

I+IV strains formed the largest single group in this study. They were proportionately similar to the distribution seen on the Indochina peninsula (Nicolle *et al.* 1975). Before 1955 this designation was not in use, but even the 'non-typable' category in earlier studies could not account for so large a group, since non-typables were only one-third the amount of I+IV strains found here. Thus, it would seem that the increase in these strains represented a real change in south-east Asian *S. typhi* distribution.

This study documented the occurrence of the newer phage types 46 and 53 in Indonesia for the first time. These types were not available for use in the earlier studies, having been distributed by the International Reference Laboratory for Enteric Phage Typing in 1961 and 1972 respectively. Elsewhere, phage type 46 has been reported primarily from Europe, with the exception of France. Its highest numbers were generally found in England, the Netherlands, Belgium, Spain, and central Europe (Anderson & Nicolle, 1973). Previous studies indicated that it had been rare in south-east Asia (Nicolle *et al.* 1975), but in the present study it ranked ninth at 3·1%. It may be that this prevalence could be due to Indonesia's close ties to the Netherlands through business, travel, and trade.

The recently recognized phage type 53 was a unique finding. It made its only appearance in this study as a confined outbreak of 10 typhoid cases. The source of this outbreak remained obscure despite our intense epidemiological studies. Phage type 53 was introduced into the international system of phage typing by ICEPT in 1972. Therefore, its true frequency and distribution is difficult to define. Following its discovery in Japan, phage type 53 was reported from diverse places including Sweden and Thailand (Anderson, 1974; Anderson, 1976). It has been found by the Pasteur Institute among recent *S. typhi* collections from South Korea, Sudan, Central African Republic, Iraq, and France (J.-F. Vieu, personal communication). It appears that phage type 53 may be rather widely distributed. Thus, this study suggests two possible typhoid contaminations of Indonesia from external sources, phage types 46 and 53.

Phage type 25 was originally discovered in Indonesia (Lie Kian Joe, 1949), and

in subsequent studies it continued to represent a considerable position of the *S. typhi* strains isolated in Jakarta. However, since no strains of this type were found in Jakarta and only a few in Yogyakarta, it seems that this phage type is becoming less frequent in Java.

Another significant decline was noted in the frequency of phage type D6. It was the predominant type in the three previous studies, representing 24, 28, and 27 % of the strains isolated. In this study it ranked eighth at 4 %.

Finding the cosmopolitan phage type E1a was not unexpected. It has been common in previous Jakarta studies and throughout Indochina. However, chemotype analysis revealed that one-third of our strains were mainly from the Jakarta area.

Sub-typing the phage type A strains revealed a preponderance of Tananarive among the three sub-types and untypable strains found. There were also three strains of Dakar, a sub-type usually restricted to West Africa.

There was a significant difference between the phage type distributions of Jakarta and Yogyakarta. Phage type E2 was much more prevalent in Yogyakarta, 6·8 % *v.* 0·4 %, and M1 was more prevalent in Jakarta, 6·2 % *v.* 0·4 %. Phage type M1 has been relatively common in the Far East and is generally found around the borders of the Pacific Ocean, including Japan (Anderson & Nicolle, 1973). Its occurrence in Jakarta was similar to, but somewhat lower than, that found on the Indochina peninsula (Nicolle *et al.* 1975), perhaps reflecting partial contact between this major centre of Indonesian commerce and other parts of Asia. The fact that it was rare in Yogyakarta provided evidence that central Java might be somewhat epidemiologically isolated.

The frequency of phage type E2 in Yogyakarta was even more interesting. This phage type has been limited to Cambodia, Viet Nam, and the Philippines. In the Philippines it was isolated frequently from 1953 through 1958 and again in 1972 (Basaca-Sevilla *et al.* 1974). It is possible that an epidemiological link exists between the Philippines and Yogyakarta, one not shared by Jakarta and the Philippines.

Strains positive in the colicinogeny test are very rare, except for phage type 40, where all strains are colicinogenic (Nicolle & Prunet, 1964). This phage type was not found in Indonesia; our strains were all negative, as expected.

Apart from the rare chemotype of phage type E1a mentioned earlier, the two chemotypes were evenly distributed throughout the culture collection. Shifts in this pattern, an easily performed test, could prove to be a useful epidemiological reference.

Of the 394 strains tested by the TTR test (Nicolle & LeMinor, 1965) 0·8 % were negative. These strains were examined for distribution among phage types as well as geographical distribution. As with the phage type distribution, there was no significant difference in the TTR negative strain distribution between Jakarta and Cilandak. However, significantly fewer TTR negative *S. typhi* strains were found in Yogyakarta. This finding supports other evidence for the epidemiological or ecological isolation of Yogyakarta, as noted above and with *S. paratyphi* A strains (Sanborn *et al.* 1977).

In conclusion, the epidemiology of *S. typhi* on Java shows several features:

(1) A current phage type formula: A, D2, D6, E1, E2, M1, and 46, plus I+IV and degraded Vi+ strains.

(2) Persistence over 28 years of the following phage types: A, D1, D2, D6, E1, E2, M (M1).

(3) I+IV strains predominant.

(4) Significant differences in phage type and tetrathionate reductase-negative strain distributions between geographically separated localities on the same island, Java.

(5) Reduction in phage type 25 strains, a type originally discovered in Indonesia.

(6) Antibiotic resistance rare among these Indonesian *S. typhi* strains.

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