

PREVALENCE OF TYPHOID CARRIERS AFTER TREATMENT WITH CHLORAMPHENICOL¹

Drs. Rolando Armijo,² Aída Pizzi,² and Hernán Lobos³

How many typhoid fever patients who have been treated with chloramphenicol during the acute phase of their illness remain carriers of Salmonella typhi after their release? A study in Chile identified 7.4 per cent of such cases and made it possible to suggest factors of possible etiological significance.

Introduction

William Budd (1), anticipating the discovery of the typhoid bacillus by 24 years, probably intuited the existence of carriers when he said that "the first case may be foreign or may be due to the local poison that arises, like a fire from its ashes, as a sleeping legacy from a similar previous outbreak." At the end of the nineteenth century, Koch demonstrated clearly the role of the human being as a reservoir. Petrusky and Cushing (1898) were the first to communicate the finding of typhoid bacilli in the excreta of cured cases up to five years after the acute episode. Anton and Fütterer (1888) and Chiari, Dupré, and Chantemasse (1891) made classic studies describing the carrier.

Ever since Drigalsky and Conradi (1904, 1907) (2), many bacteriological and epidemiological researchers have suggested that carriers, by causing localized outbreaks, must play a very important role in keeping the disease endemic.

The proportion of clinically cured patients who remain carriers has varied according to place, treatment method used, length of observation, criteria used for definition, and other factors. The findings prior to the ad-

vent of chloramphenicol are summarized in Table 1.

Little is known about what has happened to the carrier rate since the introduction of chloramphenicol. Kraljević, Perroni, and their collaborators indicate that 5.9 per cent of patients are still excreting bacilli at the time of their release (3).

In Chile typhoid fever is one of the major public health problems. About 5,000 cases are reported annually. What is more, morbidity rates have tended to remain practically constant in recent decades despite a marked decline in case fatality (Figure 1) and consequently in the death rate, a decline that suggests the clinical impact of chloramphenicol. As a result of the high morbidity rate, Kraljević presents probably the largest number of cases treated with chloramphenicol in the world—more than 15,000.

Vildósola (4) observed the regularity with which cases occurred in limited geographic areas that he called "historical foci," which in his view suggested the existence of chronic carriers there. Romero (5), Moroder and López (6), and Garcés and Prado (7) accumulated observations that back up this notion. Borgoño and Latorre (8) estimated the number of carriers in Santiago around 1953 at 70,000.

These facts led the authors to ask themselves some fundamental questions: What is the part played by carriers in spreading typhoid fever in an endemic area? What

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² Professor of Epidemiology, School of Public Health, University of Chile, Santiago, Chile.

³ Laboratory Department, Bacteriological Institute of Chile, Santiago, Chile.

TABLE 1—Frequency of Typhoid Carriers Found among Clinically Cured Cases, before the Advent of Chloramphenicol, 1904-1952.

Year	Investigator	Percentage found to be carriers
1904	Drigalsky	3-5
1905	Lentz	7.5
1906	Klinger	1
1907	Kayser	3
1910	Brückner	2.8
1912	Fornet	2.4
1937	Stebbins and Reed	2.5
1938	Gray	3.3
1943	Ames and Robbins	{ 2.1 in males 3.8 in females
1947-52	O'Connor	{ 0.7 in persons under 20 years of age 2.5 in persons 20 years of age and over 5.2 in females 40 years of age and over 2.4 in males 40 years of age and over

is the rate of carriers remaining after treatment with chloramphenicol? The present paper reports on the results of their work. Their objectives were as follows:

1. To determine the proportion of typhoid cases treated with chloramphenicol that become chronic carriers.
2. To study possible associations between the condition of carrier and certain variables

in the acute phase, such as age, period between first symptoms and the beginning of treatment, relapses, and biliary disorders.

3. To measure the impact of the carrier on the family group.

Material and Methods

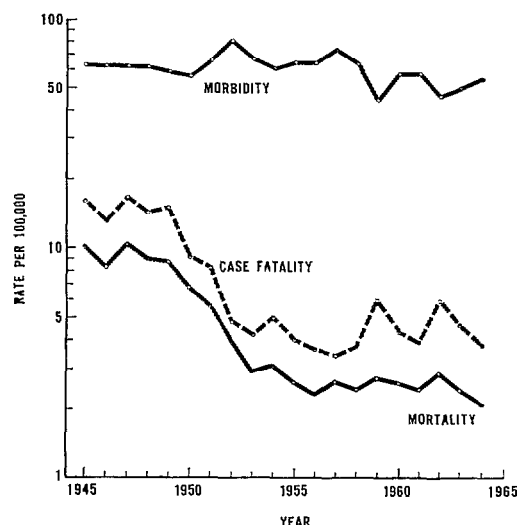
To carry out these objectives, it was decided to study women only, for the following reasons:

1. According to classic studies—Ames and Robbins, Tynes and Utz, O'Connor—a larger proportion of carriers is to be expected among females.
2. Women are more important epidemiologically in Chile, because they are all potential food handlers.
3. The country's cultural patterns made it more likely that women would be in when a home visit was paid.
4. Generally speaking, previous experience had shown women to be more cooperative.

Only those who were still excreting *Salmonella typhi* in the feces at least a year after an acute episode were considered chronic carriers.

The records of women released from the Hospital for Infectious Diseases between 1

FIGURE 1—Trends in Typhoid Fever Rates in Chile (Morbidity, Case Fatality, Mortality), 1945-1964 (Rate per 100,000).



July 1960 and 30 June 1964 were examined. During that period about 2,400 women were hospitalized. To ensure that the sample was accurate diagnostically, the choice of cases was based on certain bacteriological criteria. It was decided, in agreement with the professors of bacteriology and infectious diseases, Drs. Eduardo Dussert and Roque Kraljević, respectively, that an unequivocal case of typhoid fever would be one that was confirmed bacteriologically through blood culture, fecal culture, or both, besides having a clinical picture compatible with that diagnosis.

There were 763 patients who met these conditions. In the field work stage, 460 of these were located through home visits. Their diagnosis was confirmed as follows: blood culture, 283; fecal culture, 103; both, 74.

A significant number of cases were excluded because the patients' homes were outside the urban area of Santiago. Others could not be found because the addresses on their clinical records were incorrect or because the buildings had been demolished and it was impossible to learn where their inhabitants had gone. Also excluded were another 50 cases that for one reason or another had not received chloramphenicol. Some had gone to other provinces or had left the coun-

try; a few had died of other causes. The 460 cases studied were considered representative of the original 2,400, since exclusion was governed by chance. They came from socioeconomic strata and geographic areas representative of the total hospital clientele. They were also similar in age distribution.

A simple form (Figure 2) was drawn up for filling in all the data of concern in the study.

Each case was visited at home by a physician, who informed her about typhoid fever and obtained her cooperation in furnishing two samples for fecal culture after the administration of a cholagogue (in this case Dauropal), which was given in two doses of two capsules each. Those under 12 years of age were given two doses of one capsule each. The samples were furnished a week apart, in some cases oftener, or even as far apart as two weeks, depending on the individual circumstances. Over a period of two years more than 3,000 home visits were made, to locate cases, question index cases, and collect samples. From samples taken from the index cases and contacts, about 2,000 fecal cultures were made by the Laboratory Department of the Bacteriological Institute.

In the case of the family contacts of the

FIGURE 2—Form Used for Recording Results of Home Visits.

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HOSPITAL DATA:		TYPHOID CARRIERS		HOME VISITS:	
Last name	Given name(s)	Date of 1st visit		Date of 1st visit	
Age	Address	Date of 2nd visit		Date of 2nd visit	
Date of first symptoms	Date of initial treatment	Bact. report {	1st	Serolog. report	Present occupation
Date admitted	Date discharged		2nd		
Days elapsed from time of onset of the disease to the beginning of treatment (chloramphenicol)					
Relapse					
Total dose (grams) chloramphenicol administered		Other treatment		Intolerance: {	Fats
Strain isolated					
				Fried foods	
				Butter	
				Pains	Distension
				Urination	
				Excreta elimination	

TABLE 2—Age Distribution of *S. typhi* Carriers, Santiago, Chile, 1960-1964.

Age (years)	Number of cases investigated	Carriers		Carriers among contacts
		Number	Per cent	
Under 15	173	4	2.3	6
15 to 24	188	10	5.3	1
25 to 34	67	12	17.9	—
35 and over	32	8	25.0	1
Total	460	34	7.4	8

index cases two fecal cultures were studied in order to compare typhoid incidence in the group exposed to a proved carrier with that among a control group in which carriers were not identified.

The strains of *Salmonella typhi* thus isolated were studied bacteriologically for typing, determination of sensitivity to antibiotics, and so on.

Results

Prevalence. In the 460 cases investigated, 34 carriers (7.4 per cent) were discovered. According to British studies, it is possible with two fecal cultures to discover up to 72 per cent of the carriers in a given study group; it might therefore be assumed that the proportion found in the present study is considerably lower than the real one that serial fecal cultures might have discovered. In any case, the number found exceeds the classic figures of 3 to 5 per cent.

Age. Table 2 shows the distribution of the carriers by age. It suggests the existence of factors that cause the proportion of carriers to increase with age, particularly after 25. It should be noted that, besides the 34 carriers discovered among the 460 index cases, 8 more were found in families, so that the total number identified comes to 42.

Duration of carrier state. As Table 3 shows, at the time of this report the minimum period recorded for the carrier state was two years; the average period was 3.7 years.

Relationship to time elapsed before treatment. The longer the period between the first symptoms and the start of chloramphenicol

TABLE 3—Duration of Carrier State, Santiago, Chile, 1960-1964.

Time (years)	Number of index cases	Carriers	
		Number	Per cent
1	—	—	—
2	110	6	5.5
3	128	10	7.8
4	113	5	4.4
5	107	11	10.3
6	2	2	100.0
Total	460	34	7.4

treatment, the larger the proportion of carriers (Table 4).

Relationship to seriousness of case. In an attempt to study the possible relationship between the seriousness of the clinical picture and the condition of carrier, the length of stay in the hospital was taken as an index of seriousness. Where there had been a relapse, only the first hospitalization was counted. As may be seen in Table 5, the proportion of carriers was higher among those who had been hospitalized 20 days or more than among those who had been hospitalized for a shorter period.

TABLE 4—Proportion of Carriers, according to Time Elapsed between Appearance of First Symptoms and Treatment with Chloramphenicol, Santiago, Chile, 1960-1964.

Time (days)	Number of cases treated	Carriers	
		Number	Per cent
Less than 10	220	11	5.0
10 to 19	189	16	8.5
20 or more	51	7	13.7
Total	460	34	7.4

TABLE 5—Proportion of Carriers, according to Length of Stay in Hospital, Santiago, Chile, 1960-1964.

Period of hospitalization (days)	Number of index cases	Carriers	
		Number	Per cent
Less than 20	400	27	6.8
20 or more	60	7	11.7
Total	460	34	7.4

Relationship to relapse. Of the 460 cases studied, relapses had occurred in 85. It is notable that there were four times as many carriers among these cases as in the 375 in which no relapse occurred (Table 6).

Relapse and time elapsed before treatment. Altogether, a relapse rate of 18.5 per cent was observed (Table 7), but no clear relationship could be discerned between the relapse state and the period of time between first symptoms and treatment. With respect to the proportion of carriers among relapsed cases, the figure again increased as the time between the first symptoms and the beginning of treatment increased.

Relationship to biliary disorders. In view of the difficulty in assessing liver symptoms in the absence of exhaustive examinations, a

TABLE 6—Relationship between Relapse and the Carrier State, Santiago, Chile, 1960-1964.

Relapse	Number of cases	Carriers	
		Number	Per cent
Occurred	85	16	18.8
Did not occur	375	18	4.8
Total	460	34	7.4

TABLE 7—Relapse and Time Elapsed between Appearance of First Symptoms and Treatment, as Related to the Number of Carriers, Santiago, Chile, 1960-1964.

Time (days)	Number of cases	Relapses		Carriers	
		Number	Per cent	Number	Per cent
Less than 10	220	36	16.4	7	19.4
10 to 19	189	34	18.0	7	20.6
20 or more	51	8	15.7	2	25.0
Unknown	—	7	—	—	—
Total	460	85	18.5	16	18.8

simple history was taken to establish a very elementary scale of symptoms:

Slight or doubtful disorders: intolerance for certain greasy foods.

Moderate disorders: accentuated or characteristic biliary dyspepsia.

Serious disorders: presence of hepatic colic; definite diagnosis, including a history of cholecystectomy (four cases).

It is striking that, when this scale was used on the 460 cases, the proportion of carriers among cases with such disorders was twice as high (8 per cent) as in the 158 cases without them (Table 8); it is also noteworthy that there is no significant difference between an absence of such disorders and slight ones, but that as the intensity increases the number of carriers increases accordingly. In the 184 cases with serious disorders the proportion of carriers was three times as high as among healthy women.

This finding leads to conjecture about the possible etiologic association between typhoid fever and cholecystitis. It might well be asked whether typhoid antecedents should not be investigated and fecal cultures made in all cases of cholecystitis. It may also be wondered whether the association of cholecystitis and typhoid antecedents should not be considered a surgical indication for cholecystectomy.

Impact on the family group. To measure the impact of the carrier on the family group, the typhoid history subsequent to the episode of the index case in the family was investigated in 4,164 contacts, of whom 228 had been exposed to a proven carrier. The re-

TABLE 8—Relationship between Vesicular Disorders and Carrier State, Santiago, Chile, 1960-1964.

Vesicular disorders	Number of cases investigated	Carriers	
		Number	Per cent
Absent	158	6	3.8
Slight	75	2	2.7
Moderate	43	4	9.3
Intense	184	22	12.0
Total	460	34	7.4

maintaining 3,936 contacts served as a control group. As is immediately apparent from Table 9, the prevalence of typhoid fever was almost five times as high in those exposed to a carrier as in those in which no carrier was identified.

TABLE 9—Typhoid in Family Groups Subsequent to the Occurrence of the Index Case, Santiago, Chile, 1960-1964.

Family group	Number of contacts	Typhoid cases	
		Number	Per cent
With proven carriers	228	30	13.1
Without proven carriers	3,936	113	2.9
Total	4,164	143	3.4

Summary

A study of 460 female patients who had been diagnosed as typhoid fever cases and dismissed from the Hospital for Infectious Diseases in Santiago, Chile, during the period 1960-1964 was made for the purpose of determining the rate of *Salmonella typhi* carriers among them. All of the patients had been treated with chloramphenicol during the acute stage of the disease.

Over a two-year period more than 3,000 home visits and nearly 2,000 fecal cultures were made to detect carriers among both the index cases and their suspect contacts. Thirty-four carriers (7.4 per cent) of a minimum duration of two years and an average of 3.7 years' duration were detected, and another eight carriers were found among the contacts.

Attention is drawn to the following associations: the proportion of carriers increases with age and depending on the length of time elapsed between the first symptoms and treatment; the proportion is significantly higher when there has been a relapse; there is observable association between being a carrier and the presence of biliary disorders.

The proportion of typhoid fever among contacts exposed to a proven carrier was almost five times higher than among the families in which no carrier was detected. □

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