J. Hyg., Camb. (1960), **58**, 263
Printed in Great Britain

Heredity, infection and chemoprophylaxis in rheumatic carditis: an epidemiological study of a communal settlement

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(*Received* 16 *March* 1960)

INTRODUCTION

Children with a strong family history of rheumatic heart disease are peculiarly at risk (Wilson & Schweitzer, 1954), but it has been very difficult to separate the effect of the family genes from that of the family environment (Bywaters, 1959). On the other hand, children with no known family trait may develop rheumatic fever if exposed to frequent streptococcal sore throats. Under the semi-institutional society of the Israeli kibbutz (Spiro, 1956) both groups of children are equally (and heavily) exposed to infections and their relative susceptibilities may be studied under controlled conditions.

The present paper describes the situation in a settlement with a high prevalence of rheumatic heart disease and a long history of streptococcal sore throats, in which an attempt was made to break the vicious circle of infection by mass chemotherapy.

MATERIAL

The kibbutz

Kibbutz S. is a farming settlement of 373 souls established 12 years. At the beginning of this study the community comprised 166 adults, 80 agricultural trainee youths, 104 children aged 18 months to 10 years and 23 infants. Situated in the centre of the country, near Beersheba, the kibbutz enjoys a fairly hot, dry climate for 9–10 months of the year. Being far to the left politically (*Mapam*), there is a strict social framework in which the children are reared communally (cf. Smilansky, Weintraub & Hanegbi, 1960). Married couples occupy small apartments, but all adults eat in a communal dining room. A number of older girls (aged 17–20) and married women are assigned to duties in the children's houses as nursemaids, i.e. nursery teachers, helpers, cleaners and so forth.

Children's houses are modern, even luxurious, airy buildings and comprise schoolroom or playroom, bedrooms for three to five children, dining room, toilet and washing facilities. The children of each house represent an age class of school or kindergarten level.

The children. Attention was directed mainly to the 104 children aged 1½–10 at the beginning of this study. For over a year the whole population, especially the children, had suffered from endemic streptococcal sore throat and otitis media

with, latterly, some 10–30 new infections each month. The experience of the eighty-eight children aged 4–10 is given in Table 1. Each new infection received prompt treatment with penicillin (aureomycin in the few cases of patients sensitive to penicillin) but it was not uncommon for a child to have 3–4 attacks in a year.

Thirty children with proven or probable rheumatic heart disease (*vide infra*) henceforth referred to as 'prophylactics' received continuous chemoprophylaxis both before and throughout the present study. Twenty-five of them took oral

Table 1. *Previous history of infections in children aged* 4–10 *years*

Attacks per year ...	0–1	2–3	3+	Totals
Acute sore throat	54	16	18	88
Acute otitis media	76	1	11	88

Table 2. *Child population by house, age group and prophylaxis status*

House ...	I	II	III	IV	V	VI	VII	Total
Age* (years)	1½–3	3–4	4–5	5	6–7	8	9–10	1½–10
No. children	6	12	15	17	18	17	19	104
No. receiving penicillin regularly	0	4	3	3	9	6	5	30
No. per bedroom	3	3	3	4–5	4–5	3	4	3–5

* At commencement of observation period.

penicillin 200,000 units daily under supervision, four received an injection of 600,000 units of benzathine penicillin every 3 weeks and one, allergic to penicillin, received 0·5 g. sulphadiazine daily. These children, like their peers, suffered frequent throat infections and were given additional chemotherapy as necessary. Table 2 shows the distribution of all 104 children over the age of 1½, by house, age and prophylaxis status.

METHODS

Medical care

The kibbutz boasts a trained nurse and two aides as well as a resident, though part-time, doctor. All cases of illness or suspicion of illness, are referred by parent, nursemaid or teacher to the nurse who decides whether to give symptomatic treatment or to refer the case to the doctor. A mild sore throat in an adult might be treated with sulphonamides on the nurse's own responsibility; with children, the doctor's opinion was always sought.

Medical records

Before the present study, records were incomplete, although there were full notes on all hospital investigations and the nurse kept a log-book of all injections. During this investigation, all diseases, however trivial, were recorded and a detailed note made of any antibiotic given. To standardize comparisons, analysis is made here only of those diseases commencing during the 15 days preceding each throat swab. Where swabs were taken at regular fortnightly intervals, all incidents

are included. On eight of the twenty-five occasions there were gaps of a few days or more between the fortnightly periods.

Diagnosis of heart disease

Children with suspected systolic murmurs, detected after an acute illness or at a routine examination, were referred to a consultant pediatrician for his opinion. All cases were screened by a radiologist and subsequently re-examined by a specialist in pediatric cardiology. Of forty children so referred, twenty-four were classified by all three consultants as cases of rheumatic heart disease and in a further six there was sufficient doubt to warrant the giving of chemoprophylaxis.

Adult cases were classified on the basis of history, often several hospitalizations and cardiologist's opinion. Similarly, suspected cases picked up at routine examination were referred to a cardiologist. There were twenty-seven proven cases in adult parents.

Bacteriological methods

Throat swabs were taken of all children, all 'nursemaids' (i.e. adults working with children) and a variable number of other adults, on twenty-five occasions between 6 January 1958 and 8 March 1959. These occasions are designated by the letters A, B, C, ..., Y on the graphs and in the tables.

The swabs were taken by the same technician, usually in the forenoon, and were immediately inserted into transport medium contained in the tube (Holmes & Lermitt, 1955). The medium consisted, per litre, of brain heart infusion (Difco), 37·5 g.; agar, 12·5 g.; gentian violet, 10 ml. of a 1:10,000 solution; sodium azide, 10 ml. of a 1·25 % solution. About 2 ml. was placed in the bottom of each swab tube.

On receipt at the laboratory, the swabs were incubated at 37° C. overnight and the next day plated out on 5 % rabbit blood in brain heart agar (Difco) with the addition of 1 p.p.m. gentian violet. Plates were incubated aerobically and inspected after 24 and 48 hr. Typical colonies showing β-haemolysis were transferred to brain heart broth or subcultured on to blood agar to obtain pure cultures. Suspected colonies were examined for their typical growth in brain heart broth, checked by microscopy and again for typical haemolysis on blood agar and their sensitivity to bacitracin (Maxted, 1953).

In a preliminary survey of 200 consecutive strains of bacitracin-sensitive β-haemolytic streptococci, only one failed to show precipitation with Lancefield Group A antiserum. Sensitivity to bacitracin was subsequently taken to be the criterion for diagnosis of *Streptococcus pyogenes*. Typing was not performed.

Mass chemotherapy

(*a*) *Penicillin*. An attempt was made to eradicate the streptococcal reservoir in the nose and throats of the community by mass chemotherapy. All kibbutz members above the age of 1 year, with twenty-seven exceptions, received a single injection of 'Durabiotica forte' (Teva), 1·2 mega units for adults and children over the age of 10, half the dose for younger children. The 'Durabiotica forte' consisted

of 300,000 units crystalline, 300,000 units procaine and 600,000 units benzanthine, penicillin, the combination being used in order to attain a high initial bactericidal level. The exception, four children and twenty-three trainees and adults, who showed conjunctival sensitivity to a drop of penicillin, received 10 days' intensive sulphonamide or tetracycline therapy.

Streptococci isolated subsequently, as well as all strains from children receiving 'prophylaxis', were examined for their sensitivity to penicillin by the disk method, using Griffith type strains as controls.

(*b*) *Sulphamethoxypyridazine.* When the effect of mass penicillin had worn off (*vide infra*), a second trial was made using sulphamethoxypyridazine (kindly donated by Lederle and Company in the form of 'Lederkyn'). This was given in two series. The first consisted of 7 days' therapy for the whole community and a further 7 for children. After a 3-week interval, the second series was given, to children only, for 28 days. The dose was 0·5 g. (one tablet) per day for adults and a quarter to half that amount for children according to weight. In the second series, when the sulphamethoxypyridazine was given only to children, different dosage schedules were tried without affecting the results.

A number of strains of *Str. pyogenes* isolated during the period of sulphamethoxypyridazine therapy were tested for their sensitivity to sulphanilamide by the disk method using 'Roskilde' (Denmark) disks equivalent to 10 mg. of the drug.

Terminology

(*a*) *Carrier rates*, as used in the present paper, refer to the percentage of children or adults from whose throat-swabs was isolated *Str. pyogenes*.

(*b*) *Upper respiratory infections* comprise all cases of 'sore throat', 'tonsillitis', 'pharyngitis' and 'acute otitis media' in children, who reported to the nurse and/or physician during the 15 days preceding the taking of the throat swabs. It is unlikely that any clinically recognizable case escaped combined attention of the 'throat conscious' nursemaids, teachers and parents. The streptococcal aetiology of most, but not all, of these infections, was confirmed by culture.

RESULTS

A. *General results*

The high streptococcal carrier rates during the first three examinations, averaging 28 % in children and 24 % in adults, are shown in Fig. 1, as are the relatively high numbers of upper respiratory infections in children. Examinations were carried out approximately each fortnight, the only major gap being in October and November due to the holidays and the wait for supplies of sulphamethoxypyridazine.

Mass penicillin chemotherapy given directly after Examination C caused an immediate fall in the carrier rates to zero (Fig. 1) and a marked drop in the numbers of infections. The carrier rates remained low for 3 months and only began to rise significantly in the fourth month. At the beginning of April (between Examinations F and G), during the Passover holidays, the kibbutz entertained some 200 visitors and many of its own members paid visits of a day or more to friends and

neighbours in other kibbutzim. The result of this social intercourse was eight cases of sore throat in the children and a temporary rise in their carrier rate but no virulent strain of streptococcus established itself in the community. Streptococci isolated both during this period and subsequently, showed no diminution in their sensitivity to penicillin when compared with the type strains.

Carrier and infection rates rose during the summer months to a peak in September and October. After administration of sulphamethoxypyridazine to all members of the kibbutz in the second half of November (Fig. 2) the carrier rates fell to 9%

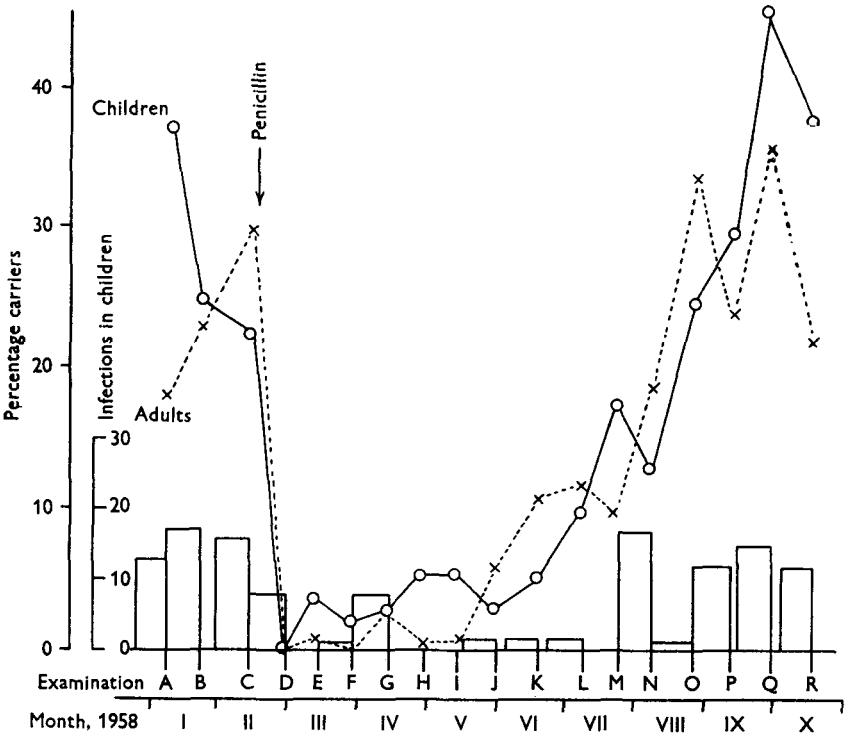

Fig. 1. Streptococcal carrier rates in children and adults and upper respiratory infections in children: before and after mass penicillin administration.

only to rise immediately afterwards. The second period of sulphonamide therapy, given to the children, caused a similar fall in rates and cases but on this occasion, both the carrier rates and the numbers of sore throats began to rise *during* the period of chemotherapy.

After March 1959 (Examination Y) the accuracy of registration declined and penicillin was administered with a freer hand than previously. The experiment was thus terminated.

B. *Results in children*

This section is concerned with children aged 1½–10 at the beginning of the survey. They have been divided into two groups: 'prophylactics', the thirty children receiving continuous prophylaxis and 'others', the remaining seventy-four children.

https://doi.org/10.1017/S0022172400038377 Published online by Cambridge University Press

(1) *Influence of heredity*

Where one or both parents suffer from rheumatic heart disease, half of their children over the age of 18 months are affected (Table 3). Where the parents are free of heart disease, the prevalence in their offspring is 19%. Infants under 18 months of age, whose fate is unknown, are ignored in this comparison (cf. Gauld & Read, 1940).

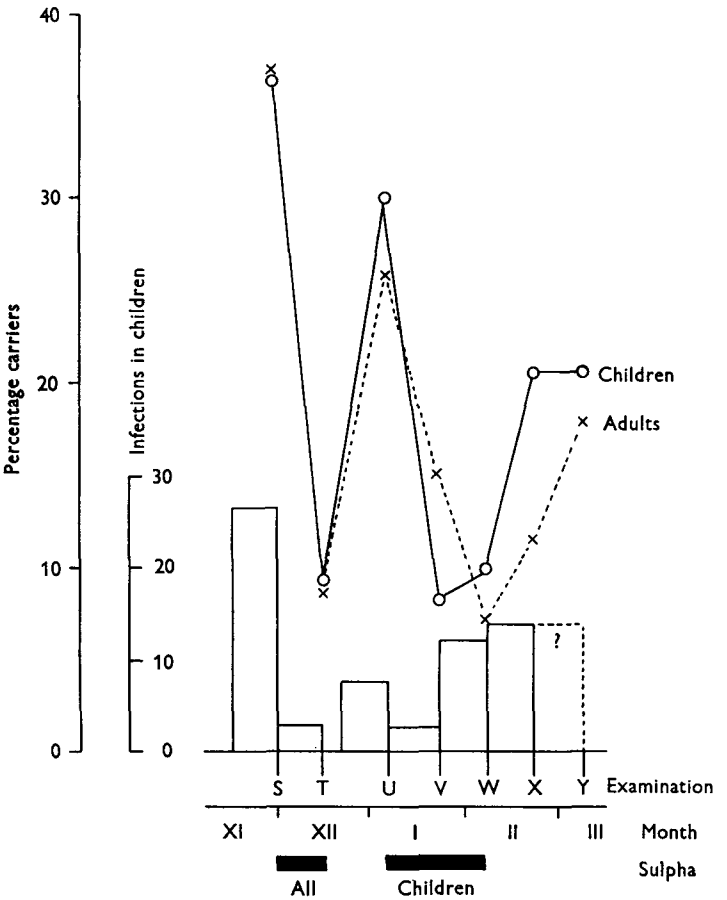

Fig. 2. Streptococcal carrier rates and infections: effect of giving sulphamethoxypyridazine.

Table 3. *Rheumatic heart disease in children and their parents*

Affected parent ...	Either	Both	Neither	Unknown	Totals
No. families	19	4	45	8	76
'Prophylactic' children	15	2	11	2	30
'Other' children	12	5	47	10	74
Infants	7	1	15	0	23
Total siblings	34	8	73	12	127

Comparing prevalence in children of families with one or both parents affected, with those from families with neither parent affected (neglecting infants), $\chi^2 = 10{\cdot}42$ D.F. $= 2$, $P \approx 0{\cdot}005$.

https://doi.org/10.1017/S0022172400038377 Published online by Cambridge University Press

The difference in prevalence between the two types of families is significant at the 0·5 % level. When the figures are standardized for the numbers of families, i.e. when prevalence is calculated on the basis of 100 families in each group, they become significant at the 0·1 % level and this holds true when correction is made for the small differences in family size.

Thus the prevalence of rheumatic heart disease in the offspring of affected parents is over $2\frac{1}{2}$ times that in the children of parents without rheumatic heart disease, living under the same roof under identical conditions.

Table 4. *Positive throat swabs* in children during 4 months after mass penicillin*

Group ...	'Prophylactics'			'Others'		
Examinations ...	A–B–C	D, E–K	Totals	A–B–C	D, E–K	Totals
Positive	23	7	30	60	22	82
Negative	66	227	293	143	528	671
Totals	89	234	323	203	550	753
Significance	$\chi^2 = 39{\cdot}56$, $P \ll 0{\cdot}001$			$\chi^2 = 99{\cdot}80$, $P \ll 0{\cdot}001$		

* For Beta haemolytic streptococci, group A.

Table 5. *Effect of mass penicillin on upper respiratory infections in the two groups of children*

(Unit is child-fortnight.)

Group ...	'Prophylactics'				'Others'			
Examinations ...	A–B–C	D, E–K	L–O	P–S	A–B–C	D, E–K	L–O	P–S
U.R.I. attacks	32	7	5	14	14	12	16	51
U.R.I. negative	58	233	115	106	189	580	280	245
Totals	90	240	120	120	203	592	296	296
Significance	$\chi^2 = 66{\cdot}9$, $P \ll 0{\cdot}001$		$\chi^2 = 4{\cdot}6$, $P < 0{\cdot}05$		$\chi^2 = 9{\cdot}6$, $P < 0{\cdot}005$		$\chi^2 = 20{\cdot}6$, $P \ll 0{\cdot}001$	
	—	$\chi^2 = 0{\cdot}4$, N.S.		—	—	$\chi^2 = 7{\cdot}4$, $P < 0{\cdot}01$		—

N.S. = not significant.

(2) *Effect of mass penicillin therapy*

(*a*) *On carrier rates.* The general effect shown in Fig. 1. is further analysed in Table 4. For the few months following the mass penicillin administration the number of positive throat swabs was significantly lower in both groups with no marked difference between them.

A similar comparison of positive throat swabs obtained in Examinations D to K with those from Examinations L to O, shows a highly significant rise in both groups ($P < 0{\cdot}001$). The further rise in carrier rates during Examinations P to S is also highly significant. Children receiving continuous oral penicillin chemoprophylaxis showed no difference in carrier rate from children who only had the one injection.

(*b*) *On upper respiratory infections* (U.R.I.). The greater immediate effect of the penicillin was on the 'prophylactics' (Table 5), perhaps by cutting off their sources of infection. Although they showed a significantly higher number of sore throats

than the 'other' children during the first three examinations ($\chi^2 = 43{\cdot}6, P \ll 0{\cdot}001$) there was subsequently no difference between the two groups. The continued prophylaxis failed to reduce the incidence of sore throat.

The incidence of respiratory diseases, unidentified pyrexias and other infectious diseases was the same in both groups of children over the whole period of observation (Table 6).

Table 6. *Non-streptococcal diseases in children*

Group ...	'Prophylactic'		'Others'	
No. children ...	30		74	
Attacks of	Observed	Expected	Observed	Expected
Respiratory disease*	34	38	97	93
Unidentified pyrexia	23	19·5	45	48
Infectious hepatitis	7	3·5	5	8·5
Skin diseases	1	0·6	1	1·5

* Bronchitis, bronchiolitis, pneumonia and cough with fever.

Table 7. *Effect of sulphamethoxypyridazine on streptococcal carrier state*

Group ...	All children					'Others'				
Examinations ...	S	T	U	V	W	S	T	U	V	W
Sulphamethoxypyridazine	−	+	—	+	+	−	+	−	+	+
Positive	34	9	28	8	9	22	7	18	7	8
Negative	59	85	66	88	83	44	59	49	61	56
Total children swabbed	93	94	94	96	92	66	66	67	68	64

(3) *Effect of sulphamethoxypyridazine*

(*a*) *On carrier rates.* In some of the examinations, the numbers of positive swabs were small and comparisons have therefore been made between all children ('prophylactics' and 'others') and 'others' (Table 7). Comparing the carrier rates immediately before sulphonamide therapy (Examinations S and U) with those during and immediately after therapy (T and V–W), there is a significant reduction both for all children ($P \ll 0{\cdot}001$) and for 'others' ($P < 0{\cdot}005$). It may thus be assumed that the drug was effective also in the case of 'prophylactic' children. The efficiency of the sulphamethoxypyridazine was somewhat greater in the first series than in the second (Table 7).

Unlike penicillin, the effect was short-lived (Fig. 2). There were no significant differences in the carrier rates of the two groups of children between Examinations S (before sulphonamide therapy) and U (2 weeks after). The rise in carrier rates after stopping the drug (T *versus* U) was significant.

(*b*) *On upper respiratory infections.* There is a significant drop in infections amongst children not on regular chemoprophylaxis ($P < 0{\cdot}001$) when the total incidence during and after sulphamethoxypyridazine (Examinations T, V, W) is compared with that before (Examinations P, Q, R, S). Twenty-six of 104 children suffered an episode of infection during the fortnight preceding sulphonamide therapy (S)

and only three, during the sulphonamide period (T). Thus the reduction in incidence appears to be significant but the numbers are too small for analysis.

For the second period of sulphamethoxypyridazine therapy, the results are set out in Table 8. The numbers of sore throats increased, also not significantly, during the administration of the drug (V, W). Thus, at best, the drug had no effect on sore throats when given only to the child population. This may be associated with the appearance of sulphonamide resistant strains of *Streptococcus pyogenes* during Examination V. Five of twenty-one strains tested were resistant.

Table 8. *Effect of sulphamethoxypyridazine on upper respiratory infections*

Group ...	All children			'Others'		
Examination ...	U	V–W	Totals	U	V–W	Totals
Sulphamethoxypyridazine	−	+	− +	−	+	− +
U.R.I. attacks	7	15	22	7	12	19
U.R.I. negative	97	89	186	67	62	129
Totals (child-fortnight)	104	104	208	74	74	148
Significance	$\chi^2 = 3{\cdot}25$, N.S.			$\chi^2 = 1{\cdot}51$, N.S.		

N.S. = not significant.

Table 9. *Correlation between streptococcal carrier rates and upper respiratory infections*

(All children, all examinations.)

Examinations	Child-fortnights	Carriers	U.R.I.
A, B, C	292	83	45
D, E, F, G	394	9	16
H, I, J, K	390	20	4
L, M, N, O	360	59	21
P, Q, R, S	331	121	56
T	94	9	3
U	94	28	7
V, W	188	17	15
X, Y	180	38	14

Coefficient of correlation, $r = \dfrac{\sum_{i=1}^{n}(x_i-\bar{x})(y_i-\bar{y})}{\sqrt{\left[\sum_{i=1}^{n}(x_i-\bar{x})^2 \sum_{i=1}^{n}(y_i-\bar{y})^2\right]}} = 0{\cdot}9335,$

and the t test of significance, $t_{n-2} = r\sqrt{\dfrac{n-2}{1-r^2}}, t_7 = 6{\cdot}89$, thus $P < 0{\cdot}001$.

(4) *Correlations between carrier rates and upper respiratory infections*

For the whole child population during the total period of observation there is a highly significant correlation between the carrier rates and the episodes of infection (Table 9). This correlation also holds good when absolute numbers are used rather than percentages and each of the twenty-five examinations is considered separately ($r = 0{\cdot}6$, $t_{23} = 3{\cdot}6$, $P < 0{\cdot}002$).

https://doi.org/10.1017/S0022172400038377 Published online by Cambridge University Press

The correlation was not significant for the 'prophylactic' children taken separately ($r = 0{\cdot}53$), but was significant in the case of the 'others' ($r = 0{\cdot}87$, $P = 0{\cdot}02$). The correlation coefficients were practically unchanged when the numbers of U.R.I. in the following fortnight, rather than the preceding one, were used for comparison.

Before mass penicillin therapy (Examinations A, B, C) the children receiving prophylaxis suffered thirty-two upper respiratory infections in ninety child-fortnights, a much higher rate than in the other children (14 episodes in 203 child-fortnights). For the whole twenty-five examinations, the mean frequency was $2{\cdot}5 \pm 1{\cdot}8$ attacks for the 'prophylactic' child and $1{\cdot}6 \pm 1{\cdot}5$ for the 'other' child. When allowance is made for the excess number of attacks in the first three Examinations, A, B, C, the mean-frequencies for the subsequent twenty-two examinations become $1{\cdot}3 \pm 1{\cdot}2$ and $1{\cdot}4 \pm 1{\cdot}4$ respectively.

Table 10. *Comparison between streptococcal carriage and upper respiratory infection in individuals*

Positive throat swabs	0	1	2	3	4	5	6+
Mean no. U.R.I. attacks	0·25	1·0	1·05	1·80	1·33	2·42	1·7
Mean no. U.R.I. attacks	0	1	2	3	4–5	—	—
Positive throat swabs	2·0	3·1	3·2	3·1	4·3	—	—

Table 11. *Streptococcal carrier rates by house-age*

(All examinations.)

House ...	I	II	III	IV	V	VI	VII	Totals
Age* (years)	1½–3	3–4	4–5	5	6–7	8	9–10	1½–10
Child-fortnights	118	275	348	395	412	400	376	2,324
Positive swabs	15	36	62	76	76	71	50	383
Percentage positive	13	13	18	19	18	18	13	16

* At commencement of period of observation.

For individual children there was no clear rise in U.R.I. with increased carrier rate, nor the converse, as is illustrated in Table 10.

(5) *The effect of age and house*

As the children are raised in peer groups, these two factors cannot be separated. The grouping of the children by age and house was shown in Table 2. There is a tendency for the carrier rate to increase with age with a peak at 8 years and subsequent drop (Table 11) and the same trend exists for 'prophylactic' and 'other' children separately, although in no case are the differences statistically significant. Ages are given as those at the commencement of the study, the children being 14 months older at its completion.

Before mass penicillin, carrier rates were significantly higher—50% amongst the 4–5 years old, both for total population ($P < 0{\cdot}01$) and for 'others' ($P = 0{\cdot}025$), while the rate for the 9–10 years old was lower (26%) than expected. This age difference did not hold for the 'prophylactic' children.

Mass chemotherapy, both penicillin and sulphonamide, abolished the age effect, which did not return until Examinations U–X and Y. At this point, the 9-year-old children (the 8-year-old children at the start of the investigation) showed significantly higher carrier rates.

It was thus not possible to demonstrate a consistently susceptible age group nor a 'dangerous' house.

C. *Results in adults*

Of the 166 adults, 133 were registered on our list, but participation varied between 55 and 100 after the first occasion and was only 35 at Examinations M and Q. Of the 20 nursemaids, 15 or more were swabbed on each occasion. The fall and rise in carrier rates, paralleling that of the children, is shown in Figs. 1 and 2. Morbidity data was too patchy for analysis.

The mean carrier rate for adults, during all twenty-five examinations, was 15·5%, just significantly higher ($P = 0{\cdot}05$) than that for nursemaids. This difference was mainly manifest at the time of greatest carriage (Examinations P, Q, R, S) when the nursemaids showed a mean rate of 20% compared with 37% for the other adults.

Table 12. *Correlations between streptococcal carrier rates in children and adults*

Examination ...	A, B, C	D–G	H–K	L–O	P–S	T	U	VW	XY	Correlations
Children, % carriers	28	2	5	16	37	10	30	9	21	—
Adults, % carriers	24	1	5	21	32	9	24	11	15	$r = 0{\cdot}95$, $P < 0{\cdot}001$
Nursemaids, % carriers	23	1	3	16	20	10	15	10	16	$r = 0{\cdot}88$, $P = 0{\cdot}002$

After the drop in carrier rate following mass penicillin, the subsequent rise (comparing Examinations L, M, N, O with P, Q, R, S) was not significant in nursemaids, although highly so ($P < 0{\cdot}005$) in other adults. The effect of the first period of sulphonamide therapy (Examinations S, T) was highly significant but the figures for the nursemaids were too small to be tested separately. During the second period of sulphonamide therapy, when only the children received the drug (Examinations U and V, W), the drop in the carrier rate was again not significant in the nursemaids, although highly so ($P < 0{\cdot}005$) in the other adults.

D. *Adults and children*

The close similarity between the streptococcal carrier rates in children and adults is apparent from the graphs. The drop in adult carrier rates after Examination U when only children received sulphonamide and their subsequent rise, following that of the children, would seem to indicate that the adults are infected by the children.

This relationship is analyzed in Table 12 for nine groups of examinations. The correlation for adults and children is high ($r = 0{\cdot}95$, $P < 0{\cdot}001$) and for adults,

other than nursemaids, $r = 0{\cdot}94$. For nursemaids, the correlation is positive but somewhat less marked ($r = 0{\cdot}88$, $P = 0{\cdot}002$). Thus throughout the study, children appear to form the reservoir of infection for the adult population. During the periods of sulphamethoxypyridazine therapy (Examinations S–Y) the correlation between carrier rates of children and of adults other than nursemaids is high, $r = 0{\cdot}90$, while that between children and nursemaids is very low, $r = 0{\cdot}37$. It is not possible to say whether adults are infected more than nursemaids due to intimacy of contact (e.g. kissing children) or to increased susceptibility.

DISCUSSION

The uncertainty as to the role of heredity in susceptibility to rheumatic heart disease is due to the difficulty of separating environmental from genetic influences (Annotation, 1955; Bywaters, 1959). Diamond (1957) attempted to eliminate the environmental factors by examining the effect of heredity in four different environments, and Wilson & Schweitzer (1954) have followed the children of affected parents, rather than the other way round. These studies, as those of Wilson (1940), Stevenson & Cheeseman (1956), Saslaw (1958) and others, make a convincing case for the importance of genetic factors. They are open to bias, however, due to the method of selection of families which must, of necessity, include an affected child, while the controls are chosen on a different basis (cf. Gauld & Read, 1940; Annotation, 1955).

The unique social organization of the kibbutz, sharing characteristics of both family and institution, provides rigidly controlled conditions for the study of children of parents with and without rheumatic heart disease. Children of these two groups are mixed with their peers, share the same living and sleeping quarters, the same diet and exposure to streptococcal infection and enjoy the same medical care and diagnostic facilities.

There was no difference in streptococcal carrier rates between the two groups (cf. Price, Lee, Harshman, Schaub, Matanoski, Ibler, Lachaine, Ferencz, Guild, Bramley & Weaver, 1958) in spite of continuous chemoprophylaxis in children with heart disease. Children who developed rheumatic carditis were more susceptible to streptococcal infections than other children, that is, they developed more clinical infections under standard conditions of exposure. More than half of them were the offspring of affected parents, and showed a prevalence $2\frac{1}{2}$ times greater than control children. This susceptibility to streptococci did not extend to other, non-streptococcal, infections.

The high streptococcal carrier rates before mass chemotherapy and after its effects had worn off, may be due, in part, to the sensitivity of the swab enrichment method (Stoppelman, 1959), although rates of 60% (Quinn, Denny & Riley, 1957) and 38% (Poskanzer, Feldman, Beadenkopf, Kuroda, Drislane & Diamond, 1956) have been reported from schoolchildren under endemic conditions, and Zanen, Ganor & Van Toorn (1959) found carrier rates of up to 60% in normal children in an institution. Our material illustrates the failure of even prompt treatment of clinical cases to limit streptococcal spread and control the attack rate in large

groups of children. The success of the mass penicillin treatment was much greater than that reported from studies in American air-force personnel (Davis & Schmidt, 1957; Morris & Rammelkamp, 1957) both in extent and duration. On the other hand, sulphamethoxypyridazine, recently favoured because of its convenience (Johnson, Mathews & Stollerman, 1959), proved no more effective than other sulphonamide prophylaxis and less so than oral penicillin (Schulz & Frank, 1958).

Perhaps the most disturbing fact was the failure of continuous prophylaxis with oral penicillin to reduce streptococcal infections below those of the control children. It is known that oral penicillin does not abolish the streptococcal carrier state (Cruickshank & Glynn, 1959) nor completely prevent infection (Markowitz, 1957; Breese & Disney, 1958) and it may be that the dose of 200,000 units given daily was too low (Wehrle, Feldman & Kuroda, 1957). Be this as it may, the complete absence of any effect supports the case for increased susceptibility of the rheumatic child to streptococcal infection, in addition to (? because of) his hereditary susceptibility to rheumatic heart disease.

SUMMARY

1. Children and their parents in a communal settlement (kibbutz) were followed for 14 months with special regard to the influences of streptococcal carrier rate, streptococcal infections, chemotherapy and heredity on the pattern of rheumatic heart disease.

2. Children with proven or probable heart disease showed the same streptococcal carrier rates as controls in spite of continued chemoprophylaxis with oral penicillin.

3. A single injection of penicillin, given to all kibbutz members on the same occasion, reduced the streptococcal carrier and infection rates to zero and maintained a marked drop for 3 months. Thereafter, the rates rose to higher levels than before. Courses of sulphamethoxypyridazine ('Lederkyn') given first to the total population and then to children only, caused only temporary interruption in the attack rate.

4. The prevalence of rheumatic heart disease in children of parents themselves affected was $2\frac{1}{2}$ times greater than in controls exposed to the same environmental risks.

5. Affected children were more susceptible to streptococcal infections than controls with identical exposure.

Grateful thanks are due to Miss Pearl Weiskopf, B.Sc., for the statistical analysis. Without the close collaboration of Dr J. Yauluss, Nurses Tova and Ziva and the members of Kibbutz S this study would have been impossible. Thanks are also due to Lederle Laboratories Department of Cynamid International and their Israeli agent, Dr L. Goldshmidt, for the gift of 'Lederkyn', and to Mrs Rachel Kosh for help beyond the call of her secretarial duties.

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