

## Absence of epidemicity of severe leptospirosis in Barbados

S. BENNETT<sup>1</sup> AND C. O. R. EVERARD<sup>2</sup>

<sup>1</sup> *Tropical Health Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT, UK*

<sup>2</sup> *Leptospira Laboratory, Enmore 2, Lower Collymore Rock, St Michael, Barbados*

(Accepted 30 August 1990)

### SUMMARY

The possibility of micro-epidemics of severe leptospirosis occurring on the island of Barbados was investigated by examining the space-time clustering of the disease in 212 laboratory-confirmed cases admitted to Queen Elizabeth Hospital, Bridgetown, over a 7-year period. A series of 109 patients with symptoms compatible with leptospirosis but shown to be otherwise by laboratory examination were also examined for comparison. No significant space-time clustering was found among the leptospirosis cases, indicating no evidence for micro-epidemics. By comparison, statistically significant clustering was apparent among the smaller non-leptospirosis series. Possible explanations for the absence of observed micro-epidemics of leptospirosis are discussed.

### INTRODUCTION

Leptospirosis is endemic in Barbados, but severe illness due to the infection is relatively rare. Thus, although about 18·5% of urban and rural householders have leptospiral antibodies at any one time, and some occupational groups have even higher proportions (for example 58% of outdoor labourers) [1], on average only 32 people (0·13 per 1000 population) are hospitalized with the disease each year (Everard, unpublished observations). It is not known why some of those infected develop severe disease whereas most infections are mild or even subclinical. One possible explanation is that the more pathogenic serovars of *Leptospira* are circulating only for limited periods in specific areas. This could lead to 'micro-epidemics' in which a number of severe cases arise in close proximity to each other over a short space of time. Because leptospirosis is a zoonosis, transmission generally taking place from animal to human rather than from human to human, micro-epidemics might be more difficult to detect than in infections acquired directly from another person.

Clearly, because the population is more dense in some areas than in others, there will be an apparent clustering of cases when plotted on a map ('clustering in space'). Similarly, because of the seasonal association with rainfall, and possibly with crop harvesting and some other outdoor activities, there will also be clustering when the cases are marked on the calendar ('clustering in time'). However, micro-epidemics are demonstrated not by such clustering in space or

time alone but by clustering in both space and time together, i.e. a number of cases occur in the same place, at the same time, where 'same' has some convenient definition. We report here on a search for micro-epidemics of leptospirosis in Barbados.

#### MATERIALS AND METHODS

##### *Subjects*

Of the 242 non-paediatric patients with laboratory-confirmed severe leptospirosis who were admitted to the Queen Elizabeth Hospital (QEH), Bridgetown, Barbados between late 1979 and the end of 1986, 212 (88%) had complete records and were included in this study. There were, in addition, 133 non-paediatric patients who were admitted over the same period with the same provisional diagnosis but in whom a diagnosis of leptospirosis was not confirmed in the laboratory. One hundred and nine of these (82%) had complete records, and they were studied for comparison. A further 37 patients with the same provisional diagnosis who were positive for HBsAg and 21 who died before the diagnosis could be laboratory-confirmed were excluded. The provisional diagnosis of all of the above patients was 'pyrexia of unknown origin (PUO) with clinical symptoms compatible with leptospirosis'. These symptoms usually included headache, nausea, anorexia, vomiting, severe muscular aches and pains, conjunctival suffusion, and for 96% of the leptospirosis cases, obvious jaundice. The QEH is the major general hospital on the island, and the *Leptospira* Laboratory did not confirm any cases among patients referred by any other institution or clinic. Further, since all parts of the island are easily within 2 h drive of QEH over metalled roads, these patients were very likely to represent all the severe cases of leptospirosis on the island. Additional information about the patients, including the distribution of the cases throughout the island over the study period, is given elsewhere [2].

##### *Methods*

Each case was identified by place of residence ('space') and date of onset ('time'). Where possible, the date of onset of illness was obtained by interviewing the subject. Where this was not possible the date of onset was estimated as 5 days before admission.

Clustering was evaluated using the method of Knox [3] by examining all possible pairs of cases, there being 22366 ( $= 212 \times 211/2$ ) pairs with leptospirosis and 5886 pairs without leptospirosis. The place of residence of each case was plotted on a map of Barbados, and numerical co-ordinates measured. A pair of cases was adjudged to be close in space if the places of residence were within a given distance of each other. Seven levels were used: 0.5, 1, 2, 3, 5, 10 and 20 km. Similarly, a pair was adjudged to be close in time if their dates of onset occurred within a given time of each other. Six time intervals were used: 15, 30, 60, 91, 183 and 365 days. These criteria give 42 ( $= 7 \times 6$ ) definitions of 'close together in space and time'. Using the algorithm of Pike and Bull [4], the observed number of pairs which were 'close' according to each definition was counted, and the expected number and its variance under the null hypothesis of no space-time clustering calculated. Clustering would show up as an excess of observed over expected

pairs at the lower time and space intervals. Statistical significance was tested by comparing  $(\text{observed} - \text{expected})/\sqrt{(\text{variance})}$  with a standard normal distribution.

#### RESULTS

Table 1 shows the observed and expected numbers of pairs of leptospirosis cases which were close in space and time, using each of the above-mentioned criteria for closeness. For example, eight pairs of cases occurred within 1 km and 30 days of each other. This is very similar to the expected number of 8.37, given the overall distribution of cases in space and in time, and so provides no evidence of clustering. In fact, whatever definitions of closeness in space or in time are used the observed counts are very close to the calculated expected values. There is no statistically significant difference for any criterion of closeness.

Table 2 shows the same results for the comparison group of non-leptospirosis patients. These showed significant evidence of clustering (as shown by the observed number of pairs being greater than the expected) for distances up to 3 km and time intervals up to 30 days. Clustering can also be discerned (although non-significant) up to 5 km and 60 days.

#### DISCUSSION

The lack of evidence for micro-epidemics of severe leptospirosis over the study period is interesting, given the existence of reservoirs of leptospira in wildlife and domestic animals, the presence of the organisms in alkaline soil and water, and the seasonal association of the disease with rainfall ([5], and Everard and colleagues, unpublished observations) and possibly certain outdoor activities, such as harvesting. Even though the island measures only 450 km<sup>2</sup>, rain does not fall evenly throughout, and this, with the possible existence of epidemics in the animal population, might be expected to lead to micro-epidemics of severe disease among the human population.

A number of possible reasons for this absence of space-time clustering may be advanced. Our unpublished data show that among these hospital patients there is a positive association with outdoor manual occupation, although this cannot always be linked with any specific occupation. Further unpublished survey data from Barbados show that more than 40% of sugarcane workers, 45% of garbage loaders and up to 64% of drain cleaners have leptospiral agglutinins, rates much higher than the general population. The finding that risk is often related to occupation suggests that exposure may frequently occur at the workplace. A household survey in Barbados and Trinidad for leptospiral antibodies was unable to demonstrate any clustering within households [1]. Thus place of residence may be an insensitive measure of the place of infection, especially since commuting is very common on the island. Place of work was not recorded for patients in the present study, but it would clearly be advisable to include it in any future studies of clustering. Even so, it is unlikely that this insensitivity could explain such a complete absence of clustering.

The lack of observed micro-epidemics cannot be explained by the length of the incubation period, which is normally a few days to 2 weeks, well within the

Table 1. *Observed (upper) and expected (lower) cumulative numbers of pairs of cases of severe leptospirosis on Barbados within each space-time classification*

Space (km)	Time (days)						All
	15	30	60	91	183	365	
0.5	1	5	10	13	25	40	137
	2.00	4.18	8.41	12.44	23.27	42.09	
1	3	8	17	25	44	80	274
	4.01	8.37	16.82	24.88	46.54	84.17	
2	15	33	60	100	170	301	994
	14.53	30.35	61.02	90.26	168.84	305.36	
3	29	66	125	189	339	583	1938
	28.33	59.18	118.97	175.98	329.18	595.37	
5	50	117	242	372	664	1170	3922
	57.34	119.77	240.76	356.15	666.18	1204.87	
10	139	301	615	913	1736	3105	10218
	149.39	312.03	627.26	927.87	1735.59	3139.04	
20	296	627	1249	1857	3500	6394	20631
	301.63	630.02	1266.49	1873.45	3504.30	6338.00	
All	327	683	1373	2031	3799	6871	22366

Table 2. *Observed (upper) and expected (lower) cumulative numbers of pairs of non-leptospirosis cases on Barbados within each space-time classification*

Space (km)	Time (days)						All
	15	30	60	91	183	365	
0.5	4*	4	4	5	10	17	63
	1.34	2.29	3.67	5.34	9.72	17.56	
1	8*	10	12	13	22	40	150
	3.19	5.45	8.74	12.72	23.14	41.82	
2	18**	24**	31	40	70	136	457
	9.71	16.62	26.63	38.74	70.50	137.41	
3	29**	42*	58	71	132	246	835
	17.73	30.36	48.66	70.79	128.81	232.80	
5	43	62	97	131	238	442	1544
	32.79	56.14	89.97	130.90	238.18	430.46	
10	70	115	183	260	493	900	3191
	67.77	116.02	185.95	270.52	492.26	889.64	
20	119	203	323	467	853	1537	5455
	115.85	198.33	317.88	462.46	841.51	1520.84	
All	125	214	343	499	908	1641	5886

\*  $P < 0.05$ ; \*\*  $P < 0.01$ .

resolution of the time intervals considered. The exclusion of paediatric cases (aged less than 12 years) is unlikely to have had any effect on this study of general space-time (as opposed to household) clustering. Nor is the exclusion of the small number with incomplete records, due to a variety of reasons, mainly administrative shortcomings and non-participation.

Another possible explanation for lack of clustering is that human infection is acquired, usually indirectly, from animal urine. Leptospire can survive for

several months in natural surface waters and moist soil [6], and their survival would be especially favoured in the coralline soils of Barbados. Heavy rains or floods are likely to flush these organisms to the surface, but a long time may intervene before severe infections are detectable from the same source. Also, in some areas of the island water movement may cause considerable spatial distribution of the organisms.

An alternative, and more likely, reason for absence of clustering is that small outbreaks do arise from a point source but remain undetected because most infections are mild and do not require hospitalization. Certainly micro-epidemics of leptospirosis can occur: three probable cases (two of them fatal) were recorded on a pig farm in Trinidad between August 1981 and February 1982. Twelve of the 13 workers on the farm had leptospiral agglutinins, but these would not have been detected unless an epidemiological follow-up had been undertaken [7]. In another example a small outbreak occurred in Pietracuta, Italy, in July 1984 where 33 cases (caused by serogroup Australis) occurred in people who had drunk or used water from a fountain. It was likely that a hedgehog trapped in a reservoir connected to the fountain was the source [8]. There is no reason to believe that such incidents are unusual. Where the disease is endemic and there is a high background prevalence of agglutinating antibodies (as in Barbados), case rates are more likely to be stable and occur randomly in space and time because humans and animals are exposed to leptospire from an early age and acquire protective antibody while young. The few who become ill might have an unusual exposure history or some physiological/immunological reason for succumbing. Such cases would be unlikely to cluster.

Using similar techniques and broadly similar sample sizes to those used here, highly significant epidemicity has been detected in viral diseases such as poliomyelitis and hepatitis [9] and measles [10]. However, these viral diseases are transmitted person-to-person or via food or drinking water. Only exceptionally is leptospirosis transmitted through direct human contact (sexually or by infected urine) and relatively infrequently through ingesting contaminated food or water. The most likely cause of familial leptospirosis would be contamination of the immediate environment by household animals or rodents. It would be interesting to investigate to what extent human micro-epidemics can be detected in other zoonoses.

In the present study the technique has successfully detected clustering, indicating micro-epidemics, in the smaller comparison series of non-leptospirosis cases, justifying the validity of the method and its power with such a sample size. Examination of case notes indicated that the significant excess in the four cells in the top left-hand corner of Table 2 (< 30 days, < 1 km) could be attributed to three pairs representing three cases of salmonellosis in one family, all at the same address and occurring within 4 days of one another.

#### ACKNOWLEDGEMENTS

This study was supported by the UK Medical Research Council and Overseas Development Administration, and the Barbados Ministry of Health. We are grateful to Debbie Carson for carrying out the computations for this analysis, and

to Peter Smith and Richard Hayes for their helpful comments. We should also like to thank the staff of the *Leptospira* Laboratory for their technical and organizational assistance and Dr C. N. Edwards and colleagues at the Queen Elizabeth Hospital for their clinical expertise.

## REFERENCES

1. Everard COR, Maude GH, Hayes RJ. Leptospiral infection: a household serosurvey in urban and rural communities in Barbados and Trinidad. *Ann Trop Med Parasit* 1990; **84**: 255–66.
2. Edwards CN, Nicholson GD, Hassell TA, Everard COR, Callender J. Leptospirosis in Barbados – a clinical study. *W I Med J* 1990. In press.
3. Knox G. Detection of low intensity epidemics; application to cleft lip and palate. *Br J Prev Soc Med* 1963; **17**: 121–7.
4. Pike MC, Bull D. Knox test for space-time clustering in epidemiology. *Appl Statist* 1974; **23**: 92–5.
5. Damude DF, Jones CJ, White HStC, Myers DM. The problem of human leptospirosis in Barbados. *Trans Roy Soc Trop Med Hyg* 1979; **73**: 169–77.
6. Johnson RC. Leptospirosis. In: Warren KS, Mahmoud AAF, eds. *Tropical and geographic medicine*. New York: McGraw Hill, 1985: 839–43.
7. Everard COR, Ferdinand GA, Butcher LV, Everard JD. Leptospirosis in piggery workers on Trinidad. *J Trop Med Hyg* 1989; **92**: 253–8.
8. Cacciapuoti, B, Cicerone L, Maffei C, et al. A water borne outbreak of leptospirosis. *Am J Epid* 1987; **126**: 535–45.
9. Ederer F, Myers MH, Mantel N. A statistical problem in space and time: do leukaemia cases come in clusters? *Biometrics* 1964; **20**: 626–38.
10. David FN, Barton DE. Two space-time interaction tests for epidemics. *Br J Prev Soc Med* 1966; **20**: 44–8.