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The epidemic cycle of *Chlamydia pneumoniae* infection in eastern Finland, 1972–1987

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SUMMARY

The epidemic cycle of *Chlamydia pneumoniae* infection was examined in two areas in eastern Finland over a period of 15 years, 1972–87. The *C. pneumoniae* IgG antibody prevalence was determined with 5-year intervals in a random sample of the population aged 25–59 years. The total number of sera studied using immunofluorescence was 2387. In 1972 the antibody prevalence was 57% and it increased to 66% in 1977. Over the next 5 years the prevalence decreased to 44% in 1982, but by 1987 it had again increased to 59%. The temporal variation in prevalence was statistically significant ($P < 0{\cdot}001$) and similar for both genders. Throughout the observation period the overall prevalence was 7–11% higher in men than in women ($P < 0{\cdot}01$). The antibody prevalence increased with age, being the highest among the oldest study subjects of both genders. The periods of high and low prevalence alternated in an epidemic cycle ($P < 0{\cdot}001$) of about 10 years.

INTRODUCTION

We have earlier shown that *Chlamydia pneumoniae* was endemic in Finland as early as the late 1950s [1]. The IgG antibody prevalence was 56% among the adult population in rural areas. Exceptionally high *C. pneumoniae* IgG antibody prevalence among the adult population was found in the sparsely populated areas in eastern Finland, where the rates of coronary disease have been and still are higher than in the more densely populated southern and western part of the country [1]. Other outbreaks caused by *C. pneumoniae* were reported in Finland in 1977 and 1987–8 in young males attending military service and also in the general population [2–4]. In Scandinavia the outbreaks of *C. pneumoniae* were documented during 1976–7, 1981–2 and 1987–8 [5, 6].

A recent case-control study in Finland reported a strong association between the high antibody titre to *C. pneumoniae* and both chronic coronary heart disease and acute myocardial infarction [7, 8]. Evidence of an association between infection with *C. pneumoniae* and coronary artery disease in individuals undergoing diagnostic coronary angiography was documented in the USA [9, 10].

The occurrence of coronary disease and total mortality in the middle-aged

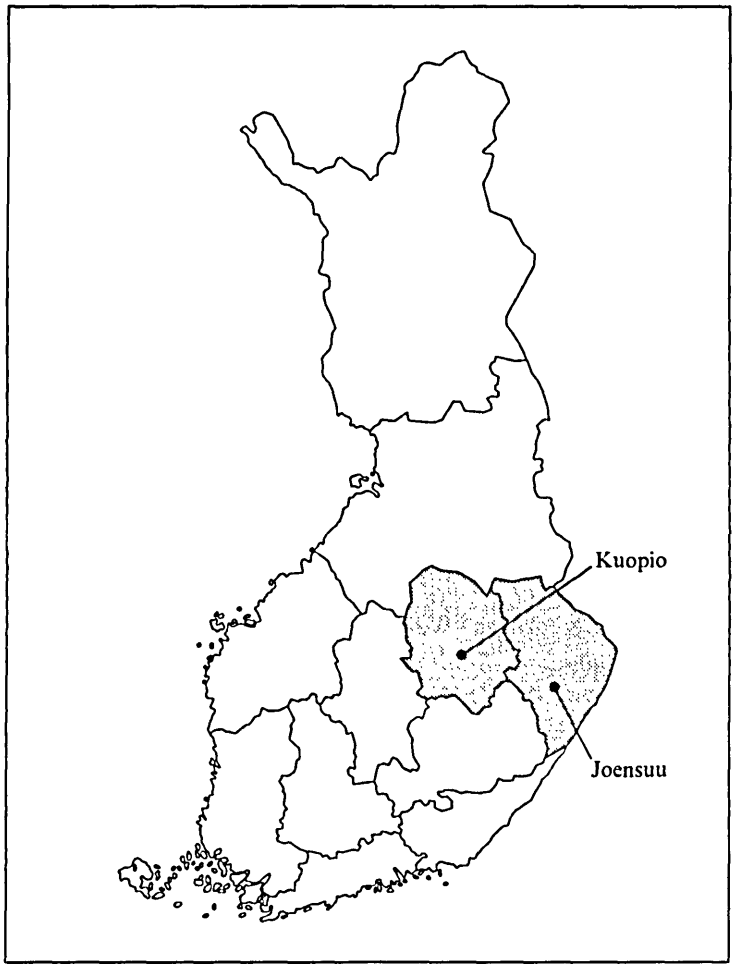

Fig. 1. Study area: the provinces of Kuopio and North Karelia.

Finnish population, especially among men, was the highest in the industrialized world until the late 1970s [11–13]. From the beginning of the 1970s mortality from ischaemic heart disease (IHD) has been declining in Finland [14]. In the province of North Karelia the prevention programme for cardiovascular diseases, the North Karelia Project, was launched in 1972 [15]. IHD mortality declined steeply in the province of North Karelia throughout the 1970s, and later on similarly also in the rest of Finland [14].

In connection with the North Karelia project in 1972 and 1977 and the FINMONICA project in 1982 and 1987 serum samples were collected from the adult population living permanently in the provinces of North Karelia and Kuopio in eastern Finland (Fig. 1). In order to determine the epidemic cycle of *C. pneumoniae* infections over a period of 15 years in this area we determined the *C. pneumoniae* IgG antibodies from these stored sera.

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MATERIALS AND METHODS

Study population

Serum specimens were collected in the two independent cross-sectional surveys carried out in the provinces of North Karelia and Kuopio, in eastern Finland, from February to April in 1972 and in 1977. The surveys evaluated the North Karelia Project, the community-based control programme for cardiovascular diseases. The study population in both surveys consisted of people aged between 25 and 59 years living permanently in these provinces. A 6·6% random sample was taken from the National Population Register in each survey. Details of the surveys have been described elsewhere [15]. In connection with the FINMONICA Project, i.e. Finland's contribution to the WHO multinational MONICA Project (monitoring trends and determinants in cardiovascular diseases) further cardiovascular risk factor surveys were carried out from January to April 1982 and again in 1987 in the same geographical areas as before. Independent random samples of the population aged 25–64 years were taken from the National Population Register for both FINMONICA surveys and serum specimens were also stored as in previous surveys [13].

Study sample

For the present study we chose a subsample comprising 2400 subjects using stratified sampling with an equal quota. The stratification was done according to gender, age, and the degree of urbanization of the home municipality of the subjects. Both genders were divided between the urban and rural population and further into three age groups: 25–36 years, 37–48 years and 49–59 years. Stratification by age and gender was carried out because it had been shown earlier that the *C. pneumoniae* IgG antibody level may vary in the population by gender and age [16]. Stratification of the rural and urban population was carried out because in our previous prevalence study of *C. pneumoniae* antibodies in Finland in 1958 the antibody prevalence was highest among the rural population in sparsely populated areas [1]. There are two towns in the survey, considered to be urban communities, Kuopio (76792 inhabitants in 1983) and Joensuu (45920 inhabitants in 1983) [17]. The rest of the survey area was defined as rural. The distinction between urban and rural was based on internationally used criteria, both in terms of physical characteristics (the size and density of a continuous built-up area) and functional criteria reflecting both the degree of employment as well as occupations engaged in [18]. A sample of 50 subjects from each stratum was obtained. Altogether the final study material consisted of 2400 persons, 600 persons per survey year. For the final antibody assay 2387 serum samples were available. The size of the sample varied from 593 to 600 per year and from 48 to 52 within each strata.

Statistical methods

Prevalence was modelled using the GLIM statistical package [19]. Hierarchical Generalized Linear Models were fitted assuming the prevalence to have binomial distribution [19]. The prevalence was assumed to be a function of the year and subjects' gender, age and place of residence, and a stepwise approach was used to

select significant effects. In addition, the birth cohort effect was also tested. The interactions of the main effects were fitted in the model. Significances of the main effects and their interactions were tested in the model by looking at differences in deviances. The mode of the change in the prevalence was tested using orthogonal polynomials [20] (all years together). Four new variables were fitted describing the level, linear, quadratic and cubic change in the prevalence, 1972–87.

C. pneumoniae *antibody test*

IgG antibodies to *C. pneumoniae* were measured by immunofluorescence [21], with formalinized elementary bodies of *C. pneumoniae* strain Kajaani 6 [22] as the antigen. The antibodies were detected with fluorescein-conjugated anti-human IgG (Kallestad). The limit of positivity was a titre $\geqslant 16$ [9, 16, 23, 26]. The reading of the results was performed by one person (M.K.) and from randomly mixed specimens.

RESULTS

Figure 2 shows the *C. pneumoniae* IgG antibody prevalence in the four cross-sectional surveys at 5-year intervals, 1972–87. In 1972 the antibody point-prevalence was 57%, increasing further to 66% in 1977 (Table 1). During the next 5 years the prevalence decreased to 41% in 1982, but by 1987 it had again increased to 59%, approximately to the level of the year 1972. Throughout the observation period the prevalence was higher in men than in women and the absolute difference varied from 7 to 11% (Table 1). The gender difference in the prevalence was clear in urban areas in each year, while in rural areas it was changing from year to year. When all years were analysed together (Table 1) the prevalence increased steadily with age in women, whereas in men it increased prominently only after the age of 49 years. In the oldest men (aged 49–59 years) the prevalence was the highest of all age and gender strata.

All years together

Table 2 describes the overall results from modelling of the pooled prevalence (all years together). The year produced the strongest effect ($P < 0{\cdot}001$) on the prevalence and both the effect of age and gender were also significant ($P < 0{\cdot}001$). The interaction term between year and the area became significant, indicating that there were differences in the prevalence between rural and urban areas depending on the year.

In order to find out the character of the yearly variation in prevalence we fitted the linear trend and quadratic curve, which did not become significant ($P > 0{\cdot}10$ and $P > 0{\cdot}05$, respectively (Table 2)). On the contrary, the fitted cubic form of variation was statistically significant ($P < 0{\cdot}001$), indicating the cyclic change in *C. pneumoniae* prevalence.

One year at a time

In 1972 the prevalence was 57% and it diverged significantly according to age, area, and gender of the study subjects ($P < 0{\cdot}01$, $P < 0{\cdot}01$ and $P < 0{\cdot}05$ respectively) (Table 2). The interaction term between age and gender was statistically significant ($P < 0{\cdot}01$), indicating different age-specific antibody patterns for men and women. Among men, in the youngest age group (25–36 years) the prevalence was 39% and increased sharply to 68% in the middle age

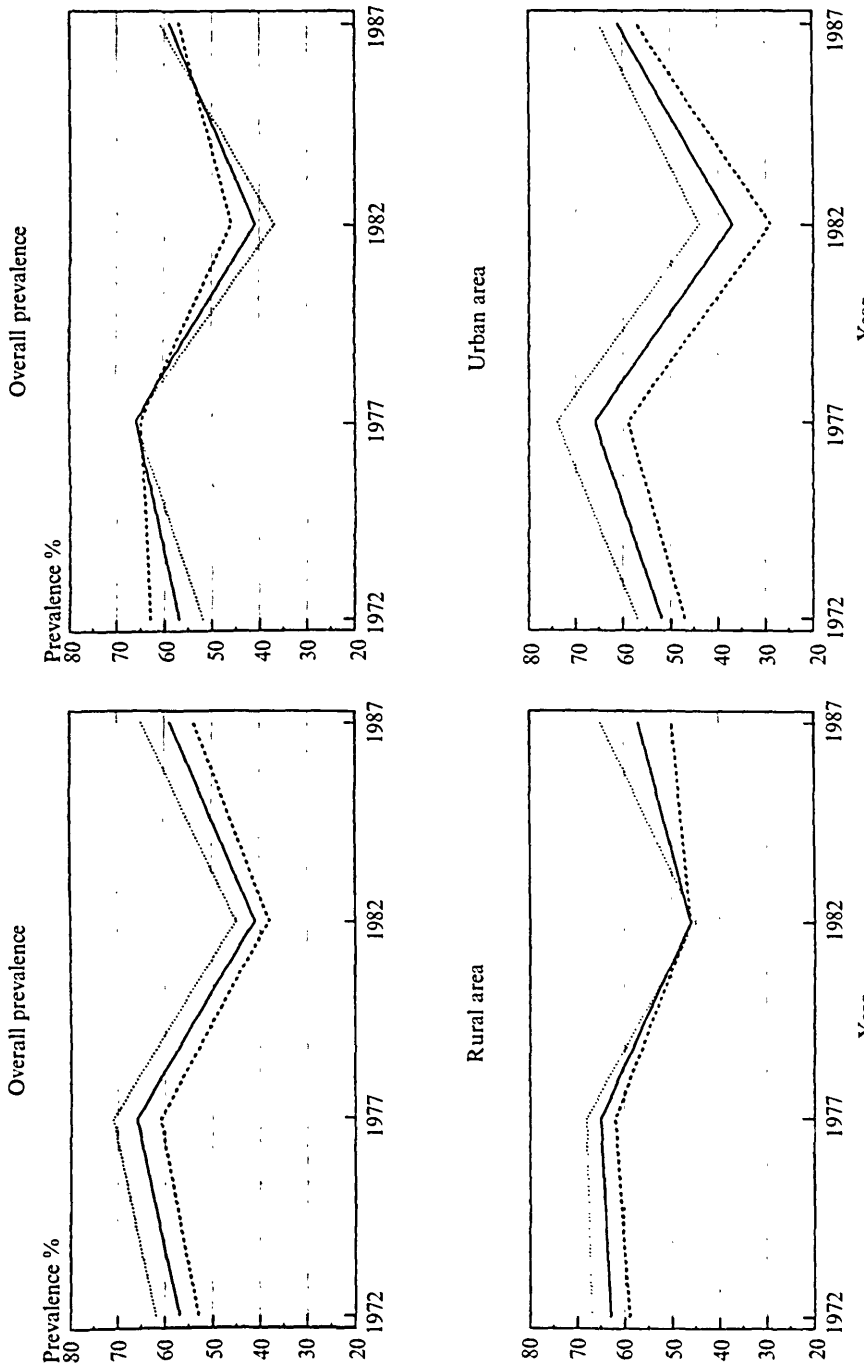

Fig. 2. *C. pneumoniae* IgG antibody prevalence in men and women aged 25–59 years in the provinces of North Karelia and Kuopio, 1972–87. 'Overall prevalence' is prevalence in all study subjects. 'Rural area' is prevalence in rural study subjects. 'Urban area' is prevalence in urban study subjects. Men, ····; women, ——; all, – – –.

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Table 1. *Prevalence of* C. pneumoniae *antibody in population in the provinces North Karelia and Kuopio, 1972–87*

Year	Age (years)	No. tested	Percent with IgG antibody: Rural Men	Rural Women	Rural All	Urban Men	Urban Women	Urban All	Total Men	Total Women	Total All
1972	25–36	200	46	60	53	32	38	35	39	49	44
	37–48	200	76	56	66	60	46	53	68	51	59
	49–59	200	78	60	69	78	58	68	78	59	68
	Total	600	67	59	63	57	47	52	62	53	57
1977	25–36	202	60	58	59	70	43	56	65	50	58
	37–48	199	74	64	69	74	71	73	74	67	71
	49–59	198	70	64	67	77	63	70	74	64	69
	Total	599	68	62	65	74	59	66	71	61	66
1982	25–36	199	40	41	40	42	18	30	41	29	35
	37–48	197	43	35	39	34	36	35	38	36	37
	49–59	197	53	62	58	56	34	45	54	48	51
	Total	593	45	46	46	44	29	37	45	38	41
1987	25–36	198	60	44	52	62	46	54	61	45	53
	37–48	199	50	36	43	56	82	69	53	58	56
	49–59	198	86	70	78	76	45	61	81	57	69
	Total	595	65	50	57	65	57	61	65	54	59
All years	25–36	799	52	51	51	51	36	44	52	43	47
	37–48	795	61	48	54	56	58	57	58	53	56
	49–59	793	72	64	68	72	50	61	72	57	64
	Total	2387	61	54	58	60	48	54	60	51	56

group (37–48 years) and was the highest, 78%, in the oldest age group (49–59 years). In women the prevalence was already as high as 49% in the youngest study subjects (25–36 years) and it remained at the same level before it increased to 59% in women aged 49–59 years. The overall prevalence was significantly higher ($P < 0{\cdot}01$) in rural than in urban areas. The rural–urban difference in prevalence was equal for both genders.

In 1977 the antibody prevalence was 66% (Table 1), the highest during the entire observation period. The difference in prevalence according to both age and gender was significant ($P < 0{\cdot}01$) (Table 2). The prevalence increased similarly with age in both genders, and it reached the maximum already by the age of 37 years in both genders: 74% in men and 68% in women. There was no difference in overall prevalence between rural and urban areas in 1977. However, the prevalence in urban areas increased from 52% in 1972 to 66% in 1977, but in rural areas the prevalence remained practically unchanged. In 1982, prevalence was 41% (Table 1), which was the lowest during the observation period. The prevalence increased significantly ($P < 0{\cdot}01$) (Table 2) with age, but the increase was clear only between the youngest (25–36 years) and oldest (49–59 years) study subjects. In rural areas the prevalence was slightly higher, 46%, than in the urban areas 37% ($P < 0{\cdot}05$). The difference in the prevalence between the genders in 1982 was the smallest during the observation period; the absolute difference was 7%. The interaction between the gender and the place of residence was statistically significant

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Table 2. *Variables in age, gender and place of residence models of* C. pneumoniae *prevalence in the provinces of North Karelia and Kuopio, 1972–87*

Model	D.F.*	Deviance	ΔD.F.*	ΔDeviance	*P*-value*
All years together					
1. Constant	47	246·8	—	—	—
2. +year	44	167·3	3	79·5	< 0·001
3. +gender	43	145·6	1	21·7	< 0·001
4. +age	41	97·1	2	48·4	< 0·001
5. +area	40	93·6	1	3·5	NS
6. +year × age	34	82·7	6	11·0	NS
7. +year × area	37	83·8	3	9·8	< 0·05
8. +year × gender	37	92·8	3	1·0	NS
1972					
1. Constant	11	52·7	—	—	—
2. +gender	10	48·1	1	4·6	< 0·05
3. +age	8	22·7	2	25·4	< 0·01
4. +area	7	15·3	1	7·4	< 0·01
5. +gender × age	5	3·4	2	11·9	< 0·01
6. +gender × area	4	3·4	1	0·0	NS
7. +area × age	2	0·6	2	2·8	NS
1977					
1. Constant	11	20·9	—	—	—
2. +gender	10	13·9	1	7·0	< 0·01
3. +age	8	5·2	2	8·7	< 0·01
4. +area	7	5·0	1	0·1	NS
5. +gender × age	5	4·5	2	0·5	NS
6. +gender × area	4	3·2	1	1·3	NS
7. +area × age	2	2·6	2	0·6	NS
1982					
1. Constant	11	31·9	—	—	—
2. +gender	10	28·9	1	3·0	NS
3. +age	8	16·3	2	12·6	< 0·01
4. +area	7	11·1	1	5·1	< 0·05
5. +gender × age	5	10·2	2	0·9	NS
6. +gender × area	4	6·0	1	4·2	< 0·05
7. +area × age	2	5·2	2	0·8	NS
1987					
1. Constant	11	61·8	—	—	—
2. +gender	10	53·9	1	7·9	< 0·01
3. +age	8	41·3	2	12·6	< 0·01
4. +area	7	40·5	1	0·7	NS
5. +gender × age	5	29·9	2	10·6	< 0·01
6. +gender × area	4	28·9	1	1·0	NS
7. +area × age	2	7·2	2	21·7	< 0·001
Fitting linear, quadratic and cubic curves to yearly variation (all years together)					
1. Constant	3	62·1	—	—	—
2. +linear	2	62·1	1	0·04	NS
3. +quadratic	1	59·0	1	3·02	NS
4. +cubic	0	0·0	1	59·09	< 0·001

* Change in the degrees of freedom (ΔD.F.) and the *P*-value correspond to the term last entered.

($P < 0·05$), indicating the different prevalence pattern in genders depending on the place of residence of the study subjects. Among men the prevalence was practically the same in both rural and urban areas, while among rural women

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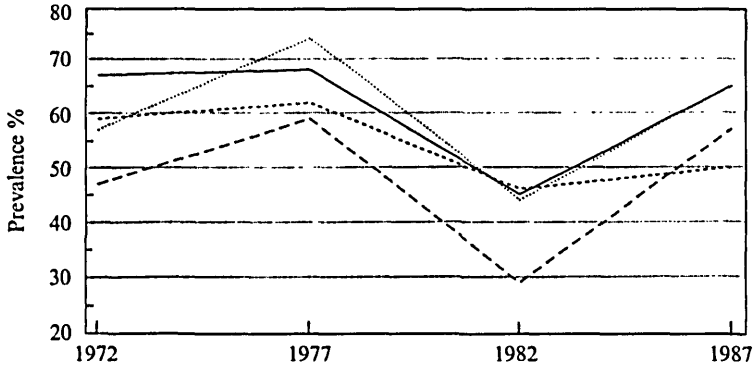

Fig. 3. The absolute temporal changes in antibody prevalence over time in men and women aged 25–59 years living in rural or urban areas in the provinces of North Karelia and Kuopio, 1972–87. Rural men, ——; rural women, · · · · ·; urban men, ...; urban women, – – –.

prevalence was 17% (absolute difference) higher than that in urban women ($P < 0{\cdot}01$) (Fig. 3).

The year 1987 was the only time during the 15-year study period, when the overall prevalence was slightly higher in urban than in rural areas, 61% and 57% respectively (Table 1). Although the prevalence among men was the same (65%) in both areas, in urban women it was slightly higher than in rural women for the first time during the entire study period. The prevalence increased significantly with age ($P < 0{\cdot}01$) (Table 2) and the difference in prevalence between gender was clear ($P < 0{\cdot}01$). The interaction terms between area and age and between gender and age were both statistically significant ($P < 0{\cdot}001$ and $P < 0{\cdot}01$ respectively), indicating that the age-specific antibody pattern was different in genders according to the place of residence of the study subjects. Both in rural men and women and in urban men the prevalence was the lowest at the age of 37–48 years, while in urban women it was the highest in this age group. In women the prevalence increased with age and reached the maximum (58%) as early as at age of 37 years. In men between 25 and 48 years old the prevalence decreased from 61% to 53% and increased to 81% in over 48-year-olds.

DISCUSSION

Population-based seroprevalence studies of *C. pneumoniae* have not been published thus far. The earlier prevalence estimates have been derived in relatively limited selected population groups [2, 6, 16, 23, 24]. Data on the secular trend of the infection are not available either.

In the present study the antibody prevalence was measured at four cross-sections with 5-year intervals. During the observation period there was one clear epidemic peak around the year 1977 (overall prevalence was 66%) and 10 years later around 1987, the epidemic cycle was either approaching or had already passed the peak of the infection (overall prevalence was 59%). Between those two

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epidemic peaks there was an endemic low prevalence period during the early 1980s, the prevalence had declined to 41% in 1982. Although the overall prevalence in 1972 was approximately the same as in 1987, *C. pneumoniae* infection had not reached an epidemic phase in the entire study population in 1972. The temporal changes in prevalence showed that the prevalence increased only in the urban study population from 1972 to the epidemic peak in 1977.

Our findings that overall antibody prevalence was higher in men than in women and that antibody prevalence increased with age, being the highest among the oldest study subjects of both genders, correspond to the findings of earlier studies [16, 24]. Although the pooled prevalence (all years together) showed a steady increase in prevalence with age in both genders, prevalence increased by age differently according to the epidemic cycle of the infection. The difference was clear only between the youngest study subjects (25–36 years) and the oldesr (49–59 years). In addition, the difference of 7–11% in prevalence between gender was smaller in eastern Finland than that (25%) reported in Scandinavia [24]. The gender difference in prevalence was clear in urban areas throughout the observation period, whereas in rural areas the prevalence in men was noticeably higher than in women only in 1987. In that year, the epidemic was clear among all other subgroups, except among rural women.

Our present study was based on cross-sectional population samples and we have measured only IgG antibodies. Thus it was not possible to differentiate the effects of acute infections and past or reinfections by antibody class. During an epidemic period the antibodies from acute infections are mostly found in younger persons, among whom susceptible individuals are to be found without earlier contacts with *C. pneumoniae*. The gradual decrease of antibodies to a very low level in about 3 years after an acute infection has been reported [25]. However, the age-specific antibody patterns show that antibodies could persist longer than has been speculated. In addition, also low titre antibodies seem to be protective. The highest antibody prevalence in the oldest age group (49–59 years) was apparently due to reinfections or chronic infections, which have been reported to be common in older people [24, 27].

The overall prevalence was slightly higher in the rural than in the urban population. Rural–urban difference varied according to the epidemic phase of infection. It was clear in endemic low prevalence years, whereas in epidemic periods (1977 and 1987) the prevalence in urban areas reached the rural level. Constant higher prevalence in rural areas is reasonable according to the theory that discontinuous, infrequent and short contacts generally lead to endemicity, but continuous contacts in densely populated urban areas produce epidemics. There were large differences in prevalence also according to the place of residence of the affected individuals. Among men the difference in the antibody pattern between urban and rural areas was small, whereas among women this difference was substantial. Higher prevalence among rural women already in the first study year 1972 indicates that women living in rural areas had experienced *C. pneumoniae* infection at an earlier age than urban women. It is also likely that the epidemic had started earlier in rural than in urban areas, particularly among women. The rural–urban difference in women remained the same until 1987, when

the prevalence among urban women was for the first time higher than that in rural women. This suggests that there was a high endemic level of *C. pneumoniae* infection among rural women throughout the 15-year observation period.

We have earlier shown that *C. pneumoniae* had already affected the rural population in Finland throughout the country in the late 1950s. The total IgG antibody prevalence was 56% in 1958 and sporadically higher, especially in eastern Finland, where the prevalence was 88% in the northern part of the province of North Karelia [1]. Obviously there was a period of high incidence in an epidemic cycle around 1958. Subsequently outbreaks of *C. pneumoniae* infections were reported in 1977–8 and in 1985–7 in different parts of Finland, among both military trainees and the civilian population [2–4]. According to our results eastern Finland was not reached by the epidemic in Scandinavia during 1981–3. On the other hand, epidemics were reported in Scandinavia around 1977 and 1987 [5, 6]. The *C. pneumoniae* infection is considered to be an inter-human infection with a long interval between cases [3]. Therefore, because of the slow velocity of the infection, circulation to neighbouring countries may be prolonged in sparsely populated regions. However, our earlier results show that *C. pneumoniae* had been established in Finland already in the 1950s; thus it appears to have been endemic in the country. The time span between epidemics is dependent on the time required for susceptible individuals to be born or to migrate to the population. The rise and fall of the epidemic could be associated with the proportion of susceptible individuals and disease carriers in the population and the degree of contact between them.

Although the serum samples were stored for a long time, the micro-immunofluorescent pattern typical of *C. pneumoniae* was clear, indicating that the IgG antibodies had not deteriorated during storage. The MIF test is shown to be specific for *C. pneumonia* [8, 26], and serum samples were collected from a healthy population, thus the cross-reacting group antibodies, common in acute chlamydial infection, did not interfere.

The cyclical fluctuations in prevalence within a 15-year period was clear. There was neither a linear trend nor signs of peaks in prevalence in those three 5-year periods between study years when the changes in prevalence in four time points was tested. Although we have defined the *C. pneumoniae* IgG prevalence for 5-years cross-sections, our present findings and earlier observations (2–5) indicate that *C. pneumoniae* is endemic in Finland and has caused continuous infections, at least in eastern Finland, and that the periods of high and low prevalence occur alternately within about a 10 year epidemic cycle. *C. pneumoniae* antibody prevalence was higher in rural than urban areas, particularly among women living in rural regions. The epidemic phases of infection were clearly seen in the urban population, also particularly among women.

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