Epidemiology of Sindbis virus infections in Finland 1981–96: possible factors explaining a peculiar disease pattern

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SUMMARY

Pogosta disease (PD), an epidemic rash-arthritis occurring in late summer is caused by Sindbis virus (SINV) and is transmitted to humans by mosquitoes. Altogether 2183 PD cases were serologically confirmed 1981–96 in Finland, with an annual incidence of 2·7/100 000 (18 in the most endemic area of Northern Karelia). The annual average was 136 (varying from 1 to 1282) with epidemics occurring in August–September with a 7-year interval. Studies on 6320 patients with suspected rubella (1973–89) revealed 107 PD cases. The depth of snow cover and the temperature in May–July seemed to predict the number of cases. The morbidity was highest in 45- to 65-year-old females and lowest in children. Subclinical SINV infections were 17 times more common than the clinical ones. The SINV-antibody prevalence in fertile-age females was 0·6% in 1992; the estimated seroprevalence in Finland is about 2%. Among game animals the tetraonids (black grouse and capercaillie) had the highest seroprevalence (65%) in the epidemic year of 1981.

INTRODUCTION

Sindbis virus (SINV) is a mosquito-borne, enveloped RNA virus in the genus *Alphavirus* of family *Togaviridae*. The first evidence of SINV activity in Europe was the detection of two Finnish SINV antibody-positive individuals in 1965 [1,2]. The virus found its disease in 1980, when antibodies and diagnostic titre rises against SINV were detected in the sera from Finnish and Swedish patients with epidemic rash-arthritis known as 'Pogosta disease' (PD) or 'August–September disease' at the Department of Virology,

University of Helsinki [3–7]. The disease was named after the local name of Ilomantsi parish, 'Pogosta'. The viral aetiology was subsequently confirmed in Sweden [8]. Niklasson et al. [9] succeeded to isolate SINV (Edsbyn strain), also known as Ockelbo virus, from *Culiseta* and *Culex* mosquitoes in Sweden and also from birds. In Russian Karelia 'Karelian fever', identical to Pogosta and Ockelbo diseases, was recognized in the early 1980s [10] and the virus was isolated from a pool of *Aedes* sp. [11]. All SINV strains show more than 88% nucleotide identity [12]. Recently, Lundström [13], in a review on SINV in Western Europe, notes that 'although there is variation among strains from different geographical

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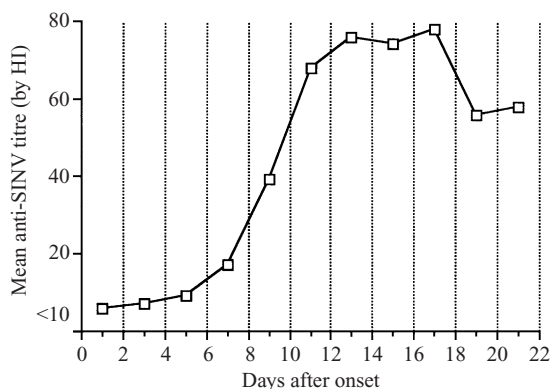
Fig. 1. Kinetics of Sindbis virus antibody titres as measured by the hemagglutination inhibition (HI) method at various time points after onset of symptoms of Pogosta disease (the values have been calculated as mean titres from sera of 950 patients with PD collected in 1981–93).

regions, the genetic and antigenic similarities show clearly that all Western European strains studied are Sindbis'.

After an incubation period of approximately 1 week, PD is characterized by a maculopapular rash and arthralgia (which may be severe and prolonged) and occasionally fever, as presented recently by Turunen et al. [14] and some dermatological aspects by Autio et al. [15]. Serological diagnosis for PD has been available in Finland since 1980. Some years PD has been of considerable public health significance and the number of patients seeking medical attention has increased to more than 1000 during a 3-month period. Although diagnostic tests for the disease have existed for two decades, the epidemiology of PD in Finland has not previously been reported and the purpose of this paper is to analyse and present the large body of data on epidemiology of PD that has accumulated up to 1996. In the following we will describe the appearance of SINV infections in Finland, the incidence of serologically confirmed PD in different parts of the country, and the SINV antibody status among Finnish people and some game animals. Finally, we will discuss the emergence of SINV in Europe in the 1960s and 1970s.

METHODS

Sera

Acute-convalescent serum pairs from patients with rash and arthritis

A total of 6320 pairs of serum samples from patients with a rubella-like illness but without rubella, taken in

the spring, summer and autumn in 1973–4 (studied retrospectively) and 1980–9 were collected. Nearly all were pregnant females with suspected rubella.

A total of 9842 serum samples of suspected PD patients from all parts of Finland taken from 1981 to 1996. The age and the location of 99 % of these patients were known and the exact day of onset of illness was known in 52 % of the cases.

Single sera from healthy humans

Sera from healthy young women of fertile age attending the maternity outpatient clinic during their first trimester of pregnancy were collected during February 1992. Altogether, 5000 successive samples were studied. The mean age was 28·4 years, varying between 14 and 51 years.

Also, 671 sera (54 % from males) from the normal healthy population of the rural commune of Ilomantsi were collected. The Ilomantsi parish, where the first clinical cases of PD were detected in 1974, is located in Eastern Finland at the border of Finland and Russia (62° 40′ N, 31° 00′ E). The serum panel was collected in 1980 and 1982 from all residents of the commune who entered the health-care centre but did not have rash and arthritis.

In addition, 121 animal samples of game mammals and birds, shot in the autumn in the above-mentioned highly endemic area around Ilomantsi in 1981–3 were collected. The bulk of the samples consisted of blood from shot game animals, dried on filter paper slips. In the laboratory the slips were eluted in phosphate-buffered saline [16].

Antibody tests

The principal method was the haemagglutination inhibition (HI) test using SINV antigen. The virus SINV (strain AR 339, obtained in the 1960s from Dr J. Casals, New Haven, CT, U.S.A.) was grown in BHK21/WI-2 cell monolayers (Eagle's MEM and 0·2 % bovine serum albumin) and treated with Tween-ether. Sera absorbed with kaolin and male goose erythrocytes were tested using microtitration equipment at pH 6·0 against 3–4 HA units of SINV (overnight at +4 °C) and a 0·2 % suspension of goose erythrocytes. The sera originating from serum banks were first screened in pools of five (each serum diluted 1 in 4), then individually at 1 in 10.

Specific SINV IgM was initially detected by the HI test after separation of immunoglobulin classes by overnight ultracentrifugation in a sucrose gradient.

Table 1. *Acute SINV infections and SINV antibody prevalence in sera from patients with suspected rubella*

| Year | Serodiagnoses | | Antibody prevalence |
	May–July Number (%)	Aug–Sept. Number (%)	Number (%)
1973	nt	0/70 (0)	4/862* (0·5)
1974	nt	2/307 (0·7)	0/305 (0)
1973–4	nt	2/377 (0·5)	4/1167 (0·3)
1980	nt	9/597 (1·5)	4/588 (0·7)
1981	0/472 (0)	36/594 (6·1)	6/1030 (0·6)
1982	0/415 (0)	6/342 (1·8)	11/751 (1·5)
1983	0/167 (0)	6/271 (2·2)	6/432 (1·4)
1984	0/174 (0)	32/308 (10·4)	11/450 (2·4)
1980–4	0/1228 (0)	89/2112 (4·2)	38/3251 (1·2)
1985	0/78 (0)	1/354 (0·3)	8/431 (1·9)
1986	nt	0/117 (0)	3/117 (2·6)
1987	0/311 (0)	0/244 (0)	9/555 (1·6)
1988	0/86 (0)	8/324 (2·5)	6/402 (1·5)
1989	0/179 (0)	7/118 (5·9)	7/290 (2·4)
1985–9	0/654 (0)	16/1157 (1·4)	33/1795 (1·8)

* Most of the samples (792) collected in October–December.
nt, Not tested.

Later an enzyme immunoassay (EIA) for both IgM and IgG was used using purified SINV antigen (Ockelbo strain) [17], directly coated on microtitre well plates. In each case, the specificity of the reaction was confirmed by HI titration.

Some antibody findings of humans and all among wildlife were confirmed by the neutralization test. It was performed using SINV (strain AR 339) infection of monolayer tube cultures of Vero cells in tubes (Eagle's MEM with 4% foetal calf serum). The heat-inactivated serum plus a standard dose of virus (100 CPE_{50}) was incubated for 1 h at 37 °C. CPE was recorded on the 3rd day p.i.

Meteorological data

The meteorological observations in Ilomantsi were done by the Finnish Meteorological Institute [18].

RESULTS

Serological reaction pattern in Pogosta disease

The specific antibody HI titre was in the majority of cases undetectable (< 10) during the first week after the onset of symptoms. However, it was possible to demonstrate a fourfold titre rise even if the first serum had been taken as late as the tenth day of illness (Fig. 1). In IgG-EIA, all samples were negative during the first week after onset of illness, but positive by the second week. IgM was detectable by EIA in 29% of the first samples taken during the first week after onset of illness from the cases with a diagnostic titre rise.

First Pogosta cases in 1973–80 among patients with suspected rubella

Two out of 307 patients with rubella-like illness, but without rubella, in August 1974 turned out to have PD. Both were females (ages 36 and 47) from Eastern Finland; one had a seroconversion, the other a fourfold titre rise against SINV antigen in the HI test. In the late summer of 1980 we detected 9 SINV infections among 597 patients with rubella-like symptoms.

In the 1980s on average 3% (105/3269) of Finnish patients with suspected rubella had a diagnostic titre rise against SINV in August–September (maximum of 10·4% in 1984), but none out of 1882 in May–July (Table 1).

Incidence of PD cases in 1981–96

Altogether, 2183 serologically confirmed PD diagnoses were made at the Department of Virology in
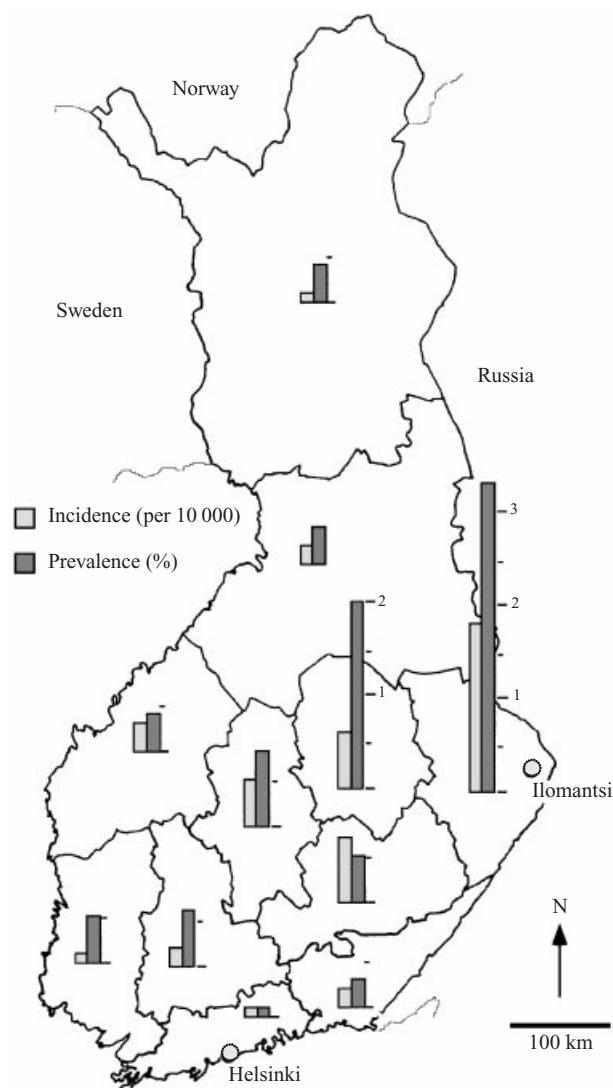
Fig. 2. Incidence (cases per 10000) of Pogosta disease, and prevalence (%) of SINV antibodies measured by hemagglutination inhibition in sera collected from healthy women attending maternity outpatient clinics in different provinces of Finland.

Helsinki in 1981–96. The annual average was 136 cases, the annual incidence 2·7/100000.

Geographical distribution of PD cases

The first cases of PD were detected in the eastern frontier parish of Ilomantsi. Also in subsequent years, most PD cases were found in eastern Finland, especially in Northern Karelia. The annual incidence in Northern Karelia was 18/100000, over six times more than in the whole Finland (Fig. 2). In the epidemic year 1981 there were 73 serologically confirmed

PD cases in the population of 10200 persons in Ilomantsi in Northern Karelia. The northernmost PD cases were located at the Arctic Circle.

## Sex and age distribution of Pogosta disease cases

The majority of PD patients (56%) were female. The disease was equally common among males and females up to the age of 45 years, after which the incidence peaked more clearly among females (Fig. 3). Females of approximately 50 years of age were at greatest risk to acquire PD, with an average incidence of 10/100000. The incidence of serologically confirmed cases among children and adolescents was relatively low. Among the serologically diagnosed SINV infections (positive IgM) there were two females who delivered stillborn children. The cases occurred early in the summer, the other case with more documentation had fever and rash in conjunction with the delivery of a stillborn child at gestational week 32. However, there is no statistical support to show a link between the foetal deaths and the SINV infections.

Annual distribution of PD

The annual number of PD cases varied extensively, from a single case in 1987 to 1282 confirmed PD cases in 1995 (Fig. 4). The morbidity in the latter year was 26/100000, nearly ten times higher than in the normal year. The mean depth of snow cover during the preceding March–April and the temperature during May to July seems to predict the number of PD cases (Fig. 5a, b).

Seasonal distribution of PD

Normally the disease appears at the end of July or in the beginning of August, peaks in late August and ceases before October when the temperature decreases and the mosquitoes die or begin to hibernate (Fig. 6a). To some extent the daily number of cases seems to correlate with the temperature with about a 10-day delay (Fig. 6c). The epidemic pattern varies somewhat from year to year (Fig. 6b). However, excluding some early cases in July (in 1984, the spring had been exceptionally warm with the earliest onset of disease on 1 July) and a few later ones during the first days of October (when the autumn has been exceptionally
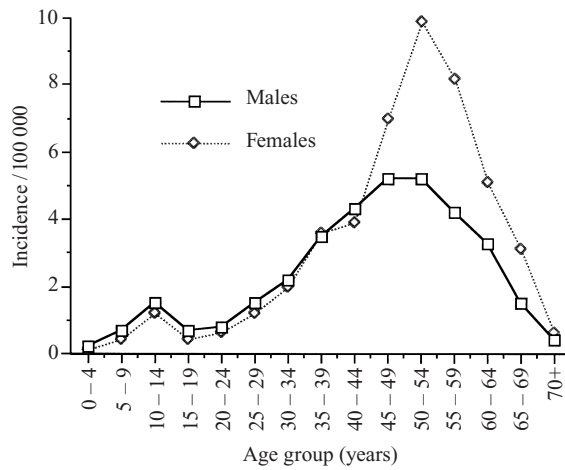
Fig. 3. Mean annual incidence of serologically diagnosed Pogosta disease in different age groups, and by gender, in Finland in 1981–96.
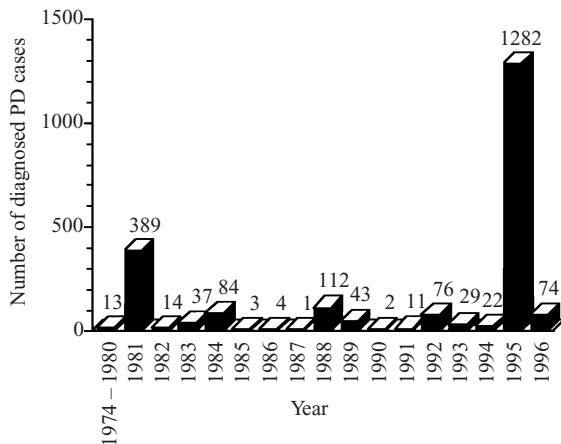

Fig. 4. Number of serologically verified cases of Pogosta disease annually in Finland 1974–96.

warm, as in 1995), the disease was strictly restricted to August and September. In the unusually cold summer of 1996 the epidemic started exceptionally late. Our attempts to detect human cases in the spring, caused by hibernated mosquitoes, were unsuccessful (Table 1).

SINV antibody prevalences in humans

Patients with rubella-like symptoms

The panel consisting of serum pairs of patients with rubella-like symptoms (but rubella was excluded by serology) revealed, in addition to those with SINV titre rises, many with stable titres without specific IgM, suggestive of old exposure. The antibody prevalence in this material was only 0·3 % in the
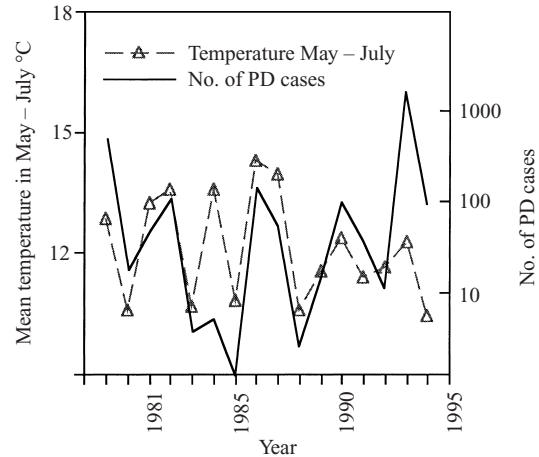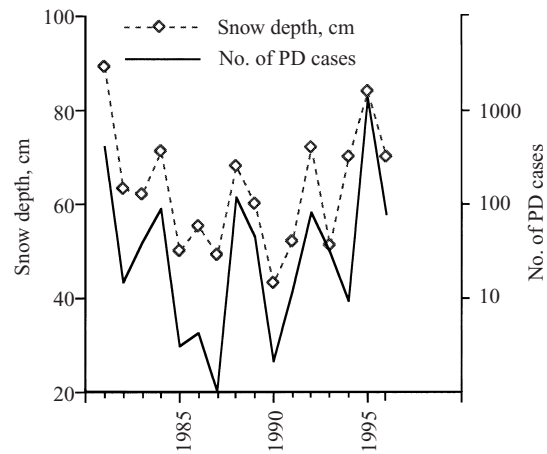
Fig. 5. Annual number of cases of Pogosta disease in Finland (logarithmic scale) plotted together with (*a*) the mean snow depth during 15 March–15 April at Ilomantsi; (*b*) the mean temperature during May–July at Ilomantsi.

1970s, in the beginning of 1980s it was 0·6 %, but increased after the epidemic of 1981 to 1·4 % and reached 1·8 % at the end of 1980s (Table 1).

Childbearing-age females in Finland

In 1992 the average prevalence of SINV antibodies among women entering the maternity outpatient clinics was 0·6 % (29/5000). The highest levels were 3·3 % in Northern Karelia (Eastern Finland) and 2·0 % in the neighbouring province of Kuopio. In other regions SINV seemed to be rarer (< 1·0 %) (Fig. 2).

Normal population in Ilomantsi

The SINV antibody prevalence in the Ilomantsi parish at the eastern frontier of Finland was high. In 1982 after the large epidemic of 1981, it was 39 % (224/578), higher among males than females, 44 % (149/335) *vs.*
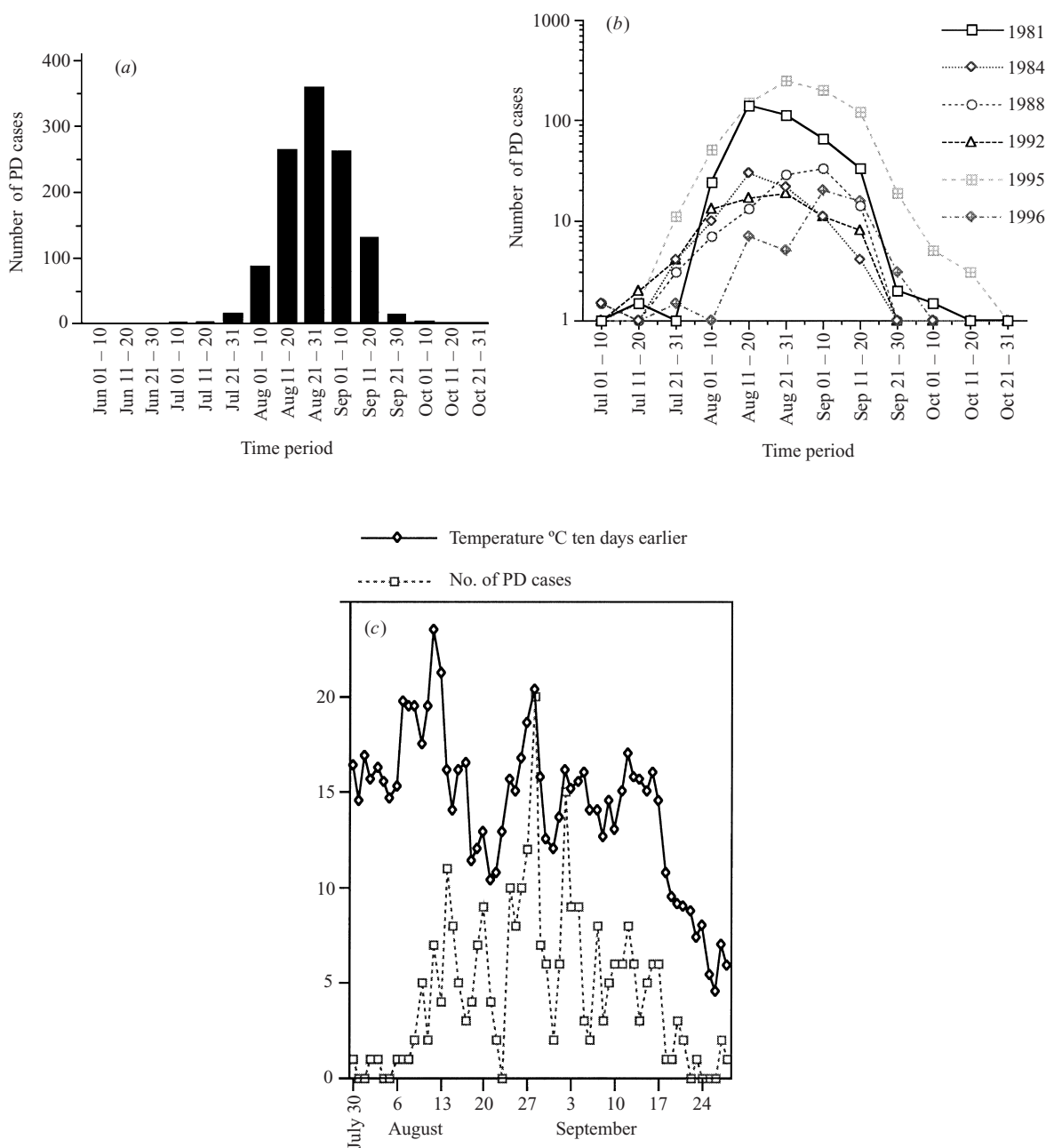
Fig. 6. Seasonal distribution of Pogosta disease. (*a*) Total number of PD cases in Finland in 1981–96 for each 10-day calendar period. (*b*) Number of PD cases in Finland in selected individual years for each 10-day calendar period. (*c*) Number of PD cases in southeastern Finland in 1995 as compared to daily mean temperature in Ilomantsi.

31 % (75/243). The prevalence increased somewhat with age (Fig. 7*a*). The total prevalence among adults was in 1982 41 % (207/506); in comparison, it had been 29 % (27/93) in 1980, before the large epidemic (Fig. 7*b*).

SINV antibody prevalences among wild animals

Altogether 30 % (24/80) of avian and 17 % (7/41) of mammalian sera, collected in 1981–3 had SINV

antibodies (Table 2). Nearly all SINV antibody positive birds belonged to the gallinaceous *Tetrao* genera. The animals had been hunted in the highly endemic Ilomantsi area.

DISCUSSION

Pogosta disease is a disease characterized by polyarthritis accompanied with a rash and caused by Sindbis virus. The disease is also known as 'Ockelbo disease'
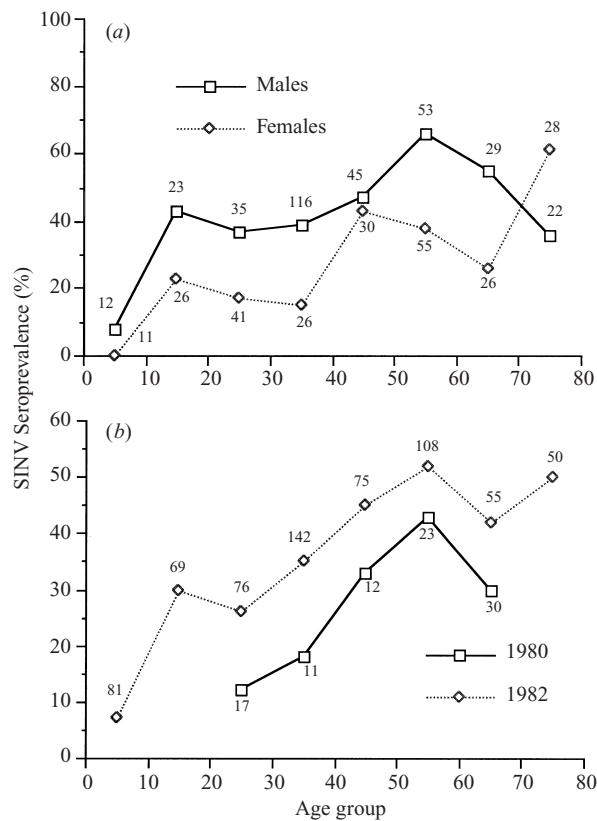
Fig. 7. SINV antibody prevalences in Ilomantsi, 1982. (*a*) According to gender and age group. (*b*) In each age group as compared to the prevalence in 1980. Number of the sera studied in each group is indicated.

in Sweden [8] and 'Karelian Fever' in Russian Karelia [10]. In addition, SINV is distributed over vast areas of Africa, Asia, Australia, but relatively few human infections (joint manifestations with rash) have been reported there [19].

Although PD is often, especially during the epidemics, diagnosed with high degree of accuracy clinically without laboratory testing, the serological confirmation is, however, important, as some other infections may imitate it. In the early 1980s, when PD was not well known and rubella was still moderately common in Finland, there were a number of PD cases among patients with suspected rubella (e.g. in August–September 1981 6·1% were caused by SINV but only 3·3% by rubella virus, Table 1). Some PD patients had been suspected as having varicella. Vene et al. [17] have documented clinical similarity between Ockelbo disease and parvovirus B19 infections. African patients with certain other mosquito-borne viral diseases, such as Chikungunya, O'nyong-nyong, dengue and West Nile fever, may present similar symptoms [19].

The annual number of PD cases varied extensively, from 1 to 1282 (Fig. 4). Also in non-epidemic years PD was found in different regions of Finland, not only in Eastern Finland. The northernmost PD cases were detected close to the Arctic Circle. The annual incidence of PD in Finland in 1981–96 was 2·7 (per 100000), however, the incidence was 18/100000 in Northern Karelia. In the endemic region in central Sweden it is 2·9/100000, in many other parts of Sweden only < 0·1/100000 [20]. The incidence was highest among females in the age group of 45–64 years (Fig. 3), presumably because they are the most likely to stroll in the countryside picking berries and mushrooms and whose bare limbs are then exposed to the attacks of mosquitoes. The PD incidence values include only the numbers of the patients who have had serodiagnoses. A large number of infections escape serological confirmation because many SINV infections are moderately mild, especially in children and adolescents, and many patients do not seek medical care. Also PD is often, especially during epidemics, diagnosed clinically and no samples are submitted for confirmation.

The mean SINV-antibody prevalence among child-bearing-aged females in Finland in 1992 was 0·6% but much higher in Central Finland and especially in Northern Karelia (Fig. 2). The prevalence among residents of Ilomantsi parish was already 39% in 1982. During the large epidemic in 1981, the incidence of confirmed cases was 72/10000 in Ilomantsi, meanwhile, the antibody prevalence among the residents increased by 12% (Fig. 7*b*). This indicates that there were 17 times more subclinical and mild (and undiagnosed) SINV infections in spite of the considerable clinical alert and interest in diagnosing the new infection. The total number of SINV infections in Finland in an epidemic year must be considerably over 1000 (in 1995 over 10000), all of them occurring during a period of 10 weeks. The SINV-antibody prevalence of the Finnish population rose during 1981–95 as reflected by the prevalences in our patients with suspected rubella (with negative rubella serodiagnosis). It was 0·3% in 1973–4, 1·2% in 1980–4 and 1·8% 1985–9 (Table 1). We can roughly estimate that the mean SINV antibody prevalence in Finnish population is today about 2%, whereas in the most endemic province Northern Karelia it is five times higher. The outcome of SINV infection during pregnancy remains a question: although we discovered two cases of SINV IgM-positive mothers who delivered stillborn children, no statistical significance can be

Table 2. *SINV antibody prevalence among game animals in Ilomantsi*

Species	1981	1982	1983	Total (%)
Beaver (*Castor fiber*)			1/9	1/9
Muskrat (*Ondatra zibethica*)			0/1	0/1
Wolf (*Canis lupus*)			1/6	1/6
Red fox (*Vulpes vulpes*)			0/1	0/1
Brown bear (*Ursus arctos*)	2/2	1/2	0/3	3/7
American mink (*Mustela vision*)	0/1			0/1
Lynx (*Felix lynx*)			0/2	0/2
Snow hare (*Lepus timidus*)	0/2		2/4	2/6
Moose (*Alces alces*)		0/4	0/4	0/8
Mammals (total)				7/41 (17)
Widgeon (*Anas penelope*)			0/2	0/2
Teal (*A. crecca*)		1/6	0/2	1/8
Mallard (*A. platyrhynchos*)			0/19	0/19
Long-tailed duck (*Clangula hyemalis*)			0/2	0/2
Goldeneye (*Bucephala clangula*)		1/1	0/3	1/4
Willow grouse (*Lagopus lagopus*)	0/1			0/1
Black grouse (*Tetrao tetrix*)	10/15	1/6	0/3	11/24
Capercaillie (*T. urogallus*)	7/11		4/7	11/18
Wood pigeon (*Columba palumbus*)		0/2		0/2
Birds (total)				24/80 (30)

attributed to these findings; however, other alpha-viruses have been reported to cause complications in pregnancy in humans [21, 22] and in animals [23–25].

Norder et al. [12] found that nucleotide sequences of SINV strains from Sweden and the South Africa cluster together supporting the theory of dissemination of SINV by migrating birds. In Northern Europe SINV has found a receptive ecosystem. In the early spring the arrival of migratory birds coincides with the ending of hibernation of the non-aedinine mosquitoes which fly around seeking blood. According to Reeves et al. [26] passeriform birds occasionally undergo chronic WEE viral infections; the migration may reactivate the latent chronic infection.

SINV and WEEV are closely related belonging to the same WEE complex of alphaviruses [27–29]. There seems to be numerous ecological and epidemiological similarities between SINV and WEEV. Both seem to be sensitive to high temperatures. According to McIntosh and Gear [30] SINV infections in South Africa are more frequent in the temperate inland plateau than in the subtropical lowlands and Kramer et al. [31] have found that *Culex tarsalis* is a less competent vector of WEE virus at 32 °C than at 18 °C or 25 °C. Hess et al. [32] have noted that most WEE outbreaks occur in United States at or above the 21 °C June isotherm; these results have been con-

firmed by Hardy et al. [33]. In Finland the high temperature is not the limiting factor for SINV, rather the opposite: the beautiful late summer days tempt people to go out and into contact with mosquitoes (Fig. 6c).

The depth of snow cover in the late winter seemed to predict the number of PD cases (Fig. 5a). *Culex* and *Culiseta* species spend the first part of the summer as larvae in temporary pools of water [34], which dry too early if the preceding winter has had a low snowfall. In Fennoscandia (excluding the North of Lapland) SINV infections seem to be most common in the regions with the highest winter snow depth: Northern Karelia [18] and Sweden between the 60th and 63rd latitudes. In South Africa unusually heavy rainfall early in the summer predicts the SINV epidemic [35, 36].

In addition to being isolated from non-aedinine mosquitoes, SINV has also been isolated from *Aedes* [11, 37] and from a frog [38]. WEEV was discovered initially in *Culex* and passerine birds. Nesting birds are the principal amplifying hosts. If suitable ecological conditions persist, virus may spill over to infect a wide variety of vertebrates including other groups of birds, large and small feral and domestic mammals by mammalophilic *Culiseta* and *Aedes* species, and occasionally reptiles and amphibians and man [39].

In Finland 30% of game birds had SINV antibodies in 1981–3, during the large epidemic of

1981 65% of *Tetrao* species (black grouse and capercaillies) were seropositive (Table 2), although the numbers studied in different species were too small to draw firm conclusions. Lundström et al. [40] studied experimental viremia in three orders of birds: *Anseriformes*, *Galliformes* and *Passeriformes*; the highest titre ($10^{8.2}$ p.f.u./ml) was in young (< 1 week) capercaillie (*Tetrao urogallus*). In our material 2 out of 6 snow hares (*Lepus timidus*) had SINV antibodies. WEEV seropositivity rates in wild mammals are generally low, but the jackrabbit (*Lepus californicus*) is one of the most frequently involved animals [39].

Is SINV disease new in Europe? In the early 1960s, no signs of SINV activity were seen. In the studies of Saikku [41] on 5000 human sera and 1000 sera of passerine and gallinaceous birds, moose, hare and cattle, collected in Finland 1958–64, and of Kunz et al. [42] on 232 human sera collected in Austria before 1963, not a single SINV reactor was found. In 1963 the first reported SINV epidemic occurred in South Africa [43] and seropositive children were found also in Israel [44]. In 1965 4% of studied birds in the Volga Delta were seropositive [45] and the first SINV reactors in Europe were detected in Finland [1] and Northern Italy [46]. The second SINV epidemic in South Africa was in 1967 and in the same year the first clinical cases were detected in Sweden. In the following years signs of virus activity were found in different parts of the Middle East and Europe [47–58]. In 1974 there was an exceptionally large epidemic of thousands of human cases in South Africa [36] and the first noted PD epidemic occurred in Finland [7]. In 1979, the fourth epidemic in South Africa [59] was followed by the detection of first serologically confirmed SINV infections in 1980 and a larger outbreak in 1981 in Finland [3–6].

Some questions still remain to be answered. First, why were there no cases of PD in Fennoscandia in the spring. Although the hibernated mosquitoes sometimes also attack humans, SINV-carrying species might be non-antropophilic in the spring. According to Schlesinger [60] temperature-sensitive mutants of SINV may arise during winter and Reeves et al. [61] reported that WEE-virus strains in hibernated mosquitoes were non-pathogenic for mice and poorly immunogenic for chicken. Secondly, what is the cause of the mysterious tendency of PD to occur in Finland in large outbreaks every seventh year (at least until now): 1974, 1981, 1988 and 1995 (and in Sweden in 1967). According to Davies [62] the opinion of the Masai is that Nairobi sheep disease occurred in epizootics 'every 7 years', when the periodic heavy and prolonged rainfall exists. According to Lindén [63] in Finland the cycle lengths of tetraonid birds are 6–7 years, there was a crash of their population in N. Karelia in 1974 and again 1981, in the epidemic years of PD. Galliforms seem to be involved in virus amplification in Finland. Could the herd immunity among birds (in Northern Europe and/or in Africa) cause the 7-year interval of SINV epidemics in Fennoscandia?

The myriads of blood-hungry mosquitoes in Northern Eurasia and Northern America are potentially susceptible populations in which a newly introduced virus could flourish. Inkoo virus, the Finnish representative of Californian encephalitis group, is one of the most abundant arboviruses, especially in Lapland [16, 64]. Vehicles for viruses, migratory birds and mosquitoes spread by air currents already exist, and especially if aided by critical changes in ecological circumstances, e.g. global warming [65] occur, a very large mosquito-borne outbreak may emerge in the North. The outbreaks of West Nile fever in Europe [66] and in USA [67] may serve as an example for emergence of a trans-continental zoonotic mosquito-borne virus in new locations.

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