Puumala Virus Infections in Finland: Increased Occupational Risk for Farmers

Katarina Vapalahti,1 Mikko Paunio,2 Markus Brummer-Korvenkontio,1 Antti Vaheri,1 and Olli Vapalahti1

Puumala hantavirus, transmitted by bank voles (Clethrionomys glareolus), causes a mild-type hemorrhagic fever with renal syndrome. The disease is common in Finland and is considered an occupational hazard for farmers, but the actual risk has not been assessed by analytical studies. Data on 5,132 serologically confirmed Puumala virus infections during 1989-1994 were analyzed, and cases among farmers and the population living in similar conditions were compared. The farmers contracted the disease earlier and more often than did the comparison group. In the province of Mikkeli with the highest incidence (70/100,000), the risk ratio was 5.1 (95% confidence interval (Cl) 3.0–8.4) for 20- to 29-year-old farmers; in the older age groups, the risk was still increased but the risk ratios were lower. The peak incidence in the comparison group was 10 years later (age group 30–39 years). For the whole country, the result was similar although less marked. The average risk ratio adjusted by age, sex, and geographic variation was 1.7 (95% Cl 1.5–1.8) for the whole country and 1.9 (95% Cl 1.5–2.3) for the Mikkeli province, where 80% of Puumala virus infections among young farmers could be estimated to be attributable to occupation. Am J Epidemiol 1999; 149:1142–51.

Puumala virus is a member of the Hantavirus genus in the Bunyaviridae family (1). Each hantavirus is carried primarily by a persistently infected rodent host and transmitted to humans most probably by inhalation of rodent excreta. The reservoir of Puumala virus is the bank vole, Clethrionomys glareolus (2). The population density of this rodent varies extensively and has a 3- to 4-year cyclicity in Finland with often two successive peak years, the densities being highest in the autumn and low in the spring. However, different parts of the country are at different phases of this periodicity (3). Toward the end of the rodent density peak, the proportion of virus-carrying rodents increases, and this is reflected by the peaking of the disease incidence from November to January (4).

Puumala virus infection, or nephropathia epidemica, has an incubation time of 2–4 weeks; is characterized by fever, headache, myalgias, nausea, renal insufficiency, occasionally myopia, and neurologic or respiratory symptoms; and is accompanied by proteinuria, thrombocytopenia, and elevated creatinine levels (5). The severity of the disease varies and is related to genetic susceptibility (6); the infection can also be subclinical. Full recovery is the rule but may take weeks. Puumala virus infection leads to lifelong immunity with a measurable antibody response for decades (7). Mortality is approximately 0.1 percent in Finland (8), and rare nephrologic or endocrinologic sequelae have been reported (9). The diagnosis of acute infection is serologic, usually based on detection of Puumala virus-specific immunoglobulin M antibodies or low avidity of anti-Puumala virus-immunoglobulin G. There is no evidence of transmission of Puumala virus from person to person, and the virus is not stable for extended periods outside the host. In Finland, about 5 percent of the total population have antibodies to Puumala virus and in endemic areas, up to 20 percent (our unpublished observations).

While the discovery of the agent and carrier rodent in 1980 (2) made the etiologic diagnosis possible, already in 1934 Swedish researchers had described the disease (10, 11) and noted that most of the patients were farmers or forest workers. Furthermore, Lähtevirta (12) described 76 cases diagnosed on the basis of typical clinical symptoms and findings from eastern Finland, of which 70 percent were farmers or their family members. He suggested that the transmission occurs especially during the cold season, when rodents seek shelter in farmhouse buildings and farmers work with hay contaminated with rodent excreta. Hantavirus antibody surveys have suggested a higher seroprevalence for farmers (13), but these studies have not controlled the role of possible confounding factors.
Farmers have also been reported to be more exposed to Hantaan virus, another member of the hantavirus group transmitted by field mice, *Apodemus agrarius*, especially in China and Korea (14). However, the ecology and habitat of this rodent species are different from those of *C. glareolus*, which is found more in forests than fields. For Hantavirus Pulmonary Syndrome, association with agricultural activities has been suggested in individual cases, but no evident occupational risk for farmers has been shown (15, 16).

We wanted to know whether farmers have an increased risk of Puumala virus infection as compared with other population groups, even when controlling the effects of age, sex, type of housing, and geographic location. We addressed the question by analyzing more than 5,000 serologically verified cases and, based on those data, describe also some basic epidemiologic features of this infection in Finland.

**MATERIALS AND METHODS**

All the serologically confirmed Puumala virus infection cases in the routine diagnostic laboratory of the Department of Virology, University of Helsinki, from July 1989 to December 1994 were selected for analysis. The serologic diagnosis of acute Puumala virus infection was done similarly during the whole period by an immunofluorescence assay using Puumala virus/Sotkamo strain (17, 18)-infected Vero E6 cells as antigen. The samples were first screened in a 1:20 dilution for the presence of Puumala virus-immunoglobulin G antibodies. The diagnosis of acute infection was based on 1) the low avidity of Puumala virus-immunoglobulin G antibodies in a Puumala virus-immunoglobulin G avidity assay, as described and evaluated by Hedman et al. (19) (utilizing the ability of a high molar urea to disrupt the weak antibody-antigen association specifically during the first weeks of the antibody response) and, in addition, on 2) a nucleocapsid protein-specific granular fluorescence in the Puumala virus-immunoglobulin G test (20) (in the early acute phase, the immunoglobulin G response is predominantly toward the nucleocapsid protein, whereas in the convalescent phase, high titers are also found toward the glycoproteins (20)). For negative sera, a second sample was recommended if the sample was taken less than 6 days after onset of illness.

These cases cover more than 95 percent of all diagnosed Puumala virus infections in the whole country, excluding most cases from the province of Turku and Pori, which was therefore not included in the study (figure 1). Finland excluding this province is referred to below as "the whole country" or "study area." Data from the National Population Registry on the place of residence and type of housing were linked to the mor-

![Figure 1: Map of Finland showing provinces and respective incidences of Puumala virus infection per 100,000 person-years during the study period, July 1989 through December 1994. Dashed line, divisions made for geographic adjusting at the nationwide level.](https://example.com/figure1.png)
family members) (Finnish Farmers’ Social Insurance Institution), 2) age and sex distribution of the population (Statistics Finland), 3) age and sex distribution of those living in one-family houses (Statistics Finland), and 4) general information on each municipality, such as the percentage of the population living in urban (densely populated) areas (21).

Thus, we had a nonconcurrent cohort study in a non-fixed cohort, where the median year population (multiplied in each study group by the 5.5-year follow-up period) served as the population denominator. The data of 1992 yield information for mid-year populations with sufficient precision because of the stable nature of the Finnish population. The basic epidemiologic factors of the epidemiology of Puumala virus presented here further provide the necessary background information for the interpretation of the risk comparisons.

Statistical methods are described below. The study was restricted to active age groups; that is, the study populations were between 20 and 64 years of age. The following parameters were used to measure the infection risk of the farmers.

1. Incidence = the number of new nephropathia epidemica cases/year/100,000 inhabitants = (the number of cases during the study period/person-years) x 100,000. (Person-years = the population in 1992 x 5.5).

2. Risk ratio (= rate ratio) = the relative morbidity risk of farmers to Puumala virus infection as compared with the reference group(s) and its accompanying 95 percent confidence interval.

3. Percentage of Puumala virus infections among farmers that is explained by occupational risk, attributable risk percentage, and its accompanying 95 percent confidence interval.

The risk ratio and attributable risk percentage were adjusted for age (age groups: 20–29, 30–39, 40–49, 50–64 years), sex, and area, by stratifying the data and calculating the weighted average of the association.
(risk ratio or attributable risk percentage) (22). To adjust for the geographic variation, the whole country was divided into four (see map, figure 1) and the province of Mikkeli into five areas (not shown), omitting urban areas. For example, within the hyperendemic Mikkeli province, five different rural areas were the strata in which the comparisons were made. More specifically, the farmers in rural communes (communes with less than 64 percent of the population living in densely inhabited areas) were compared with nonfarmers living in the same kind of houses (one-family houses) in the same area. This is important as the bank vole population density and Puumala virus carrier percentage can vary considerably. Thus, we compared farmers with the comparison group living in similar local transmission risk conditions. When the urban areas were omitted, 1,640 cases of Puumala virus infection were included in the study. Of these cases, 518 were farmers and 1,122 belonged to the comparison group. Calculations and statistical operations were done using rate analysis (23) and SURVO84C (24) computer programs.

**RESULTS**

**Puumala virus infection in Finland**

During the study period from July 1989 to December 1994, 5,132 serologically verified cases of Puumala virus infection occurred in Finland, meaning an annual average incidence of at least 18.5/100,000 for Finland (in rural areas, 38.0, and in urban areas, 13.8). Necessary data could be retrieved for 4,769 persons from the study region, upon which the results below are based (figure 2). The highest incidence for men was found to be between 30 and 39 years of age (figure 3a). In general, Puumala virus infections were more common among men: 3,215 (67 percent) of the cases were male, and 1,554 (33 percent) were female, giving an incidence of 28 and 13, respectively. The relative risk of men compared with women was 2.2 (95 percent confidence interval (CI) 2.1–2.3) (figures 2 and 3a). In the older age groups, immunity to Puumala virus is increasingly common, and the proportion of susceptible persons decreases.

The incidence of Puumala virus infection varied considerably among different provinces (figure 1; table 1). The lowest incidence (9/100,000 person-years) was in the most urban province of Uusimaa, and the highest incidence (70/100,000 person-years) was in the Mikkeli province. Local differences and temporal variation within the provinces were also encountered, partially depending on the urbanization level of the municipalities and partially on the phase of the vole population cycles.

When all the municipalities were studied, those living in one-family houses were seen to have an increased risk of nephropathia epidemica (risk ratio = 1.6, 95 percent CI 1.5–1.7). When we excluded the most urban municipalities (those where more than 64 percent of the population live in densely populated areas), the risk was no longer significant (risk ratio = 1.1, 95 percent CI 1.0–1.2). However, those living in one-family houses contracted the disease earlier (figure 3b).

The incidence of nephropathia epidemica had considerable seasonal variation, the number of serologic confirmations being highest from November to January and lowest from March to May (figure 4a). The incidence patterns of farmers and nonfarmers were otherwise similar except for an additional peak in August among the nonfarmers (figure 4b), composed mainly of cases in urban populations probably exposed during summer holidays (our unpublished observations).

**Occupational risk among farmers**

Among the active (20- to 64-year-old) farmers, comprising 5.5 percent of the population of the same age, 640 cases (representing 15.2 percent) were registered (figure 2). The incidence for active farmers was 80.7 (97.5 for males and 56.5 for females). In the whole country, the crude relative risk of Puumala virus infection among farmers compared with nonfarmers was 2.3 (95 percent CI 2.0–2.5) and 2.8 (95 percent CI 2.4–3.3) for males and females, respectively.

The incidence of Mikkeli region farmers in the first age group (20–29 years) was remarkably high (figure 5a; table 2), and the risk ratio was 5.1 (95 percent CI 3.0–8.4) compared with the reference group living in one-family houses in the same small rural subareas. In this age group, 80 percent of the Puumala virus infections were attributable to farming as a profession. Interestingly, in the comparison group, the peak incidence was 10 years later than the peak incidence of the farmers. Moreover, in the older age groups, the farmers had higher incidences than did the comparison group and increased risk ratios (although lower than for the first age group). Women tended to have lower incidences but systematically similar comparisons as the men had. Adjustment for sex and area had little effect on the associations. The average risk ratio adjusted by age, sex, and geographic variation was 1.9 (95 percent CI 1.5–2.3) and the attributable risk percentage 46 (95 percent CI 29–64) for the Mikkeli province.

At the nationwide level, the incidence was higher for farmers in all age groups (figure 5b; table 3) as compared with the reference group living in one-family houses in rural areas. A clear reduction of incidence occurred for male farmers toward older age groups,
FIGURE 3. Incidence (per 100,000 person-years) of Puumala virus infections in Finland during the study period, July 1989 through December 1994, in the whole study (for 4,769 cases) for men and women according to age (a) and by type of housing in rural communes (communes with less than 64% of the population living in densely inhabited areas) (b).
but this was less apparent among women. Whether widows would be at greater risk could not be assessed, as the marital status was not known. The comparison group again had its peak incidence in the second age group (30–39 years). Thus, farmers contracted the disease not only more often but also earlier than did other population groups. Adjusting for sex and region did not materially affect the results.

Of the four geographic regions (figure 1), the adjusted (age, sex, region) risk ratio for farmers was highest in eastern Finland, 1.9 (95 percent CI 1.6–2.2), while in other regions the risk ratio was from 1.4 to 1.6. For the whole country, the adjusted (age, sex, region) risk ratio for farmers compared with other population groups living in one-family houses in rural areas was 1.7 (95 percent CI 1.5–1.8), and occupation explained 40 percent (95 percent CI 30–49) of all Puumala virus infections of farmers in Finland.

**DISCUSSION**

This study covers over 4,700 serologically verified nephropathia epidemica cases occurring during a period of 5.5 years, representing thus the largest number of Puumala virus infections studied in detail for specific risk factors. Finland has the highest incidence of nephropathia epidemica in Europe (excluding some regions of Russia), with geographic and temporal variations mirroring the cyclic population dynamics of the carrier rodent, with a peak in the disease incidence from November to January, and males being affected twice as often as females. The infection is contracted more often in rural settings and by occupants of one-family houses. However, urban people (who have tens of thousands of country houses especially in the hyperendemic Mikkeli region) also are attacked by the Puumala virus, although at a lower rate.

Because of the large number of Puumala virus infections and still enough statistical power when the analyses were restricted to the rural subareas of the hyperendemic Mikkeli region and to people living in one-family houses, we are confident that the confounding effects of age, sex, area, and type of housing did not explain the fact that young farmers especially are attacked early in life by Puumala virus. As many as 80 percent of young farmers’ Puumala virus infections are attributable to their occupation. That the relative risks as well as attributable risk percentages decline with age is not surprising, because Puumala virus infection yields lifelong immunity (7). Thus, many immune farmers contribute person-time to the denominator, effectively diluting the effect of occupation in older age groups, as almost complete immunity in old age groups of farmers in the hyperendemic areas can be achieved. Furthermore, it is noteworthy that, in all subanalyses, the comparison group had its peak incidence 10 years after that of the farmers.

The average Puumala virus seroprevalence in Finland is approximately 5 percent (our unpublished observations) and would require more than 6,000 infections annually to be maintained, while “only” about 1,000 nephropathia epidemica cases were serologically diagnosed and registered per year. Thus, because most Puumala virus infections can go undiagnosed, a detection bias might explain some of the observed effect of farmer’s occupation on Puumala virus risk, as the Finnish Farmers’ Social Insurance Institution has the policy of compensating financial losses due to Puumala virus infection. However, it is unlikely that a nonfarmer neighbor would have different behavior or treatment compared with his farmer neighbor in the same region in response to Puumala virus infection symptoms, as nonfarmers also are compensated by the Finnish National Health Insurance. Furthermore, Swedish seroprevalence data of farmers are congruent with our data showing in endemic areas significantly higher seroprevalences as compared with other population groups (13, 25).

As farmers tend to have much more frequent exposure to the indoor air of cold farm buildings visited by the rodents compared with nonfarmers, we truly believe that farmers acquire Puumala virus infection more often and earlier in life than do other population groups. Accordingly, for contracting both Hantaan and Sin Nombre viruses, a clear risk behavior has been shown to be visiting empty or abandoned outdoor buildings or huts (26, 27). Obviously, more studies of basic epidemiology are needed to assess the risk activities of Puumala virus transmission. In any event, the finding that the absolute Puumala virus risk for farmers is especially pronounced in the eastern part of Finland could be due to 1) the particularly close proximity of fields and farm buildings to forest ecosystems.
FIGURE 4. Serologically verified Puumala virus (PUU) infections in Finland during the study period, July 1989 through December 1994, in the whole country and, separately, in the provinces of Mikkeli and Härme (peak months indicated) (a) and among farmers and nonfarmers (b).

in this region or 2) work with stored hay being more common (especially in outdoor buildings during the rodent density peak in late fall and early winter) in the Mikkeli province, as dairy cattle comprise the predominant type of agriculture in the region.

Linking Puumala virus infection in an individual case with certainty to occupation would require viral sequences from both the patient and local rodents. This is in principle possible but not routinely applicable, as viral sequences from blood or urine can be recovered from only about half of the nephropathia epidemica patients (28). However, contracting hantaviral disease as a result of occupational exposure has been demonstrated using these methods in individual cases of hantavirus pulmonary syndrome (29). Since the rodent ecology, epidemiology, and virulence of hantaviruses differ, the epidemiologic data from one hantavirus/rodent system are not directly applicable to data from another.

Information on the high risk groups of Puumala virus and other hantavirus infections is also needed.
FIGURE 5. Incidence of Puumala virus infections in Finland during the study period, July 1989 through December 1994, among farmers and nonfarmers (comparison group) by age groups in the Mikkeli province (a) and in the whole country (study region) (b). "Incidence" refers to cases per 100,000 person-years.

when vaccination strategies are planned. In addition to farmers, groups such as mammalogists (30), telephone linemen (31), forest workers (32-34), military personnel (35), and herders (15) have been suggested to have an increased risk for different hantavirus infections.

In South Korea, a formalin-inactivated virus vaccine is already in use against the severe hantaviral disease caused by Hantaan virus (36), and ongoing American and European research projects also are planning to develop hantavirus vaccines. However, no evaluation of the usefulness of a hantaviral vaccine in Europe exists. Finland has the highest recorded incidence of hantaviral disease in Europe excluding some areas (Bashkiria, Samara) in Russia and, as shown above, the incidence is especially high among farmers. If the 150,000 farmers of Finland had been successfully vaccinated with an effective vaccine (although about 20 percent were already immune) in 1989, 640 nephropathia epidemica cases could have been prevented in the 5 years of this study. By extrapolation,
TABLE 2. Puumala virus infections (cases), incidence (cases per 100,000 person-years), risk ratios, and attributable risk percentages in the province of Mikkeli, Finland, in different age groups, 1989–1994

<table>
<thead>
<tr>
<th>Age (years)</th>
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<th>Comparison group</th>
<th>Risk ratio</th>
<th>Attributable risk (%)</th>
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* Numbers in parentheses, 95% confidence interval.

we could anticipate preventing perhaps 2,500 more cases (and three deaths) in this cohort over 30 years. That is, about 50 persons should be vaccinated to prevent one acute disease. If we choose the small, but high-risk group of 1,000 farmers aged 20–29 years in the Mikkeli province, the anticipated ratio could be in the range of 10 to 1.

Whether an effective vaccine will be available for preventing the disease in the near future remains to be seen. Meanwhile, more basic epidemiologic work on Puumala virus infections needs to be done, including prospective case-control studies, to further define the risk groups, risk behavior, different ways of transmission, and effective preventive measures.

TABLE 3. Puumala virus infections (cases), incidence (cases per 100,000 person-years), risk ratios, and attributable risk percentages in the whole country in different age groups, Finland, 1989–1994

<table>
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* Numbers in parentheses, 95% confidence interval.

Am J Epidemiol Vol. 149, No. 12, 1999
ACKNOWLEDGMENTS

This work was supported by a grant from the Farmers’ Social Insurance Institution of Finland.

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