Risk factors for pneumonic and ulceroglandular tularaemia in Finland: a population-based case-control study

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SUMMARY

Few population-based data are available on factors associated with pneumonic and ulceroglandular type B tularaemia. We conducted a case-control study during a large epidemic in 2000. Laboratory-confirmed case patients were identified through active surveillance and matched control subjects (age, sex, residency) from the national population information system. Data were collected using a self-administered questionnaire. A conditional logistic regression model addressing missing data with Bayesian full-likelihood modelling included 227 case patients and 415 control subjects; reported mosquito bites [adjusted odds ratio (aOR) 9·2, 95% confidence interval (CI) 4·4–22, population-attributable risk (PAR) 82%] and farming activities (aOR 4·3, 95% CI 2·5–7·2, PAR 32%) were independently associated with ulceroglandular tularaemia, whereas exposure to hay dust (aOR 6·6, 95% CI 1·9–25·4, PAR 48%) was associated with pneumonic tularaemia. Although the bulk of tularaemia type B disease burden is attributable to mosquito bites, risk factors for ulceroglandular and pneumonic forms of tularaemia are different, enabling targeting of prevention efforts accordingly.

Key words: Case-control study, epidemiology, Francisella tularensis, risk factors, tularaemia.

INTRODUCTION

Tularaemia is a zoonotic disease caused by the facultative intracellular bacterium Francisella tularensis, a highly virulent Gram-negative bacterium belonging to the γ-subclass of Proteobacteria [1, 2]. Four subspecies of F. tularensis with different geographical distribution and virulence have been identified [3, 4]. Clinical tularaemia is caused by two of the subspecies: F. tularensis ssp. tularensis (type A), which occurs
mainly in North America and ssp. holarctica (type B), which is endemic in many countries of the Northern Hemisphere, including Finland [3]. The ecology of tularemia is complex and it is still not clear where the bacterium persists in the environment and what factors induce disease outbreaks [4, 5]. Clinical manifestations depend mainly on the route of infection and disease severity on the infecting subspecies. After an incubation period of about 3–5 (range 1–14) days, disease onset is acute with non-specific flu-like general symptoms, especially fever, chills and headache [5, 6]. If the bacteria enter by skin or mucous membranes, ulceroglandular, glandular, oculoglandular or otopharyngeal tularemia may result [6]. In Fennoscandia, the ulceroglandular form is most common and mosquito bites are thought to be an important transmission mechanism [7]. However, few controlled studies are available to demonstrate this association. Inhalation of aerosolized F. tularensis causes respiratory or pneumonic tularemia, the most severe form of the disease [8, 9]. Laboratory diagnosis of tularemia relies mainly on serology, although antibodies only develop 2–3 weeks after illness onset [6].

To determine specific risk factors associated with ulceroglandular and pneumonic tularemia and their public health impact in Finland, we conducted a population-based case-control study during the largest epidemic on record. Information was also collected on clinical features of the disease and patients’ characteristics.

METHODS

Laboratory-based surveillance

The Finnish National Healthcare system is organized into 20 geographically and administratively distinct healthcare districts. Laboratory-confirmed tularemia has been a notifiable disease by the diagnosing laboratory since 1995 and clinical microbiology laboratories report cases directly to the National Infectious Disease Register (NIDR) which is maintained by the National Institute for Health and Welfare (THL). Diagnostic criteria for reporting include isolation of F. tularensis in a clinical specimen or a ≥ fourfold rise in serum antibody titre or a single IgG titre of ≥160.

Population-based case-control study

Case definition and identification

A case patient was defined as a person with laboratory-confirmed tularemia whose first specimen (specimen date) was obtained either from 1 July to 11 August (south-western Finland cases) or from 1 September to 6 October 2000 (northern Finland cases) and tested at one of two laboratories performing tularemia diagnostics in Finland (Etelä-Pohjanmaa Central Hospital in south-western Finland or Oulu University Central Hospital in northern Finland), and who were residents of the endemic health districts (Fig. 1) served by these laboratories. For the case-control study, we identified case patients directly through active surveillance of these two laboratories to accelerate the case identification process.

Case classifications

Patients with laboratory-confirmed tularemia and physician-diagnosed pneumonia were classified as pneumonia cases. Patients with laboratory-confirmed tularemia who reported enlarged lymph nodes and/or skin ulcers were classified as ulceroglandular cases.

Selection of control subjects

Control subjects were identified in the general population of the tularemia endemic health districts. For each enrolled case patient, four controls who matched the patient by year of birth, sex and postal code of residency were randomly selected from the national population information system. Potential controls were excluded from the study if they reported having had febrile illness during the 2-week exposure period or if they were away from their permanent place of residence for more than 1 day during that time.

Data collection

A standard questionnaire was mailed to tularemia case patients and to four selected control subjects. For children aged <15 years, the parents were requested to complete the questionnaire. The first part of the questionnaire included questions on clinical symptoms, history of febrile illness, medications, referrals to hospital, possible symptoms in household members and pet ownership. The second part of the questionnaire included questions about exposures to presumed risk factors for tularemia. For both cases and controls, the questions referred to the 2 weeks before the illness onset date in the case patient (the exposure period). The following exposures were recorded: time spent outdoors (logging, hiking, hunting, picking berries or mushrooms), participating in farming activities (including harvesting and handling hay, cleaning barns), handling dead animals,
swimming in natural waters, drinking water from lakes or wells, and insect bites (mosquito, tick, deer fly, horse fly, or other insect). Study subjects were also asked about use of insect repellents or other protective measures.

**Statistical analyses**

Matched odds ratios (mORs) and their 95% confidence intervals (CIs) were calculated using conditional logistic regression for three main outcomes in univariable analysis: (1) all tularaemia cases, (2) ulceroglandular cases and (3) pneumonia cases. We also constructed composite variables such as ‘exposure to hay’ which included activities such as harvesting hay, cleaning hay, barns or harvester. In univariable analysis, we assumed that missing data were missing approximately at random [10, 11]. We used a $P$ value of $\leq 0.2$ in the univariable analyses as a screening criterion for selection of variables for multivariable analyses [12]. Since self-reported exposures had varying proportions of missing responses, which may introduce bias and reduce statistical power, two different multivariable models were developed. Model 1 was a frequentist model where the variable selection strategy was the backward elimination method with Akaike’s Information Criterion (AIC) corresponding to binary variables with a $P$ value $<0.157$ for inclusion in the model [13]. In model 1, only subjects with complete information on variables in the final model were included. Model 2 was a Bayesian full-likelihood analysis where missing data were taken into account and became a multidimensional additional parameter [14]. In Bayesian model 2 we performed a Gibbs’ variable selection. To include a variable in the final model, the required posterior probability had to be $>50\%$ [14]. We also used the Kolmogorov–Smirnov test to compare distributions.
and the $\chi^2$ test to assess associations between variables in case patients (independent observations). Adjusted population-attributable risks (PARs) and their 95% CIs for each independent risk factor were calculated by using the formula: $\text{PAR} = \frac{pd \times (\text{RR} - 1)}{\text{RR}}$ and adjusted odds ratios (aORs) from model 2 ($pd =$ proportion of cases exposed to a risk factor). This formula produces an internally valid estimate when confounding exists and when adjusted relative risks (i.e. aORs) are used [15]. Analyses were performed using Stata version 9.2 (Stata Corporation, USA) and Winbugs 1.4.3 (Imperial College and MRC, UK).

RESULTS
National laboratory-based surveillance
In 2000, a total of 926 cases of laboratory-confirmed tularemia were reported nationally to the NIDR; 897 (97%) cases had specimen dates during the epidemic period from 1 July to 31 October 2000. Figure 2 shows the reported cases by date of first specimen. The overall annual incidence was 18 cases/100 000 population. Rates were highest in the health districts included in the case-control study (North Bothnia, South Bothnia, Central Finland) (Fig. 1). Tularemia diagnosis was based on serology in 97% (of which ~13% were single titres) and on bacterial culture in 3% of cases. Median age was 48 years (range 0–85 years); 60% of the cases were males.

Population-based case-control study
Questionnaires were mailed to 261 laboratory-confirmed case patients and 780 control subjects. Completed questionnaires were returned by 227 (87%) case patients and 480 (62%) control subjects. The median time from onset of symptoms to laboratory confirmation of diagnosis of tularemia in cases was 22 days (range 1–53 days) and the median time from illness onset to completing the questionnaire was 84 days (range 8–148 days) for all study subjects. Fourteen control subjects were excluded because of febrile illness compatible with tularemia during the exposure period and five because of absence from their permanent place of residence for >1 day during the period. Forty-four control subjects were excluded because their respective case patients did not return the study questionnaire. An additional two control subjects were excluded because they were not residents of the three endemic districts. After exclusions, 227 case patients and 415 control subjects were included in the analysis.

Clinical characteristics of case patients
Signs and symptoms reported by 167 case patients (74%) met the definition of ulceroglandular tularemia and in 20 case patients (9%) the definition of pneumonic tularemia. The remaining 40 laboratory-confirmed tularemia case patients did not report symptoms fulfilling definitions for either form of
tularaemia; these cases were included in the study under the category ‘other’.

Ulceroglandular cases. Seventy-six per cent of ulceroglandular cases resided in North Bothnia, 7% in South Bothnia, 5% in Central Finland and the rest in other healthcare districts (Table 1, Fig. 1). In case patients with ulceroglandular disease, both genders were represented equally; age ranged from 4 months to 84 years (mean 42 years). Illness onsets were from 22 May to 1 October 2000. The most common symptoms of ulceroglandular tularaemia were fever, lymphadenopathy, cutaneous ulcer and myalgia. The median duration of illness was 18 days (range 4–81 days); 37% of cases with ulceroglandular tularaemia were hospitalized.

Pneumonia cases. Seventy-five per cent of the pneumonia case patients resided in North Bothnia, the remaining 25% in South Bothnia (Table 1, Fig. 1). All pneumonia case patients were adults with a mean age of 52 years (range 22–71 years) and 70% were males. Onset of illness was from 23 June to 2 September 2000. All of the patients with pneumonic tularaemia reported fever. The majority of patients with pneumonic tularaemia also reported weight loss, myalgia, cough, dyspnoea and chest pain. Other commonly reported symptoms were headache and exhaustion. Median duration of symptoms was 21 days (range 7–40 days); 70% of the pneumonia patients were hospitalized.

Factors associated with tularaemia

All cases. In univariable analysis, arthropod bites (any arthropod) and specifically, mosquito and horse-fly bites, outdoor activities, handling dead animals (rabbits, voles) and farming activities (land or field preparation, cleaning hay or grain barns,
Table 2. Univariable logistic regression analyses of factors associated with tularemia, Finland 2000

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>All tularemia cases</th>
<th>Ulceroglandular disease</th>
<th>Pneumonic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case n/N (%)</td>
<td>Control n/N (%)</td>
<td>Case n/N (%)</td>
</tr>
<tr>
<td></td>
<td>Case n (%)</td>
<td>Control n (%)</td>
<td>Case n (%)</td>
</tr>
<tr>
<td>Outdoor activities</td>
<td>145/214 (68·2)</td>
<td>222/395 (56·2)</td>
<td>114/157 (72·6)</td>
</tr>
<tr>
<td>Forestry work</td>
<td>29/215 (13·5)</td>
<td>30/389 (7·7)</td>
<td>2/105 (2)</td>
</tr>
<tr>
<td>Farm work</td>
<td>105/216 (48·6)</td>
<td>101/374 (27·0)</td>
<td>66/157 (42·0)</td>
</tr>
<tr>
<td>Land or field preparation</td>
<td>64/217 (29·5)</td>
<td>79/384 (20·6)</td>
<td>50/160 (31·3)</td>
</tr>
<tr>
<td>Exposure to hay (any)</td>
<td>65/210 (31·0)</td>
<td>47/371 (12·7)</td>
<td>30/153 (19·6)</td>
</tr>
<tr>
<td>Cleaning hay or grain barns</td>
<td>35/213 (16·4)</td>
<td>23/378 (6·1)</td>
<td>15/157 (9·6)</td>
</tr>
<tr>
<td>Harvesting hay</td>
<td>51/222 (23·0)</td>
<td>34/401 (8·5)</td>
<td>23/163 (14·1)</td>
</tr>
<tr>
<td>Cleaning harvester</td>
<td>26/222 (11·7)</td>
<td>13/385 (3·4)</td>
<td>9/163 (5·5)</td>
</tr>
<tr>
<td>Producing silage</td>
<td>24/221 (10·9)</td>
<td>17/389 (4·4)</td>
<td>6/162 (3·7)</td>
</tr>
<tr>
<td>Handling dead animals (any)</td>
<td>23/223 (10·3)</td>
<td>11/393 (2·8)</td>
<td>14/165 (8·5)</td>
</tr>
<tr>
<td>Rabbits</td>
<td>7/225 (3·1)</td>
<td>2/397 (0·5)</td>
<td>4/66 (6·7)</td>
</tr>
<tr>
<td>Voles</td>
<td>15/225 (6·7)</td>
<td>3/397 (0·8)</td>
<td>8/166 (4·8)</td>
</tr>
<tr>
<td>Arthropod bites (any)</td>
<td>176/228 (95·1)</td>
<td>247/374 (71·2)</td>
<td>143/146 (97·9)</td>
</tr>
<tr>
<td>Mosquito</td>
<td>156/217 (90·2)</td>
<td>249/354 (70·3)</td>
<td>123/133 (92·5)</td>
</tr>
<tr>
<td>Horse fly</td>
<td>26/177 (14·7)</td>
<td>20/352 (5·7)</td>
<td>19/134 (14·2)</td>
</tr>
<tr>
<td>Black fly</td>
<td>43/171 (25·2)</td>
<td>94/352 (26·7)</td>
<td>34/82 (41·5)</td>
</tr>
<tr>
<td>Deer fly</td>
<td>29/208 (2·8)</td>
<td>13/124 (5·4)</td>
<td>2/72 (2·7)</td>
</tr>
<tr>
<td>Tick</td>
<td>0/104 (0)</td>
<td>1/238 (0·4)</td>
<td>0/77 (0)</td>
</tr>
<tr>
<td>Drinking water from natural water sources</td>
<td>27/214 (12·6)</td>
<td>87/384 (22·7)</td>
<td>19/160 (11·9)</td>
</tr>
<tr>
<td>Swimming in lake, river, pond</td>
<td>68/221 (30·8)</td>
<td>120/397 (30·2)</td>
<td>56/161 (34·8)</td>
</tr>
<tr>
<td>Owning a pet (any)</td>
<td>108/223 (48·4)</td>
<td>178/408 (43·6)</td>
<td>75/165 (45·5)</td>
</tr>
<tr>
<td>Cat</td>
<td>50/224 (22·3)</td>
<td>119/394 (30·4)</td>
<td>31/166 (18·7)</td>
</tr>
<tr>
<td>Dog</td>
<td>66/223 (29·6)</td>
<td>112/408 (27·5)</td>
<td>50/164 (30·5)</td>
</tr>
<tr>
<td>Picking strawberries</td>
<td>84/225 (37·3)</td>
<td>136/393 (34·6)</td>
<td>67/165 (40·6)</td>
</tr>
</tbody>
</table>

mOR, Matched odds ratio; CI, confidence interval; n.a., not available.

Bold values indicate statistically significant (P < 0·05 when 95% CI lower limit > 1) mORs.

Denominator indicates persons for whom data were available for a given variable.
Table 3. Multivariable models and population-attributable risks for factors associated with tularaemia, Finland 2000

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>All tularaemia cases</th>
<th>Ulceroglandular disease</th>
<th>Pneumonic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>PAR†</td>
</tr>
<tr>
<td></td>
<td>aOR* (95% CI)</td>
<td>aOR* (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Outdoor activities in woods</td>
<td>1·8 (1·0–3·1)</td>
<td>1·9 (1·0–3·7)</td>
<td></td>
</tr>
<tr>
<td>Farming activities</td>
<td>2·3 (1·3–4·2)</td>
<td>5·5 (2·7–7·6)</td>
<td>40 (14–65)</td>
</tr>
<tr>
<td>Exposure to hay</td>
<td>4·1 (1·1–15·2)</td>
<td>5·8 (2·3–15·9)</td>
<td>8 (0–24)</td>
</tr>
<tr>
<td>Handling dead animals</td>
<td>4·6 (2·0–10·6)</td>
<td>5·4 (2·8–10·9)</td>
<td>73 (42–92)</td>
</tr>
<tr>
<td>Mosquito bites</td>
<td>2·5 (1·0–6·5)</td>
<td>6·6 (1·9–25·4)</td>
<td>48 (3–78)</td>
</tr>
<tr>
<td>Horse-fly bites</td>
<td>1·0 (0·3–3·1)</td>
<td>1·0 (0·3–3·7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4·1 (1·1–15·2)</td>
<td>5·8 (2·3–15·9)</td>
<td>8 (0–24)</td>
</tr>
<tr>
<td></td>
<td>4·6 (2·0–10·6)</td>
<td>5·4 (2·8–10·9)</td>
<td>73 (42–92)</td>
</tr>
<tr>
<td></td>
<td>2·5 (1·0–6·5)</td>
<td>6·6 (1·9–25·4)</td>
<td>48 (3–78)</td>
</tr>
</tbody>
</table>

Model 1: Conditional logistic regression model (traditional).
Model 2: Bayesian full-likelihood conditional logistic regression model.

* Each aOR is adjusted for the remaining variables shown in the table in addition to the matching factors (see Methods section for details).
† Calculated from aORs derived from multivariable logistic regression model 2.

Pneumonia cases. In univariable analysis (Table 2), the composite variable ‘exposure to hay’ was significantly associated with pneumonia tularaemia. In the 2 weeks before illness onset, 55% of pneumonia patients were exposed to hay, compared to 15% of controls. However, due to missing values only 55% of the statistical units were included in model 1. In model 2 where missing data were excluded, values for 62% of cases and 58% of controls were reported. Exposed to hay remained a strong risk factor for pneumonia tularaemia with PARS of 48% (Table 3). In the pneumonia group, 85% of the statistical units were included in the analysis in model 1. In model 2 (Bayesian), farming activities and handling dead animals were independently associated with pneumonia tularaemia with PARS of 73% for mosquito bites and 8% for handling dead animals.

Ulceroglandular cases. Of case patients, 93% reported arthropod bites in the 2 weeks before illness compared to 70% of controls (Table 2). Of the specified arthropods, mosquito bites were significantly associated with disease. Of the case patients, 93% reported mosquito bites. However, only mosquito bites were independently associated with ulceroglandular tularaemia with PARS of 73% for mosquito bites and 8% for handling dead animals.

Model 2, Bayesian, farming activities, and handling dead animals were included in model 2 (Bayesian), farming activities and handling dead animals were independently associated with ulceroglandular tularaemia with PARS of 32% and 5%, respectively.
DISCUSSION

We report results from national surveillance of tularemia and a large, population-based case-control study during a major tularemia epidemic in Finland. Our results indicate that mosquito bites, farming activities and handling dead animals were independently associated with tularemia infection overall, and that some 73% of all cases could be attributed to mosquito bites. Analyses focusing on risk factors for different clinical outcomes of tularemia showed that mosquito bites and farming activities in general were associated with ulceroglandular tularemia, while exposure to hay dust was the only risk factor independently associated with pneumatic tularemia.

Mosquito-borne transmission has been considered an important mode of transmission of *F. tularensis* holarctica in Fennoscandia [16–18] and some of the largest epidemics have reported a link to mosquito bites. However, no previous studies have included a population-based, controlled design or quantification of the public health impact attributable to various exposures. Our results are consistent with a Swedish study conducted during the same outbreak year which also found an association between tularemia infection and mosquito bites and farming [18]. Mosquitoes may already acquire the bacterium as larvae from their aquatic habitat [16, 17, 19], and persistence of the bacterium in natural waters of endemic areas could explain the uneven geographical distribution of tularemia [20–23]. In Finland, the provinces of Central Finland and North and South Bothnia have the highest incidence of human disease, with fewer cases in other districts. The association of farming with all forms of disease is probably an indicator of outdoor exposure to mosquitoes.

In the case-control study, study participants were asked about being bitten by the most frequent arthropods present in Finland. Mosquito and horse-fly bites were the only specific species associated with tularemia infection in univariable analysis; after adjustment for other variables in multivariable analysis, only mosquito bites remained statistically significant. However, few subjects were exposed to arthropods other than mosquitoes thereby reducing the statistical power to evaluate these associations. Study participants may also have had difficulties in indentifying the various arthropod species or even noticing being bitten by an arthropod, potentially resulting in misclassification of exposure. Because the link to mosquito bites is widely known in the population in the epidemic area in Finland, case patients may also have reported bites more readily than controls creating the potential for recall bias. Although ticks are an important vector for *F. tularensis* in the USA [24], none of the case patients in our study reported tick bites.

Exposure to hay dust was the only exposure significantly associated with pneumonic tularemia; some 55% of these patients reported exposure to hay. Farming activities, such as harvesting hay, have the potential of aerosolizing environmental pathogens and airborne tularemia outbreaks have been linked to farm work [25–28]. However, this is the first study quantifying the association in a controlled study design. Interestingly, five (26%) of the patients with pneumatic form of disease also reported having had a cutaneous ulcer. It is possible that their illness may have been caused by haematogenous spread of *F. tularensis* to the lungs as a complication. Respiratory tularemia is considered an occupational hazard for farmers in endemic areas. Most patients with pneumatic tularemia were males, supporting the link with farming occupation. Some small outbreaks of airborne tularemia in Central Europe an North America have also been associated with other outdoor activities such as lawn mowing [29, 30] or hunting [31, 32].

An association with cat ownership and tularemia was suggested in a Swedish study in which the authors hypothesized that the association could be due to rodents brought home by the cat [18]. Although cat ownership was more common in cases than controls with pneumatic tularemia (32% vs. 13%) in our study, the number of cases was small and this association was not statistically significant. However, cats are common on farms and their potential association with pneumatic tularemia may be confounded by the overall association with farm work.

The main limitation of all case-control studies includes potential for selection and recall bias. Because of active surveillance for cases, population-based design and relatively high participation rates in both cases and controls in the study, selection bias does not appear to be a major concern in our study. Although the control subjects who reported febrile illness were excluded from the study, it was not feasible to test control subjects serologically and some may have had subclinical infection. This potential for misclassification of subjects, however, is probably small and non-differential.

Possible recall bias in reporting various exposures, however, must be considered, since clinical diagnosis of tularemia relies on serology and increased...
antibody levels are generally only present 2 weeks after illness onset. Although we identified the case-patients rapidly through active, laboratory-based surveillance, a few weeks’ delay from the date of specimen collection to completing the questionnaire was inevitable. Control subjects may obviously have had difficulty in remembering certain exposures despite the instructions to use memory aids, such as calendars. A frequent additional problem in self-reported surveys is missing information. In our study, potential bias from missing data was reduced by a Bayesian full-likelihood modelling approach which has the ability to take missing data into account [10], further increasing the validity of our findings. Effects which are clearly significant in either the frequentist or Bayesian models are usually significant in both models, but the full-likelihood analysis has the ability to better discriminate the effects. Thus, the point estimates are generally larger in the Bayesian model.

In conclusion, this large population-based case-control study of Francisella tularensis infection contributes new information about the relative public health importance of various risk factors and provides a comprehensive description of the clinical characteristics. Tularemia causes severe illness and places a substantial burden on the healthcare system during recurring epidemics. Few population-based studies of tularemia are available, and our findings indicate that risk factors for ulceroglandular and pneumonic forms of tularemia are different, enabling targeting of prevention efforts accordingly. Physicians in the endemic areas should consider tularemia in patients with febrile illness and should be trained in how to make the diagnosis. People living in endemic areas should be educated about activities associated with increased risk of infection, preventive measures and the symptoms of tularemia. The risk of tularemia infection can be reduced by protecting against mosquito bites, using disposable gloves if handling dead rodents, and by minimizing exposure to hay dust potentially contaminated with bacteria by wearing masks for respiratory protection while performing farming and landscaping activities. Future studies should be designed to evaluate how to prevent transmission of mosquito-borne tularemia infection to humans.

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DECLARATION OF INTEREST

None.

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