Scientific Research Publishing

Advances in Infectious Diseases, 2021, 11, 185-195
https://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

Investigation of *Yersinia enterocolitica* Bioserotype 4/O:3 Clusters in Finland, 2017-2018

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How to cite this paper: Huusko, S., Salmenlinna, S., Pihlajasaari, A., Hallanvuo, S., Ollgren, J. and Rimhanen-Finne, R. (2021) Investigation of *Yersinia enterocolitica* Bioserotype 4/O:3 Clusters in Finland, 2017-2018. *Advances in Infectious Diseases*, **11**, 185-195.
https://doi.org/10.4236/aid.2021.112018

Received: March 23, 2021
Accepted: May 16, 2021
Published: May 19, 2021

Abstract

In December 2017, two suspected outbreaks of *Yersinia enterocolitica* 4/O:3 were notified in Finland. We analyzed the surveillance and outbreak investigation data and genotyped *Y. enterocolitica* strains in order to understand *Y. enterocolitica* epidemiology in Finland and to find out whether the notified outbreaks were related. A total of 13,344 *Y. enterocolitica* cases were reported in 1995-2018 to the National Infectious Diseases Register. The mean annual incidence ranged from 7.9 to 15.9/100,000 inhabitants. The highest incidence was observed in young adults (14/100,000). Incidence varied geographically. The incidence was higher in spring compared to other seasons. The most common pathogenic bioserotype was 4/O:3 but the information on bio/serotype was missing in 64% of the surveillance cases. For most of the cases, 87%, no travel history was reported. In the YE 4/O:3 outbreak investigation, whole genome sequencing was performed for isolates from 29/69 (42%) of the outbreak cases. The sequencing results showed that cases consisted of six independent clusters with 2 - 6 isolates in each cluster, and 5 sporadic isolates. No food item was found to be common to all of the clusters. In order to improve monitoring and facilitate the detection and investigation of *Y. enterocolitica* outbreaks, more comprehensive information on bio/serotype and on travel history is required in the surveillance.

Keywords

Outbreak, Whole Genome Sequencing, *Yersinia enterocolitica*

1. Introduction

Yersinia enterocolitica (YE) is a commonly reported zoonosis in the EU [1]. YE

bacteria cause human yersiniosis, which is typically manifested by acute febrile diarrhea with abdominal pain. Post-infectious complications such as reactive arthritis and erythema nodosum may occur [2] [3]. YE can be classified into six biotypes (1A, 1B, 2, 3, 4, 5) and numerous serotypes. In 2017, the most frequently reported bioserotype in the EU was 4/O:3 [1]. Infections caused by yersinia usually get better without medication. If symptoms are severe or the disease is prolonged, antimicrobial therapy may be used [2].

YE cases are mostly sporadic and outbreaks are infrequently reported in Finland. In the YE 4/O:3 outbreak in 2003, 30 people contracted gastroenteritis, but the source of outbreak remained unknown [4]. In the YE 2/O:9 outbreak in 2010, 42 cases were identified, but YE could not be found in salad and shredded carrot was suspected as the source [5].

Pigs are a known reservoir for YE [6] [7] [8] and eating or tasting raw or medium-done pork is a risk factor for YE infection [2]. Direct transmission from other animals or through contaminated food is also possible routes of infection in humans [9] [10] [11].

In Finland, YE findings are reported to the National Infectious Diseases Register (NIDR) maintained by the Finnish Institute for Health and Welfare (THL). In addition, municipal food safety authorities notify suspected food and waterborne outbreaks to the National Registry for Food and Waterborne Outbreaks (FWO) maintained by the Finnish Food Authority and THL [12]. FWO notifications are monitored in real time in order to detect large outbreaks affecting more than one municipality simultaneously and to ensure rapid control measures if needed.

In December 2017, two suspected YE outbreaks were notified to the FWO from separate municipalities. We analyzed YE surveillance and outbreak investigation data and genotyped YE strains in order to understand YE epidemiology in Finland as well as to find out whether the notified outbreaks were related to each other and to apply appropriate control measures.

2. Material and Methods

2.1. Surveillance of *Yersinia enterocolitica* Infection

Since 1995, clinical microbiology laboratories have reported YE findings to NIDR. Data on sex, age, place of residence, travel history as well as data on sampling date are reported. In addition, mortality data were obtained from NIDR. To estimate the case fatality, deaths within 30 days of sampling were presumed to be related to yersiniosis. In 2010, clinical laboratories were recommended to use a set of biochemical and microbiological tests for YE identification and notify the bio- and serotypes of YE species to the NIDR [13]. Currently, also MALDI-TOF (matrix-assisted laser desorption ionization-time of flight) analysis is commonly used for YE identification. A surveillance case was defined as a positive laboratory-confirmed YE identified by culture, PCR combined with culture, or antibody typing, and reported to NIDR.

2.2. Microbiological Methods

Clinical laboratories are not requested to routinely send YE isolates to the THL. Yersinia isolates are analyzed at THL, however, if species confirmation is challenging or in case of outbreak investigations. In this outbreak investigation, clinical laboratories were asked to submit the YE 4/O:3 cases reported throughout November and December to the THL for whole genome sequencing (WGS). DNA was purified by using a MagAttract HMW DNA kit (Qiagen, Germany), and the library was prepared by using a Nextera XT sample preparation kit (Illumina, USA). Pair-end sequencing with MiSeq Reagent Kit V2 was performed on a MiSeq sequencer (Illumina, USA). The species confirmation, serotype and 7-gene MLST were inferred from the sequence data, and a core genome multilocus sequence typing (cgMLST) scheme was used for cluster analysis of the isolates by using the INNUENDO platform [14]. In brief, the quality control and trimming of raw reads as well as assembly was performed by using INNUca, the gene-by-gene comparison of alleles was performed by ChewBBACA, and the visualization of allele profiles was performed by PHYLOViZ online. This scheme uses a dynamic cut-off value of 0.37% (no. of allele differences/total number of shared alleles) for *Y. enterocolitica* clusters. The serotype was deduced from raw reads by using ReMatCh.

Microbiological analysis of the food samples was performed locally (PCR screening by ISO/TS 18867:2015; Annex A, method 2). The Finnish Food Authority conducted further analysis of the samples. Three parallel samples were analyzed according to EN ISO 10273:2017, including Annex D for cold enrichment. The DNA of YE 4/O:3 isolates was purified by using DNeasy Blood and Tissue (Qiagen, Germany), and the library was prepared by using a Nextera DNA Flex sample preparation kit (Illumina, USA). The sequencing was performed as described above for human samples.

2.3. Investigation of YE 4/O:3 Cases

After two outbreak notifications in December 2017, THL requested clinical laboratories to send all available *Y. enterocolitica* serotype and biotype data to the NIDR. However, due to a technical problem, some reported cases did not appear in the registry. Hence THL also asked laboratories to send bioserotype information via a secure data transport system. An outbreak case was defined as a person with a laboratory-confirmed isolate of YE 4/O:3 sampled between November 25, 2017 and 30 January 30, 2018 who had no travel history abroad.

Trawling interviews were conducted in four health care districts (Northern Karelia, Southern and Northern Savolax, and Helsinki and Uusimaa health care districts) on the laboratory-confirmed YE 4/O:3 cases. The persons were interviewed by using an online standard trawling questionnaire. The questionnaire included detailed questions about food consumption and purchases, animal contact and environmental exposures in the week before the onset of symptoms, as well as clinical and demographic information. After January 15, 2018, the study focused on hospital districts of Northern Karelia, Northern Savolax, and

Helsinki and Uusimaa, whose isolates could be sent to THL for WGS. In addition, the questionnaire was shortened based on previous results of the standard questionnaire. Online form links were closed on March 2, 2018.

The Finnish Food Authority and local food safety authorities conducted a trace-back investigation. Possible common sources were identified through the interview data.

An outbreak enquiry was conducted on January 12, 2018 via the Food and Waterborne Diseases Network of the European Centre for Disease Prevention and Control in order to chart the possible YE clusters in other European countries.

3. Results

3.1. YE Surveillance

Between 1995 and 2018, a total of 13,344 YE cases were reported to NIDR. The annual variation was 414 - 876 cases (median 547; mean incidence 10.5/100,000 inhabitants). Of the cases, 83% (11,079) were reported as culture findings, 16% (2156) based on increased antibody level and less than 1% (108) as findings based on nucleic acid detection. The median age of the cases was 42 years (range 4 - 89 years) and 57% were female. The incidence was highest in adults in the 25 - 29 age group (mean annual incidence 14/100,000) and in children under 5 years old (11/100,000), and lowest in children 10 - 14 years of age (mean annual incidence 5/100,000).

YE was reported throughout the country (average incidence 10/100,000), but the mean annual incidence varied in hospital districts from 4 to 17 cases/100,000 inhabitants (Figure 1). Cases were more often reported in April-June compared to other months, 905 cases: February (CI 95% 848 - 962), 1399 cases: May (CI 95% 1330 - 1468) (Figure 2). For most of the cases, travel history was not reported

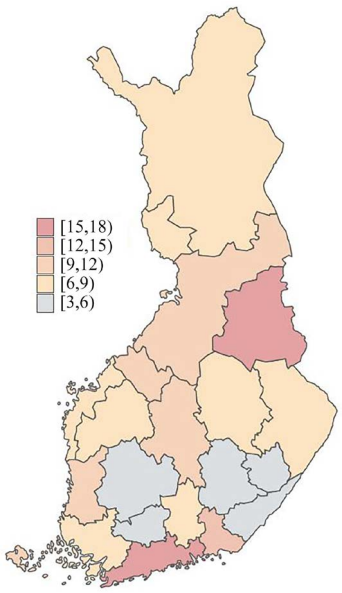

Figure 1. Mean annual incidence of reported *Yersinia enterocolitica* cases per 100,000 population in hospital districts, Finland 1995-2018.

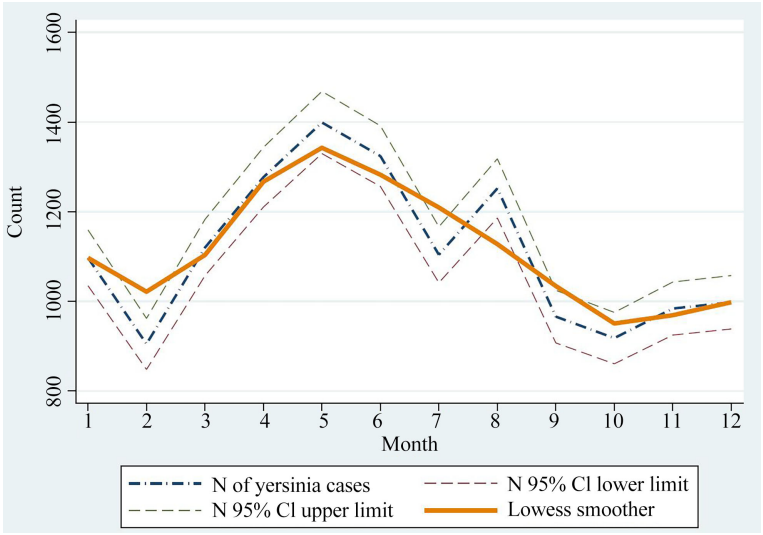

Figure 2. Monthly distribution of *Yersinia enterocolitica* cases in Finland, 1995-2018.

(87%, 11,844/13,344) while 7% (956/13,344) were notified as acquired in Finland. Of the cases, 55/13,344 (0.4%) died within 30 days of sampling.

Serotype data was notified for 25% of YE cases (3328/13,344), the most common serotype being O:3 (77%; 2562/3328) (**Figure 3**). Biotype data was reported for 13% of YE cases (1690/13,344). The most common reported biotype was BT1A (77%; 1296/1690) followed by bioserotype O3 BT4 (20%; 336/1690) and bioserotype O9 BT2 (3%; 49/1690) (**Figure 4**).

3.2. Investigation of Increased YE 4/O:3 Cases

Between November 25, 2017 and January 30, 2018, 69 YE 4/O:3 cases were detected and 33 persons were interviewed by the local outbreak investigation groups. The cases ranged in age from 10 months to 90 years, the median age was 29, and 51% (35/69) were male. Cases were from nine different health care districts.

WGS was performed for isolates from 29/69 cases that were planned to be interviewed. Sequencing confirmed *Y. enterocolitica* species and serotype O:3. The cgMLST of 29 YE 4/O:3 strains showed 6 independent clusters with 2 - 6 isolates in each cluster, and 5 sporadic isolates (**Figure 5**). The allele differences within each cluster were between 0 and 12. The total number of shared alleles among all analyzed isolates was 3110, with the cluster cut-off being >12 alleles.

The traceback and food investigation was focused on two clusters. In cluster A, five out of six cases had eaten in restaurants and two restaurants were mentioned twice and in cluster G, two out of four cases mentioned eating chicken salad made by the same company. In addition, one YE 4/O:3 case mentioned eating salad made by this company, but the quality of the patient strain was not good enough for WGS analysis.

The Finnish Food Authority compared the shipping lists of the fresh vegetable products of three restaurants in cluster A and found that romaine iceberg salad

of the same manufacturer had been available in two of the restaurants. No samples were obtained from the salads. In addition, 14 ready-made salads were analyzed of which one was iceberg lettuce, made by the same producer as the chicken salad in cluster G. YE was not detected in any samples by the PCR method. No food item was found common to the clusters.

Seven countries responded to the enquiry via the Food and Waterborne Diseases Network. Detections of 4/O:3 bioserotype were not reported.

YE was found in the minced meat sample taken from the same product, but different batch, of which one case in cluster A had eaten. The YE 4/O:3 strain with virulence plasmid was isolated from the minced meat sample, but the strain was different from the patient strains in cgMLST analysis (Figure 5).

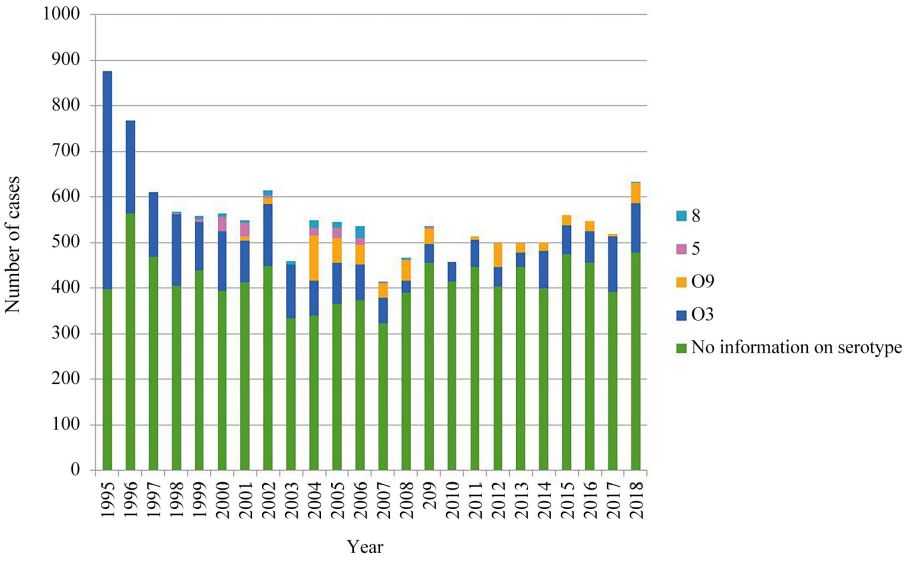

Figure 3. Annual number of reported *Yersinia enterocolitica* infections in Finland according to serotype, 1995-2018 (N = 13,344).

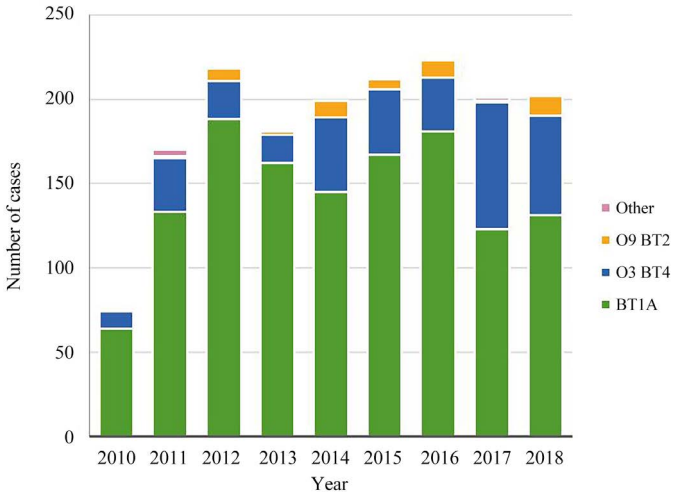

Figure 4. Annual number of reported *Yersinia enterocolitica* infections in Finland according to bioserotype/biotype, 2010-2018.

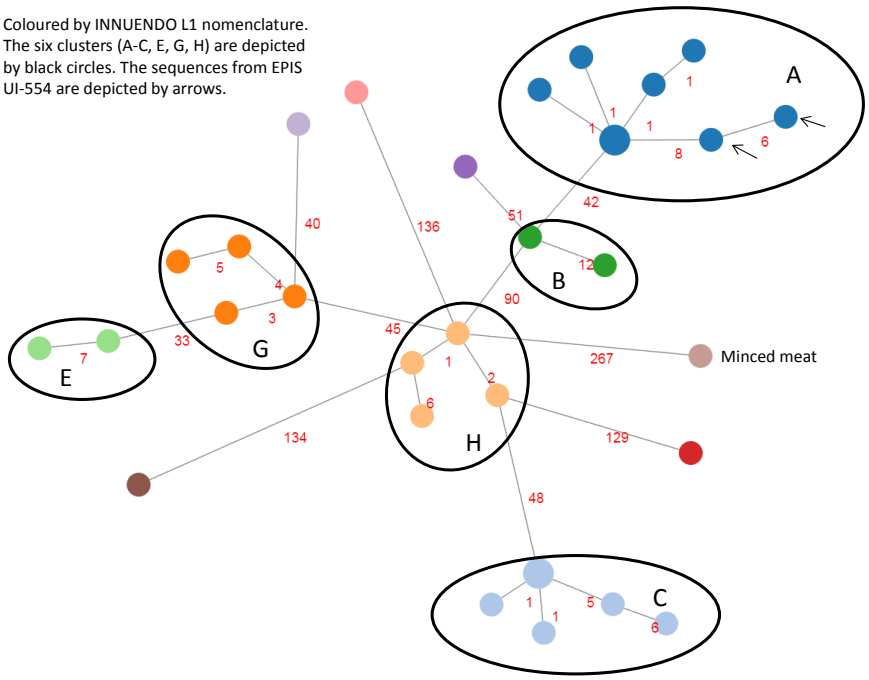

Figure 5. *Yersinia enterocolitica* 4/O:3 clusters (A-C, E, G, H), Finland 2018.

4. Discussion

In December 2017, two suspected YE 4/O:3 outbreaks were detected in separate municipalities and the national authorities in Finland were notified of them. Taking into consideration that yersinia infections are not routinely actively monitored, we started the investigation by analyzing the surveillance data in order to understand the baseline of YE infections in Finland.

Reporting of YE cases was stable in Finland from 1995-2017 (annual incidence range 7.9 - 15.9/100,000 inhabitants) while an increase in cases was seen in 2018. The incidence is among the highest in the EU [1] [15], but comparing the prevalence between countries is not unambiguous due to the differences in diagnostics and reporting systems [13] [15]. The EU definition for YE laboratory confirmed case is isolation of human pathogenic YE [16]. In Finland, the majority of surveillance cases are culture confirmed. In addition, antibody and nucleic acid detection findings are also reported to NIDR. Over half of the notifying clinical laboratories at least occasionally report YE-isolate's biotype and/or serotype or the presence of virulence plasmid [17]. Still, the information on biotype/serotype was missing in 64% of the surveillance cases' isolates. YE 4/O:3 was the most commonly reported pathogenic bioserotype in the EU in 2017 [1]. Estimating the trend of the prevalence of YE 4/O:3 in Finland is difficult given that information about the virulence and biotypes/serotypes is lacking for most of the reported cases.

Biotype 1A has been the most common reported biotype in Finland. Biotype 1A is a heterogeneous group of strains [18] lacking the pYV virulence plasmid typical of pathogenic yersinia [19]. However, some 1A strains may have other

properties that affect the ability to infect [2] and the pathogenicity cannot be reliably determined based on bioserotype classification alone [20]. The significance of 1A strain causing illness is still unclear [2] [20] [21] and further research on the molecular mechanisms is needed [20]. Currently, ECDC's instructions for EU/EEA member states are to only include cases with pathogenic YE isolates to the European Surveillance System (TESSy) [15].

In Finland, the highest incidence of YE was observed in young adults and in the elderly (13 - 14/100,000). In addition, the incidence in children under five years old was rather high (11/100,000). Previous studies from Spain and Germany have found that the incidence of YE was the highest in children under five years old, but in contrast to Finland, the incidence was low in adults [22] [23]. High incidence in children might be explained by the fact that the infective dose required is much lower than for adults, a stronger likelihood of the development of symptomatic illness and the greater demand for medical care for mild illnesses in children than in adults [22]. The mortality rate (0.4%) was low in Finland, while in other EU countries even lower rates (0.03% - 0.06%) have been reported [1] [23].

In Finland, seasonal variation in YE infections was found while other studies have reported less variation [22] [23]. The reason for a higher incidence in spring than in other seasons in Finland is unknown. The mean annual incidence also varied geographically. The travel history of YE patients was rarely reported in the surveillance data. However, a previous questionnaire study in Finland showed that traveling abroad was more common among patients with YE than in their controls [2]. To better understand the epidemiology of YE infections in Finland, a case-control study revealing the risk factors of infections including data on travel history would be necessary.

In the two notified outbreaks, the cases consisted of six independent clusters based on the WGS results. WGS was used for the first time in a YE outbreak investigation in Finland. Inns *et al.* reported an investigation of YE cluster and the first use of WGS in UK in 2017 [24]. In that investigation, YE cases were clustered in time, person and place, but the WGS results indicated that the cases were not from the same source. In April 2019, a cross-border outbreak of YE O3 was identified in Sweden and Denmark. Imported fresh spinach was deemed to be the outbreak vehicle [25]. The sequences shared by Sweden (ERR3293975 and ERR 3293974) were related to cluster A in our outbreak investigation, with an allele difference ranging between 8 and 11 (**Figure 5**). According to the shipping list, no spinach was available in menus from restaurants related to cluster A.

In addition to pork products [2], fresh produce items should be considered possible sources of YE outbreaks [25]. The risk of yersiniosis can be reduced by cooking all meat carefully, washing raw vegetables thoroughly before eating and keeping raw meat separate from other foods as well as by handling raw meat with different cooking utensils than other foods. Hands should be thoroughly washed before eating and cooking, after handling raw meat. Unpasteurized milk and milk products should not be consumed [2]. In our investigation, no food

item was found as a source of any of the clusters. Later, YE was detected in one manufacturer's striped carrot by PCR. Carrots had not been eaten by the outbreak cases, but the products of the same manufacturer had been available in two of the restaurants involved in the investigation (cluster A). However, in the deeper analysis conducted by the Finnish Food Authority, no YE 4/O:3 could be isolated from the carrot sample. Instead, a non-pathogenic YE biotype 1A, exceptionally carrying the ail gene typical of pathogenic YE, was isolated in the sample. The ail gene could explain the positive PCR reaction of the sample.

Reporting of food-borne outbreaks is mandatory according to the Zoonoses Directive 2003/99/EC in the EU [1], but outbreaks caused by YE are seldom reported in Finland. Between 2000 and 2018, six YE outbreaks were reported to the FWO register. Virtanen *et al.* (2013) showed that the occurrence of the same MLVA types in clinical samples collected over several years from human and porcine sources in four countries indicated a long-term persistence and common infectious sources [26]. Consequently, outbreaks seem to exist, although many of them have remained unidentified [26]. The public health burden of yersiniosis may be larger than the actual number of reported cases would suggest, given that the potential complications of yersiniosis are severe [27]. In order to improve monitoring and facilitate the detection and investigation of YE outbreaks, more comprehensive information on bio/serotype and on travel history is required during surveillance.

Acknowledgements

We would like to thank the local and regional health and food safety authorities, and laboratories in Northern Karelia, Northern Savolax, and Helsinki and Uusimaa for their contributions to the outbreak investigation. In addition, we would like to thank the contributing laboratory technicians at the Finnish Institute for Health and Welfare and the Finnish Food Authority.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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