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Case report

First European detection and genomic analysis of *Francisella tularensis* subsp. *tularensis* in a traveler returning from Canada

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ABSTRACT

Tularemia is a zoonotic disease caused by the gram negative coccobacillus *Francisella tularensis,* a Biosafety Level 3 pathogen and potential bioterrorism agent. We report here the first European human case of tularemia caused by *F. tularensis* subsp. *tularensis* in a patient returning from Canada to Switzerland. Successful culture and genomic characterisation revealed that the isolate belongs to the A.I lineage of *F. tularensis* subsp. *tularensis*, and clusters with strains from Canada and Alaska. This work underscores the importance of rapid diagnostics combined with genomic analysis and molecular characterization for detecting non-endemic pathogens and evaluating potential bioterrorism threats.

Clinical presentation

On September 27th, 2025, a 38-year old male returning from Canada presented at the University Hospital of Bern, Switzerland, with a necrotic bullous lesion on the right hand, tender axillar and supra-clavicular lymphadenopathy, fever and asthenia (Fig. 1). The symptoms had appeared ten days earlier and worsened despite antibiotics initiated in Canada (Fig. 1). The patient reported staying in a cabin in Yukon, Canada, where he was exposed to rodents and hunted lagomorphs. Given the recent travel history and the clinical presentation, the initial differential diagnosis included tularemia and anthrax, and treatment with doxycycline was initiated. *Francisella tularensis* was diagnosed by real-time-PCR at the Institute for Infectious Diseases of the University of Bern on September 30th. In parallel, a swab sample from the lesion was sent to the National Reference Centre for Highly Pathogenic Bacteria (NABA), Spiez Laboratory, which tested positive for *F. tularensis* subsp. *tularensis* on October 1st.

During a follow-up on October 2nd, the patient reported overall improvement but persistent pain at the lesion site and side effects from doxycycline. These side effects, together with the confirmation of *F. tularensis* as etiological agent, prompted a switch to ciprofloxacin. On October 8th, the symptoms had further improved, with reduced pain and decreased lesion severity. By October 22nd, the lesion was closed and dry and antibiotic therapy was discontinued.

Isolate characterization

Given the patient's travel history and the analytical portfolio of Spiez Laboratory focusing on bioterrorism, the suspicion for *F. tularensis* subsp. *tularensis* was raised and a molecular analysis to identify the subspecies was conducted. Compared to *F. tularensis* subsp. *holarctica*, predominantly found in Europe and Asia and causing mild disease, *F. tularensis* subsp. *tularensis* is endemic to North America and associated with more severe clinical presentations [1–3]. The two subspecies differ in their minimal infectious dose and their virulence. In rabbits, a single *F. tularensis* subsp. *tularensis* bacterium is sufficient to cause 100% mortality, whereas 10^9 *F. tularensis* subsp. *holartcia* bacteria are required to yield the same outcome [1]. Furthermore, some virulent *F. tularensis*

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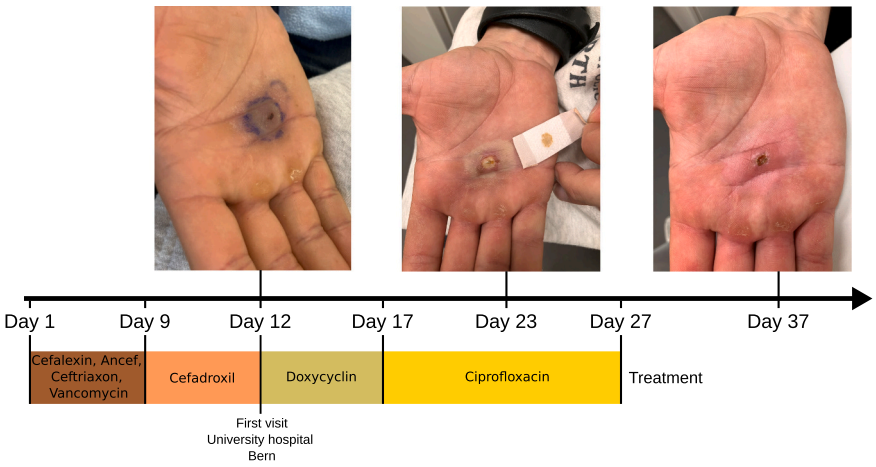

Fig. 1. Disease progression and antibiotic treatment. Right hand lesion progression and antibiotic treatment timeline, from first day of treatment (Day 1, September 16th, 2025, Canada) to last hospital visit (Day 37, October 22nd, 2025, Switzerland). The first hospital visit in Bern, Switzerland, occurred on Day 12 (September 27th, 2025), at which time treatment with Doxycyclin was initiated and the lesion first photographed.

subsp. *tularensis* strains have been reported to have a mortality rate of up to 24% in humans, which is much higher than the mortality rate commonly associated with *F. tularensis* subsp. *holarctica* (~7%) [4]. Due to these characteristics, *Francisella tularensis* subsp. *tularensis* is listed as a category A potential bioterrorism agent by the U.S. Centers for Disease Control and Prevention (CDC), and is also considered a potential biothreat and high consequence pathogen by the EU Reference Laboratory for Public Health (EURL-PH) [5,6]. To discriminate between the two subspecies, the NABA used an in-house real time PCR assay targeting the genes *AV531_03765*, specific for *F. tularensis* subsp. *tularensis*, and *F3Y03_07780*, specific for *F. tularensis* subsp. *holarctica*. This assay classified the Swiss isolate as *F. tularensis* subsp. *tularensis* (AV531_03765 positive, F3Y03_07780 negative), consistent with the patient's stay in Canada.

Whole-genome sequencing was performed to further characterize the isolate. The sample was cultured on Chocolate + PolyViteX agar in a BSL-3 laboratory, and bacteria were collected for inactivation according to a validated in-house protocol. DNA was extracted using the Qiagen DNeasy Blood and Tissue kit and sequenced on a MiniSeq (Illumina) using the Illumina DNA Prep kit for library preparation.

Sequencing data were analyzed using an in-house bioinformatic pipeline. Data quality control was performed using **FastQC** (v0.11.9) and raw reads were trimmed using **fastp** (v1.0.1) [7,8]. Genome assembly was performed using **SPAdes** (v4.2.0), **bwa** (v0.7.17), **pilon** (v.1.23), and **seqkit** (v2.10.1) and annotated using **bakta** (v1.11.4) [9–13]. Assembly quality was assessed with **BUSCO** (v6.0.0), **QUAST** (v5.3.0) and **CheckM2** (v1.1.0) [14-16]. Genotyping was carried out using two complementary approaches. First, core-genome multi-locus sequence typing (cgMLST) was performed with **chewBBACA** (v.2.8.5) using the scheme described in Antwerpen et al., 2015 [17,18]. Comparison with 41 reference genomes from NCBI showed that the Swiss isolate belongs to the A.I clade of *F. tularensis* subsp. *tularensis* **(**Fig. 2**A),** a clade found in central, eastern, and northern North America [19,20]. The A.I clade is thought to be more virulent than the A.II clade, and is associated with higher human mortality rates [4]. Interestingly, the Swiss isolate clusters closely with strains originating from Canada and Alaska **(**Fig. 2**A, orange box).** To refine this analysis, the NABA performed core-SNP typing using **Snippy** (v. 4.6.0), **gubbins** (v.3.0.0) and **IQ-TREE** (v.1.6.7), focusing on 22 strains belonging to clade A.I [21–23]. This approach identified strain FSC041 (GCF_016605695.1), a highly virulent strain isolated from a tick in British Columbia, Canada, as the closest relative **(**Fig. 2**B)** [24]. Snippy detected ten variants between the Swiss isolate and FSC041, including two deletions, one insertion and seven SNPs. All variants were classified as having low to moderate effects on gene function using **snpEff** (v.5.2) [25]. No unusual antimicrobial resistances or virulence factors were detected using **abricate** (v1.0.0) with the NCBI AMRFinderPlus and CARD databases, aside from the beta-lactamase gene *FTU-1* typically found in *F. tularensis* strains and conferring resistance to beta-lactam antibiotics [26–28].

Conclusion

To our knowledge, we report here the first human case of tularemia caused by *F. tularensis* subsp. *tularensis* in Europe. This strain was identified at the subspecies level using an in-house real-time PCR assay, and fully sequenced for subtyping. Characterizing isolates from non-endemic, highly pathogenic agents of unclear etiology by rapid and precise molecular diagnostics and genomic analysis is not only of relevance for targeted clinical treatment, but also of the utmost importance to exclude any malicious intent.

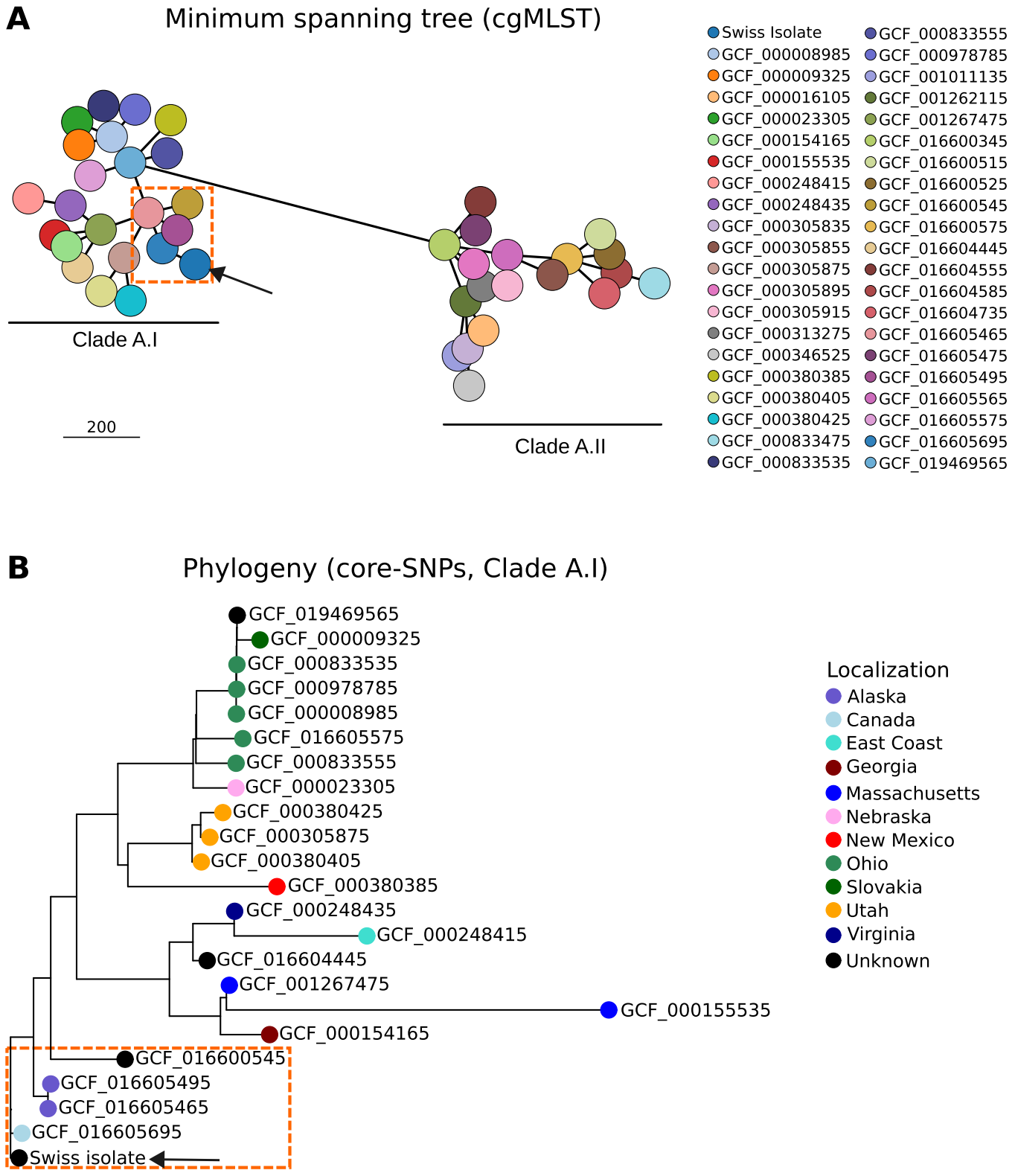

Fig. 2. Phylogenetic analysis of Francisella tularensis subsp. tularensis isolates. (A) Minimum spanning tree based on cgMLST of Francisella tularensis subsp. tularensis isolates. 41 reference genomes from NCBI were included in the analysis. Black arrow represents the Swiss isolate. Orange box highlights strains from Canada or Alaska. **(B)** Core-SNPs-based phylogenetic tree. 22 reference genomes from NCBI belonging to clade A.I were included in the analysis. Black arrow represents the Swiss isolate. Orange box indicates strains from Canada or Alaska. Strains are color-coded based on geographical origin.

CRediT authorship contribution statement

Cesar M.J.A. Metzger: Writing – review & editing, Supervision, Resources. **Schmidt Kristina Maria:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Conceptualization. **Roger Koller:** Writing – review & editing, Investigation. **Lukas Baumann:** Writing – review & editing, Investigation. **Sandra Paniga:** Writing – review & editing, Investigation. **Katia Jaton:** Writing – review & editing. **Ophélie Rutschmann:** Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **David Leuenberger:** Writing – review & editing, Investigation. **Samuel Raemy:** Writing – review & editing, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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