

1 **PEDIATRIC TULAREMIA– A CASE SERIES FROM A SINGLE CENTER IN**
2 **SWITZERLAND**

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6 **Keywords:** *Tularemia, Francisella tularensis, child, pediatrics, ulceroglandular, glandular,*
7 *case series*

8 **Running title:** Tularemia in Children

9 **Key points:** Pediatric tularemia is an emerging disease in Europe. In this case series of 20
10 patients we identify clinical factors, which may contribute to early diagnosis and targeted
11 therapy, potentially obviating the frequent need for lymph node surgery.

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1 ABSTRACT

2 **Background:** The incidence of tularemia has recently increased throughout Europe.

3 Pediatric tularemia typically presents with ulceroglandular or glandular disease and requires
4 antimicrobial therapy not used in the empirical management of childhood acute
5 lymphadenitis. We describe the clinical presentation and course in a case series comprising
6 20 patients.

7 **Methods:** Retrospective analysis of a single-center case series of microbiologically
8 confirmed tularemia in patients below 16 years of age diagnosed between 2010 and 2021.

9 **Results:** Nineteen patients (95%) presented with ulceroglandular (n=14) or glandular
10 disease (n=5), respectively. A characteristic entry site lesion (eschar) was present in 14
11 (74%). Fever was present at illness onset in 15 patients (75%) and disappeared in all
12 patients before targeted therapy was initiated. The diagnosis was confirmed by serology in
13 18 patients (90%). While immunochromatography (ICT) was positive as early as on day 7, a
14 microagglutination test (MAT) titer 1:≥160 was found no earlier than on day 13. Sixteen
15 patients (80%) were initially treated with an antimicrobial agent ineffective against *F.*
16 *tularensis*. The median delay (range) from illness onset to initiation of targeted therapy was
17 12 days (range, 6-40). Surgical incision and drainage was ultimately performed in 12 patients
18 (60%).

19 **Conclusion:** Pediatric tularemia in Switzerland usually presents with early, self-limiting fever,
20 and a characteristic entry site lesion with regional lymphadenopathy draining the scalp or
21 legs. Particularly in association with a tick exposure history, this presentation may allow early
22 first-line therapy with an agent specifically targeting *F. tularensis*, potentially obviating the
23 need for surgical therapy.

1 INTRODUCTION

2 Human tularemia, an emerging infection in Europe [1-6] caused by *Francisella tularensis*, is a
3 highly virulent zoonotic disease with sources of human infection in both wild and domestic
4 animals, such as small rodents, lagomorphs, ticks and mosquitos, and in water bodies [7-12].

5 In Central and Northern Europe, the organism is transmitted to humans predominantly
6 through a haematophagous arthropod bite (ticks in Central Europe, mosquitos in Northern
7 Europe), whereas reports from Eastern Europe, including Turkey, describe numerous
8 outbreaks linked to the ingestion of contaminated water [13-17]. Inoculation may also occur
9 through the skin, ingestion of undercooked meat, or inhalation of aerosols [18].

10 Two subspecies of *F. tularensis* are responsible for human disease [19]. *F. tularensis*
11 subspecies *tularensis* (type A) is mainly reported in North America and often causes an
12 invasive and aggressive clinical course. *F. tularensis* subspecies *holarctica* (type B) causes
13 tularemia in Europe and throughout the Northern hemisphere [20].

14 Clinical disease in humans varies according to the mode of acquisition of *F. tularensis*, and is
15 described as ulceroglandular, glandular, oropharyngeal, oculoglandular, typhoidal, or
16 pneumonic tularemia [18, 20, 21]. In Switzerland, ulceroglandular and glandular tularemia
17 account for the majority of reported cases in all age groups, with pulmonary and abdominal
18 disease being reported only in 20% and 5%, respectively [22]. Early systemic signs of the
19 disease are unrelated to the inoculation site and consist of influenza-like symptoms (e.g.,
20 fever, fatigue, headache, and rash) [18, 23].

21 Reports on pediatric tularemia in the English language literature originate mainly from North
22 America, where type A is prevalent, from Sweden and Finland, where type B causes
23 mosquito-borne infections [7, 24-28], and from Eastern Europe and Norway, where
24 oropharyngeal disease from contaminated water or food is prevalent [13-16, 29]. Reports on
25 pediatric disease in Western-Central Europe, however, are scant and limited to case reports
26 [30-38]. No case series are available. Based on case reports and expert opinion [18, 39],

1 Western-Central European tularemia is primarily considered a tick-borne disease, but may
2 also result from contact with an infected animal, with the ulceroglandular or glandular form
3 being by far the most common clinical presentation.

4 The purpose of this report is to provide a precise clinical description of a case series of
5 pediatric tularemia from a single center in Switzerland.

6 **METHODS**

7 This is a retrospective single-center case series of patients less than 16 years of age
8 diagnosed with tularemia at the University Children's Hospital, Bern University Hospital,
9 Switzerland, between January 1, 2010 and December 31, 2021. Case finding was performed
10 by searching the electronic clinical microbiology database (Institute of Infectious Diseases,
11 University of Bern, Switzerland) for cases testing positive for *F. tularensis* by serology or by
12 culture or by a positive Polymerase Chain Reaction (PCR) test amplifying a 270 bp *fopA*
13 gene fragment from a biological specimen (i.e., swab from ulcer surface or surgically
14 obtained lymph node material) [40].

15 Serology was defined as positive with a single microagglutination test (MAT) titer of ≥ 160
16 according to WHO guidelines [41, 42] or with a greater than 4-fold MAT titer increase in
17 paired sera. In addition, an immunochromatographic rapid antibody test (ICT) using the
18 Virapid[®] Tularemia assay (Viracell, Granada, Spain) was performed in all cases occurring from
19 2016 onwards. The results were determined visually and considered positive with
20 semiquantitative readings of 0.5 ("weakly positive") or 1.0-3.0 ("positive"), respectively,
21 according to the manufacturer's instructions.

22 We used the term "ulceroglandular" tularemia, when acute lymphadenopathy was
23 accompanied by an entry site lesion (ulcer, eschar) in the drainage area of the affected
24 lymph nodes. In the absence of such skin lesions, we used the term "glandular" tularemia.

25 The clinical data of each patient were extracted from the electronic medical record system
26 and included the variables listed in table 1. For the presentation of the clinical course and the

1 timing of both diagnostic and therapeutic interventions, day 1 of symptoms, i.e., fever and/or
2 lymph node swelling, was used as anchor point and the time elapsed since day 1 was
3 calculated for each subsequent event of interest (median, range). Narrative chart information
4 about time intervals was converted, if needed, to numeric data, i.e., the terms "several days",
5 "week" and "month" were converted to 3, 7 and 30 days, respectively.

6 For a standardized description of involved neck lymph nodes, we used the updated neck
7 dissection classification of the American Head and Neck Society and the American Academy
8 of Otolaryngology [43]. The narrative description of involved lymph node levels in the medical
9 records, photographs and ultrasound findings were used to anatomically locate the affected
10 lymph node levels in each patient.

11 For targeted antimicrobial therapy, oral or intravenous ciprofloxacin (10 mg/kg/dose every 12
12 hours or BID, top dose 750 mg BID) or oral or intravenous doxycycline (2 mg/kg/dose every
13 12 hours or BID, top dose 100 mg BID) was prescribed.

14 For descriptive statistics and non-parametric statistical tests of ordinal data we used
15 GraphPad Prism version 9.0.0 for Windows, GraphPad Software, San Diego, California USA.

16 **RESULTS**

17 *Epidemiology and demography*

18 The temporal occurrence of study cases between 2010 and 2021 in relation to the total
19 number of human tularemia cases reported to the Swiss Federal Office of Public Health [1] is
20 shown in the supplementary data file, figure S1. It illustrates that the temporal occurrence of
21 cases in this series parallels the increase of cases reported throughout the country in all age
22 groups. The seasonal distribution of cases ranged from February to October, with 11 cases
23 (55%) occurring between May 1 and July 31 (supplementary data file, figure S2). There was
24 no local clustering of cases. Clinical and demographic data describing the 20 patients are
25 listed in table 1. The time elapsed from day 1 of symptoms attributed to tularemia to both
26 diagnostic and therapeutic events of interest is shown in figure 1.

1 *Clinical manifestations*

2 Nineteen patients, all residing in Switzerland, presented with unilateral ulceroglandular
3 (n=14) or glandular disease (n=5). One additional patient, who acquired tularemia together
4 with his father during a stay in Eastern Europe in 2010, was considered to have
5 oropharyngeal disease. This case was excluded for the analyses in figure 1 and other time-
6 related analyses, because of his delayed presentation 3 months after illness onset. Among
7 the remainder, one patient with axillary lymphadenopathy reported a wood mouse bite to the
8 ipsilateral index finger (figure 2, panel J). All other patients (n=18) presumably had tick-borne
9 disease, although another means of transmission, e.g. direct contact with an infected
10 mammal, cannot be excluded. Of these, 10 patients (56%) or their proxy reported a tick bite
11 whose location was compatible with the entry site lesion or the affected lymph nodes,
12 respectively. A cutaneous entry site lesion in the drainage area of the affected lymph nodes
13 was clinically evident in 13 patients (72%). Figure 2 depicts the lesions of 9 patients, of
14 whom photographs were available. With the possible exception of two cases (figure 2, panels
15 H, I), all entry site lesions showed multiple distinct vesicles, ulcers or eschars. Affected lymph
16 nodes were located on the head and neck (9 patients; 6 with an entry site lesion), inguinal (8;
17 6), and axillary areas (1; 1), respectively. Figure S3 illustrates the head and neck distribution
18 of affected nodes in 9 patients. Except for one case (figure S2, dark red square) all affected
19 lymph node locations were compatible with an entry site on the scalp. The involved areas
20 were uniformly tender to touch, with or without erythema of the overlying skin (e.g., figure 2,
21 panel I), and firm to palpation. In all but one case, clinical and sonographic findings revealed
22 multiple, in part conglomerated lymph node enlargements. Systemic symptoms included
23 fever during the first days of illness in 15 of 20 patients (75%), which resolved in all patients
24 before the initiation of targeted antimicrobial therapy against *F. tularensis*. A generalized
25 scarlatiniform rash occurred in two patients. Conjunctival manifestations were not observed.
26 Blood markers of inflammation determined at the time of the first in-house presentation are
27 listed in table 1 and figure S4.

28

1 *Microbiology*

2 Of 20 patients, 18 were found to have a positive MAT (reciprocal titer range, 160-5120). In
3 two patients, tularemia was exclusively diagnosed by culturing *F. tularensis* from a skin entry
4 site. Serologic findings are detailed in table 1 and figure S4. The median time elapsed from
5 day 1 of symptoms to first serology was 10 days [range, 1-40; figure 1]. The first patient
6 contact at our institution generally resulted in swift serologic testing (median 0 days, range,
7 0-11). Whereas a significant MAT titer was found no earlier than on day 13, the ICT was
8 positive as early as on day 7 (figure S4 and table 1). PCR of surgically removed lymph node
9 material was positive for *F. tularensis* DNA in all 7 cases investigated, while the attempt to
10 cultivate a causative agent was positive in none of 5 lymph node samples. However, *F.*
11 *tularensis* was cultivated from all three entry site lesions swabbed. One isolate from a
12 patient, who clinically failed ciprofloxacin therapy despite early initiation on day 6, was
13 characterized further, identified as *F. tularensis* subspecies *holarctica*, and found susceptible
14 to all antimicrobials tested (table S1).

15 *Pathology*

16 Histopathologic examination was performed on excised lymph node material in three cases
17 (15%). It revealed areas of necrosis, acute suppurative abscess formation and granulomatous
18 inflammation with epithelioid cell reaction in two patients, and nonspecific necrosis in one.

19 *Treatment*

20 Sixteen patients (80%) received a betalactam agent (amoxicillin-clavulanate in 15, amoxicillin
21 in one patient, respectively) as empiric first-line treatment for acute lymphadenitis. Antibiotic
22 therapy specifically targeting *F. tularensis* with ciprofloxacin (n=15) or doxycycline (n=5),
23 respectively, was used exclusively as secondary option because of clinical failure. The
24 median duration of therapy was 16 days (range, 10-28 days), and was initiated with a median
25 delay of 12 days after onset of symptoms (figure 1). The median delay to targeted therapy
26 was not significantly longer in patients ultimately requiring surgical incision and drainage (15

1 [6-40] vs. 12 [8-18] days; $p=0.472$). Surgery was performed at a median of 13 days (range, -1
2 to 43) after starting targeted therapy.

3 *Outcome*

4 Sixteen patients (80%) required an in-patient stay at some time during their illness with a
5 median duration of 2 days (range, 1-7). The last outpatient follow-up was recorded at a
6 median of 39 days after day 1 (range, 12-167). All 12 patients (60%), who received surgical
7 incision and drainage of mostly purulent material ($n=10$) from affected lymph nodes, had
8 uneventful wound healing without evidence of prolonged drainage site fistulation. In one
9 patient, surgery resulted in hypertrophic scar tissue on the neck. No patient required
10 additional antimicrobial therapy after the first targeted course with ciprofloxacin or
11 doxycycline. No secondary surgical intervention was necessary.

12 **DISCUSSION**

13 To our knowledge, this is the first report describing a clinical case series of pediatric
14 tularemia from a Western-Central European country [1, 6, 44]. All cases presented with
15 ulceroglandular or glandular disease, which is in line with previous case descriptions [30-38].
16 The fact that we found no other organs involved may reflect either a lack of clinical
17 awareness for pulmonary or abdominal disease in children or truly infrequent transmission of
18 *F. tularensis* via the respiratory or intestinal routes in Switzerland. Pulmonary and abdominal
19 disease in Swiss adults does occur, but is uncommon [22]. Causes for the rapidly increasing
20 case counts in recent years may include enhanced awareness, improved performance of
21 diagnostic techniques, changes in leisure behavior, and a truly expanding animal or
22 environmental reservoir [39]. The proportion of all cases of pediatric acute lymphadenitis that
23 are caused by *F. tularensis* is therefore likely to continue to increase in the near future, which
24 calls for a reappraisal of the empirical management of this condition. It currently consists - as
25 exemplified in this study with 80% of patients (table 1) - of antibiotic first-line therapy with a
26 betalactam agent or clindamycin [45, 46], which are clinically ineffective against *F. tularensis*
27 [47] and contribute to therapeutic delays. In our series, we found a high rate of surgical

1 incision and drainage needed for controlling lymphadenitis in the purulent stage (60%). For
2 comparison, in case series of pediatric oropharyngeal disease, rates of suppuration requiring
3 surgical intervention were 47-58% [11, 13, 48]. This generally unsatisfactory outcome is likely
4 related to delayed diagnosis and therapy [41, 48-50] and may be improved by accelerating
5 early management. Currently, the diagnostic standard in cases of suspected tularemia
6 consists of the demonstration of a serum antibody titer determined by MAT of $1:\geq 160$ or a
7 fourfold titer increase in paired sera [42, 51], or by a positive PCR or culture of an entry site
8 drainage (eschar) or tissue biopsy specimen. Serology of acute and convalescent blood
9 samples remains the diagnostic mainstay, because culture is rarely positive, and PCR is
10 often not routinely available [18]. Because serologic confirmation is often delayed to the
11 second or third week of illness, the clinical suspicion of tularemia should lead to early
12 antimicrobial therapy with ciprofloxacin or, alternatively, doxycycline. Betalactams and
13 macrolides are ineffective [18]. Intravenous therapy with gentamicin is highly effective, but
14 not commonly prescribed for the generally milder infections with subspecies *holarctica*.

15 Assuming that early diagnosis and therapy with an agent active against *F. tularensis* hastens
16 the resolution of symptoms and signs [28] and potentially obviates the need for surgery,
17 including anaesthesia and subsequent wound treatment, the analysis of this case series
18 provides several insights into how the diagnostic process of tick-borne tularemia could be
19 expedited in pediatric primary care.

20 First, we found that influenza-like early systemic symptoms invariably resolved during the
21 presumably ineffective therapy with amoxicillin-clavulanate. This may have been mistaken for
22 effectiveness, while in fact representing the spontaneous evolution of pediatric tularemia, and
23 thereby contributed to diagnostic delays. The immunologic events leading to the
24 spontaneous resolution of systemic manifestations are likely linked to the adaptive T-cell
25 cellular immune response [52, 53] confining the inflammatory process to the regional lymph
26 nodes and preventing lymphohematogenous dissemination, which appears to be exquisitely
27 rare in children infected with *F. tularensis* subspecies *holarctica*. Second, as with other
28 childhood infections transmitted by *Ixodes ricinus*, the entry site is often located in the hairy

1 scalp [54] and is thus easily overlooked in a cursory physical examination. We found
2 involvement of the lymph node levels 2b, 3, 4, and 5 [43], as well as the posterior-auricular
3 and nuchal nodes, in 8 of 9 patients with tick-borne disease and head and neck involvement
4 (figure S3). These lymph nodes drain the scalp and call for a particularly diligent search for a
5 scalp lesion. Only one patient had exclusive level 2a involvement, which does not allow the
6 differentiation between scalp and oropharynx as the primary infection site. Third, the
7 morphology of the entry site lesion may be suggestive of tularemia. Our findings (figure 2)
8 concur with Byington et al [55] who described the inoculation site as “herpes-like” with
9 clustered vesicles or crusts. This may be particularly true in early stages, when lesions have
10 not yet coalesced to larger ulcers or eschars. To our knowledge, however, the specificity of
11 this finding in predicting tularemia as opposed to other etiologies has not been studied to
12 date. Fourth, blood inflammatory markers, in particular C-reactive protein (CRP), were mostly
13 low (figure S4, panel D). This finding differs from what has been reported from adult patients
14 with oropharyngeal disease [56]. Other investigators found that CRP values in pulmonary
15 disease were higher than in ulceroglandular disease in adults and peaked in the first week of
16 illness [57]. Our findings suggest that the low CRP values, which we mostly observed, are
17 related to the advanced stage of disease when determined and may not reflect a specific
18 characteristic of pediatric tularemia (figure S4, panel E). Fifth, we found that serologic testing
19 using an ICT yielded positive results earlier than a significant MAT titer ≥ 160 (figure S4,
20 panel C), which is in line with what Kilic et al reported in a large sample of patients with
21 oropharyngeal disease from Turkey [58]. Although the specificity of ICT (84-94%) may be
22 lower than that of MAT (>98%) [51], it appears to be a useful screening test and offers a very
23 short turnaround time.

24 Based off of *in vitro* activity and clinical experience, ciprofloxacin and doxycycline are
25 considered the antibiotics of choice for oral therapy and are generally preferred over
26 intravenous gentamicin [47]. Johansson *et al.* reported that early initiation of oral
27 ciprofloxacin within a few days after disease onset resulted in rapid cure without lymph node
28 suppuration in 12 children below 10 years of age in Sweden [28]. In a case series of 100

1 children with oropharyngeal tularemia in Turkey, Tezer et al [48] found that doxycycline was
2 associated with more frequent need for an eventual surgical procedure than ciprofloxacin or
3 aminoglycosides, but the finding was not statistically significant. In contrast, Oz *et al*, who
4 studied 55 children with oropharyngeal tularemia, failed to identify antibiotic-related
5 differences in outcome [50]. In vitro resistance to ciprofloxacin or doxycycline has not been
6 reported to date, which is in line with the test results of one isolate investigated in this study.
7 We did not find a differential treatment response (data not shown), but the numbers were too
8 small and treatment delays were too long to allow meaningful analysis. In general, the
9 available data emphasize the lack of high-quality, controlled treatment studies in pediatric
10 tularemia caused by *F. tularensis* subspecies *holarctica*. Considering the rapid emergence of
11 this disease, such trials are needed and will likely require a multicenter design. Further,
12 studies investigating the prevalence of *F. tularensis* in vectors in various geographic areas
13 are needed for an up-to-date risk assessment of outdoor leisure activities.

14 **CONCLUSIONS**

15 Early diagnosis of pediatric tularemia requires a high index of suspicion and should include
16 the active search for a “herpes-like” entry site lesion on clinical examination including a
17 careful scan of the hairy scalp. Detailed knowledge of head and neck lymph node drainage
18 areas facilitates entry site identification. The presence of an entry site lesion *and*
19 anatomically corresponding lymph node disease may justify first line therapy with
20 ciprofloxacin or doxycycline, with or without a history of recent tick exposure. A low threshold
21 for serologic testing, e.g. using a serum rapid antibody screening test, yields presumptive
22 diagnostic confirmation within a few hours if positive and, if negative, requires re-testing in
23 the second week of illness. This approach is likely to shorten the diagnostic delay and may
24 obviate hospitalization and surgery in a substantial proportion of patients.

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27

1 **Patient consent statement**

2 The study has been approved by the Cantonal Ethics Committee (project no. 2022-00042).
3 General or project-specific individual written informed consent was given by all patients
4 and/or their parents.

5 **Author Contributions**

6 NS and CA drafted the manuscript, NS, AD, PKAA, AB, MVK and CA were responsible for
7 patient care. PMK, FS and KMS were responsible for microbiological analyses. All authors
8 have made a substantial, direct and intellectual contribution to the work and approved it for
9 publication.

10 **Conflict of Interest Statement**

11 The authors declare no conflict of interest.

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13 None.

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ACCEPTED MANUSCRIPT

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2 We thank the physician staff of the Division of Pediatric Radiology at our institution for their
3 diagnostic contributions in each patient.

4 TABLES

5 Table 1. Demographic and clinical characteristics of 20 pediatric patients with
6 ulceroglandular or glandular tularemia

Characteristic	Finding
Female gender – no. (%)	8 (40)
Median age – yr [range]	9.0 [1.1-13.4]
Fever at illness onset	
no. (%)	15 (75)
Median duration [range]	5 [1-14]
Rash at illness onset – no. (%)	2 (10)
Tick exposure reported – no. (%)	10 (50)
Ulcer/eschar at entry site – no. (%)	14 (70) ¹
Lymph node region involved – no. (%)	
Cervical	10 (50) ²
Axillary	2 (10) ₃
Inguinal	8 (40)
Lymph node ultrasonography performed – no. (%)	19 (95)
Median C-reactive protein [range] – mg/L (n=18)	15 [1-100]
Median Erythrocyte sedimentation rate [range] – mm/h (n=9)	25 [11-66]
Microbiology – tularemia confirmed by – no. (%)	
Serology (n=20)	18 (90)
First ICT performed was positive (n=18)	13 (72) ⁴
First MAT performed was positive (n=20)	8 (58) ⁴

Culture (n=8)	3 (38)
PCR (n=7)	7 (100)
Therapy	
Empiric initial therapy with amoxicillin-clavulanate ⁵ - no. (%)	16 (80)
Targeted antimicrobial therapy – no. (%)	
Ciprofloxacin	15 (79)
Doxycycline	5 (20)
Median duration of targeted therapy [range] – days	16 [10-28]
Surgical incision and drainage – no. (%)	12 [60]
Hospitalization required – no. (%)	16 [80]
Median duration of hospital stay [range] - days	2 [1-7]
Duration of follow-up [range] - days	39 [12-167]

1

2 ¹ includes 13 patients with tick-borne disease and 1 patient with a mouse bite

3 ² includes 9 patients with tick-borne disease and one patient with oropharyngeal disease

4 ³ includes one patient each with tick-borne disease and with a mouse bite

5 ⁴ p-value 0.328 (Fisher Exact Test, two-sided)

6 ⁵ one patient was treated with amoxicillin only

1 **LEGENDS TO FIGURES**

2 **Figure 1**

3 Intervals from day 1 of symptoms to events described on the vertical axis in 19 patients with
4 tularemia. One patient of the case series was omitted because of late presentation and
5 oropharyngeal disease acquired abroad. The black lines mark the median time delay and
6 interquartile range of each event.

7 **Figure 2**

8 Photographs of the inoculation sites of 10 patients with ulceroglandular tularemia. Panels C,
9 D and E show clustered vesicles, pustules and ulcers; in panels A, B, F, G and H multiple
10 distinct lesions surrounding the major ulcer or eschar can be seen. Panel J depicts the site of
11 a wood mouse bite, from which *F. tularensis* was cultivated.

12

ACCEPTED MANUSCRIPT

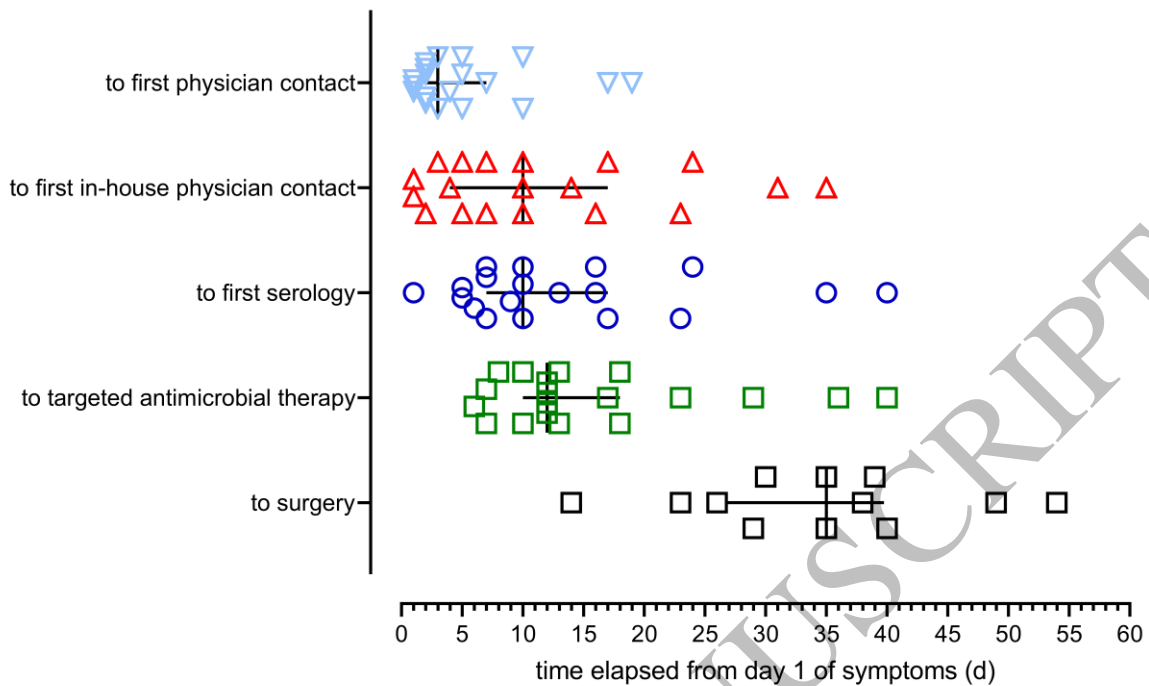


Figure 1
160x97 mm (x DPI)

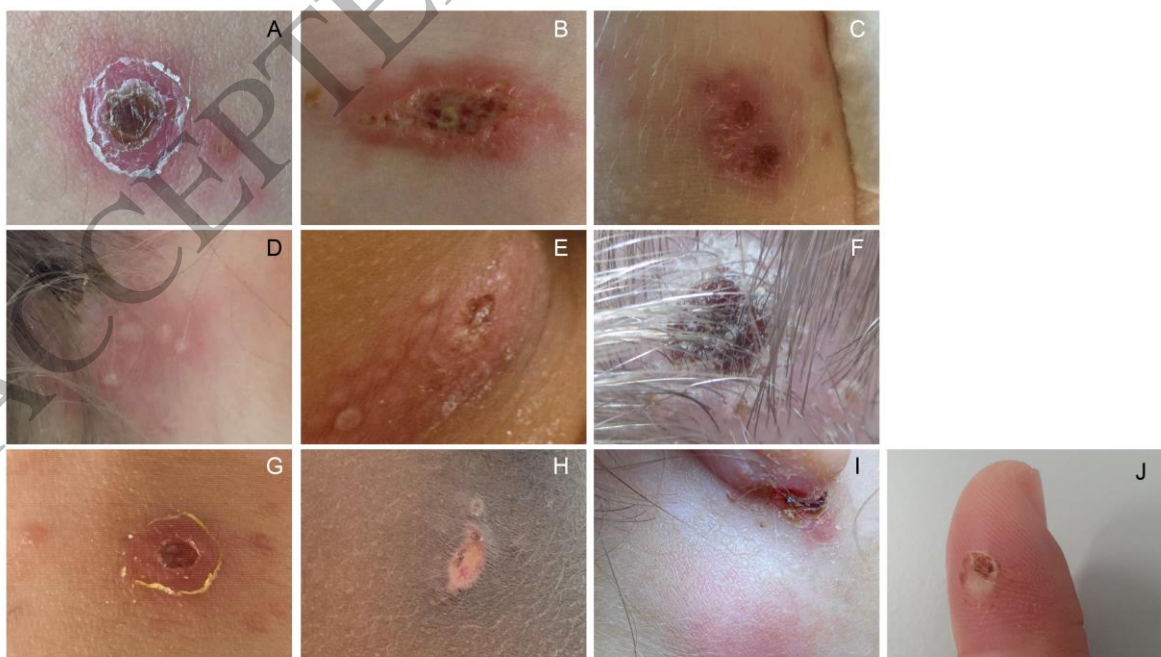


Figure 2
160x90 mm (x DPI)

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