TULAREMIA, IMPORTED - GERMANY: (BERLIN) ex TURKEY, ALERT

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Tularemia in Berlin -- 2 independent cases in travelers returning from Central Anatolia, Turkey, February 2011

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Tularemia, though rare, has recently been increasingly reported in Germany. Most cases are indigenous infections. This report describes 2 epidemiologically independent infections with _Francisella tularensis_ subspecies _holarctica_ detected in Berlin in February 2011 that were acquired in central Anatolia, Turkey. In Turkey, there have been repeated tularemia outbreaks since 2000 and the disease should therefore be considered as a differential diagnosis in travellers returning from that country.

Case description and clinical diagnosis
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In March 2011, 2 travelers returning from Turkey, both in their 20s, were diagnosed with tularemia in Berlin, Germany. Both had stayed independently in Turkey between the end of 2010 and early 2011 to visit their respective families in Yozgat, central Anatolia, 218 km [136 mi] east of Ankara in the Ak mountains. The population of Yozgat in 2008 was 71 768, the province counted 492 127 inhabitants (1).

Both patients had similar general symptoms including fever, pharyngitis, otitis and cervical lymphadenopathy, but showed different locations of the ulcerations characteristic of tularemia. Both infections were characterized by slow and subacute clinical progression.

Patient 1 stayed in Turkey between 25 Jul 2010 and 29 Jan 2011. Onset of symptoms was on 15 Dec 2010. Patient 2 had been in Turkey from 24 Dec 2010 to 8 Jan 2011 and fell ill on 10 Jan 2011. The patients were diagnosed in mid-February 2011, after their return to Berlin. Patient 1 was diagnosed with oropharyngeal tularemia, patient 2 with the ulceroglandular form. The latter form is the most common expression of tularemia. Typical symptoms are ulcerations at the inoculation site linked with regional, often purulent inflammation of the [draining] lymph nodes. The exact description of primary clinical symptoms is very important to elucidate the transmission routes and further epidemiological links (2,3). Further interviews with patient 2 revealed additional epidemiological information: the patient and one of his siblings both fell ill on 10 Jan 2011, and a further sibling 2 days later. However, these patients remained in Turkey.

Laboratory confirmation
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The detection of the pathogen by bacterial culture is difficult, special media are needed and growth is generally slow. More sensitive laboratory methods like PCR are only available in a small number of specialized laboratories (2,3). Laboratory confirmation for the cases was available on 4 Mar 2011. The German national reference laboratory for tularemia in Munich could detect _F. tularensis_ subspecies _holarctica_ (Jellison type B) via PCR in both cases. Specific DNA sequences were detected in the purulent puncture material of affected lymph nodes.
A serological diagnosis done previously in the hospital in Berlin for patient 2 had shown IgG and IgM antibodies against _F. tularensis_ lipopolysacharides. The infection in patient 1 was not proved serologically in the hospital, but was confirmed through specific antibodies in the national reference laboratory.

**Public health implications**

After the diagnoses were confirmed, information was immediately reported according to the WHO International Health Regulations (IHR) to the Robert Koch-Institute (RKI). At that time, no recent data were accessible about the tularemia situation in Turkey. Data about tularemia infections related to recent travel to Turkey or to neighboring countries were not found.

Turkish citizens are one of the larger populations with migration background in Germany. At the end of 2010 nearly 2 per cent of the German population were Turkish (1 629 480 inhabitants) (4). In Berlin at the end of 2009, 3 per cent of the population were Turkish citizens (108 000 inhabitants) (5). In addition, an unknown number of German citizens of Turkish origin still have intensive contacts with their families in Turkey and frequently travel there. Therefore, the health authorities in all 16 German federal states were informed on 8 Mar 2011 during the weekly epidemiological telephone conference (EpiLag), since more imported infections in international travellers could not be excluded.

To get further data about the situation in Turkey, but also to alert other countries, the RKI informed the Turkish IHR focal point and the WHO Regional Office for Europe about the infections. Furthermore, information was sent to the Early Warning and Response System (EWRS) of the European Union. On the national level the decision was made to involve the German National Centre for Biological Security because the pathogen _F. tularensis_ is classified as a potential biological risk agent [category A. - Mod.LL]. Overall, the risk of further transmission and the threat to public health in Germany was estimated as low.

**Epidemiological considerations**

In the past years tularaemia outbreaks in Europe were documented in Norway (6,7), Sweden (8), Spain (9), and the UN Administered Province of Kosovo in accordance with Security Council Resolution 1244 of 1999 (10). Parts of Turkey have been strongly affected by the re-emergence of tularemia and a number of outbreaks have been published since 2000 (11-16). In Germany, tularemia cases are rare, however, increasing numbers have been reported since 2007. Some travel-associated tularemia cases have been reported in Germany (10 of 74 cases between 2001 and 2009), but only 1 case dating back to 2003 originated from Turkey (17,18).

Through information exchange via the national German and Turkish IHR Focal Points with the General Directorate of Primary Health Care in the Turkish Ministry of Health, further details were provided about the current situation in Turkey and possible sources of infection (personal communication: Dr Tamer Sami Pelitli, 18 Mar 2011). More than 100 tularemia cases were reported to the national reference laboratories from central parts of Turkey, especially in the Yozgat province in 2010. The cases had been confirmed serologically and through PCR in 2 reference laboratories in Ankara and Bursa, Turkey.

Based on this information the Ministry of Health of Turkey has implemented an action plan to fight the spread of tularaemia in 2010. This action plan is focused on the rehabilitation of water systems. As a promising result the number of reported tularaemia cases decreased in 2011 compared with the previous years. After being informed by the German IHR Focal Point about the 2 cases in Berlin, the Turkish Ministry of Health started active surveillance work in the Yozgat province, but has not yet detected new transmission risks for tularemia.

In both cases from Berlin the source of infection could not be identified conclusively. However, based on the available epidemiological information, the most probable cause of the 2 infections is consumption of contaminated water during the stay in a region of Turkey endemic for tularemia. Transmission has often been associated with decentralized drinking water supply like cisterns and insufficiently treated surface water (15). The clinical presentation at least in one of the patients
diagnosed in Berlin supports this suggestion. Oropharyngeal tularemia is presumably related to oral ingestion of the pathogen.

Clinical considerations
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Due to the relatively unspecific general symptoms of tularemia and the variety of the primary disease patterns (depending on the route of infection) clinical diagnosis is not easy. Therefore, early suspicion of tularemia depends on a precise medical history and epidemiological data regarding in particular travel history, animal contacts, occupation, and insect bites. The diagnosis should subsequently be confirmed through sensitive biomolecular methods like PCR with direct identification in blood, lymph node punctuates or wound swabs, and specific serological tests, both of which are available in specified laboratories.

Early diagnosis allows immediate therapy with effective antibiotics like doxycycline or fluoroquinolones, which can be combined with aminoglycosides in severe cases. Drugs used empirically in many cases of lymphadenitis of uncertain origin are cephalosporins, amoxicillin/clavulanate, and macrolides which, however, are not effective against tularemia. Sometimes even surgical interventions to eliminate a suspected tumour are performed during infection with _F. tularensis_. In these cases, tularemia is frequently diagnosed only retrospectively by histopathological examination and/or by detection of _F. tularensis_-specific antibodies.

Clinical physicians should currently be aware of possible infections with _F. tularensis_ in travelers from some regions of Turkey. In case of clinical signs suggestive of tularemia, effective diagnostic methods should not be delayed, since diagnostic delay can easily result in extended suffering of the patient. Besides addressing the public health aspects of the disease, epidemiology plays a major role in supporting the early and effective clinical diagnosis and treatment of tularemia.

[For the citations, please refer to the source URL above. - Mod.LL]

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_F. tularensis_ can be divided into 2 clinically significant subspecies, _F. tularensis tularensis_ (also known as type A or subspecies nearctica) and _F. tularensis holarctica_ (also known as type B or subspecies _palaearctica_). Other much less clinically relevant subspecies are also described.

Type A appears to be the most prominent type in North America, primarily endemic in rabbits, and was involved in the Martha’s Vineyard (Massachusetts) pneumonic tularemia outbreaks. The infectious dose to produce infection in humans to cause moderately severe disease is as few as 50 bacilli and it is lethal to guinea pigs and rabbits.

Type B is found in Europe and Asia but also in North America. The reservoirs include rodents, voles, muskrats, and beavers. An infectious dose of 12 000 bacilli is much more likely to produce only mild, self-limited disease in humans. It is not lethal in rabbits and guinea pigs.

Regarding water-related outbreaks of tularemia, outbreaks include 64 cases in Dagestan, Russia associated with a flood-plain swamp (1), 49 cases in Tuscany, Italy linked to an unchlorinated water system (2), and an outbreak in the Smolensk province of Russia also attributed to contamination of a water supply (3).

References
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[see also:
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