



Epidemiological trends of notified human brucellosis in Germany, 2006–2018



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ABSTRACT

Objective: We describe epidemiological trends of human brucellosis in Germany over a 13 year period based on national surveillance data.

Methods: We analyzed demographic, clinical, laboratory and exposure information of symptomatic laboratory-confirmed brucellosis cases notified 2006–18. Using official population data, we calculated incidences and risk ratios (RR).

Results: From 2006 to 2018, 408 brucellosis cases were notified in Germany (mean annual incidence: 0.38/1,000,000 population), of which 75% were travel-associated. Yearly notifications peaked in 2014 (n = 47) and remained elevated compared to 2006–2013 (mean: n = 25). Asylum seekers (AS) arriving in Germany accounted for 9/44 (2015) and 15/36 (2016) cases, respectively. RR AS/non-AS 2015–2016: 28, 95% CI: 17–45. Unpasteurized milk products were most frequently notified as source of infection. Imported food and occupational exposure played a role in autochthonous cases.

Conclusions: The incidence of human brucellosis has markedly increased in recent years. Most of the observed rise in notifications can be explained by infections in AS. Exposure still predominantly occurs abroad. Risk factors for autochthonous infections need to be investigated further, though imported dairy products seem to play a role. Physicians should consider brucellosis as differential diagnosis in AS and people with travel to endemic regions with compatible symptoms.

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Introduction

Brucellosis is one of the most prevalent zoonoses worldwide caused by infection with gram-negative bacteria of the genus *Brucella*. The Mediterranean Basin, the Arabic peninsula, central Asia, India, Africa and certain countries in central and South America are considered high-prevalence regions (Pappas et al., 2006).

The three most common species causing brucellosis in humans are *Brucella (B.) melitensis* (main reservoir: goats and sheep), *B. abortus* (main reservoir: cattle/other bovidae) and *B. suis* (main reservoir: pigs).

Human exposure mainly occurs through direct contact with infected animals, consumption of contaminated food (especially unpasteurized milk products) or inhalation of contagious aerosols (Mandell et al., 2010). Typical symptoms include fever, weight loss, night sweats, arthralgia and headache that can persist for weeks to

months without appropriate antimicrobial treatment (Heymann, 2008). Every organ system can be affected and—although rare—severe manifestations like neurobrucellosis or endocarditis can occur (Dean et al., 2012; Pappas et al., 2005). However, approximately 90% of infections remain subclinical. Delay of diagnosis (and therefore treatment) is common due to the unspecific nature of symptoms and is associated with a higher complication rate (Colmenero et al., 1996).

Brucellosis is notifiable according to the German Protection against Infection Act. It was endemic in Germany until the 1980s, mainly affecting people with close contact to cattle (Al Dahouk et al., 2007). In 2000, after successful implementation of control measures, Germany was declared “officially free of bovine, ovine and caprine brucellosis” (Godfroid and Kasbohrer, 2002).

Since then human cases have decreased considerably, and today brucellosis is mostly associated with travel to endemic regions. Enhanced surveillance 1995–2000 has identified Turkish migrants as a high-risk group for brucellosis in Germany (Al Dahouk et al., 2007).

Contrary to trends in many other European countries, notifications in Germany sharply increased in 2014 and have

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remained elevated since then (EFSA and ECDC, 2016). Based on national surveillance data we describe trends, risk groups and factors associated with brucellosis in Germany 2006–2018.

Methods

Symptomatic brucellosis with laboratory confirmation is notifiable by laboratories to the local public health office of the case's district of residence. There, case information is completed and verified according to the surveillance case definition and then transmitted to the state public health office in anonymized form. From there it is forwarded to the national public health institute.

We analyzed cases of human brucellosis notified according to the national surveillance case definition (see Box 1) between 01.01.2006 and 31.12.2018 in Germany.

We analyzed demographic, clinical, laboratory and relevant exposure information coded in the case notification or transmitted as free text.

We calculated the time between onset of symptoms and notification to estimate diagnostic delay and extracted deaths attributed to brucellosis from the mortality statistic of the Information System of the Federal Health Monitoring to calculate case-fatality rates.

We used figures from the Federal Office for Migration and Refugees and the Federal Office of Statistics to calculate incidences by time and place and calculated risk ratios (RR) and 95% confidence intervals (95%-CI) comparing brucellosis incidences in asylum seekers (AS) and non-AS.

Stata 15.1 (StataCorp, College Station, Texas, United States) was used to carry out statistical analysis and Regiograph Analyse 16.0 (GfK SE, Nürnberg, Germany) to create maps on district level.

Box 1. Germany's national surveillance case definition for human brucellosis

A case of brucellosis is defined as a person meeting the clinical criteria with laboratory AND/OR epidemiological confirmation.

Clinical criteria defined as fever and/or 2 of the following 5:

- night sweats
- arthralgia
- headache
- exhaustion
- anorexia/weight loss

Laboratory confirmation defined as at least 1 of the following 3:

- cultural isolation
- detection of nucleic acids
- antibodies against *Brucella* species

Epidemiological confirmation defined as at least 1 of the following 3:

- contact with a laboratory confirmed animal or its products
- consumption of a contaminated food product
- contact with a laboratory confirmed human with whom a common source was shared

Exclusion criterion: clinical signs >12 months at the time of diagnosis

Results

Time trends and seasonality

From 2006 to 2018, 408 cases of human brucellosis fulfilling the case definition were notified in Germany, corresponding to a mean annual incidence of 0.38/1,000,000 population (range: 0.22 (2009)–0.58 (2014)).

B. melitensis was the most commonly isolated species ($n = 180/197$ with information, 91%), followed by *B. abortus* ($n = 16$, 8.1%) and *B. suis* ($n = 1$, 0.5%).

Between 2007 and 2013 annual notifications ranged from 18 to 28, then markedly increased to 47 in 2014. Since then, notifications have slightly decreased, but have remained above the levels observed prior to 2014 (range 2015–2018: 36–44) (see Figure 1).

Onset of symptoms was reported in all months with a peak in June/July ($n = 76/319$ with information, 24%).

Demographic characteristics

Cases occurred in all age groups, and overall both sexes were equally affected (51% male) with the highest age-specific incidence in women aged 60–69 (mean annual incidence 0.62/1,000,000 population) and the lowest in children under 10 years (both sexes: 0.16/1,000,000 population) (see Figure 2).

Coinciding with the increase in notifications, median age decreased (41 versus 50 years, $p = 0.001$) and proportion of males increased (44% (2006–2013) versus 58% (2014–2018), $p = 0.008$).

The mean annual incidence among males aged 10–49 years 2015–2017 was 1/1,000,000 population.

In 2014–2018, 36 cases occurred in known AS, including 7 children. Compared to non-AS, AS were significantly younger (median age 29 versus 47 years, $p < 0.0001$) and proportion of males among cases was higher (69% versus 49%, $p = 0.02$). In 2015, 20% and in 2016 42% of all notified brucellosis cases occurred among AS. Comparing incidences among AS and non-AS 2015–2016, AS had a 28-times higher risk of notified brucellosis (RR: 28, 95%-CI: 17–45).

Likely place and route of infection

Imported cases (exposure outside Germany)

Of 371 cases with information on place of exposure, 75% ($n = 277$, 288 entries) reported foreign travel prior to illness; most commonly to the Middle East including Turkey ($n = 182$), followed by Europe ($n = 55$), Asia excluding the Middle East ($n = 21$) and Africa ($n = 18$). Middle/South America was named twice, Australia once. For 5 cases the travel destination was not specified.

Most cases were exposed in Turkey ($n = 115$), followed by Iraq ($n = 23$), Syria ($n = 21$), Italy ($n = 13$), Spain ($n = 11$), Egypt ($n = 7$), Lebanon ($n = 6$), Greece ($n = 5$) and Iran ($n = 5$).

Except for a peak in 2014, the proportion of cases exposed in Turkey decreased over time, reaching the lowest point in 2016 ($n = 2$).

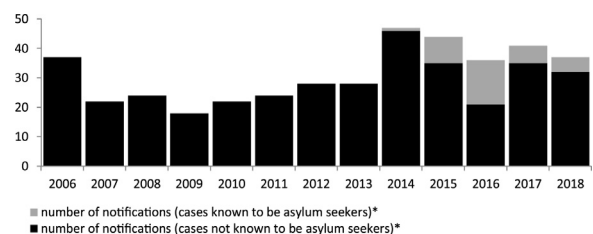
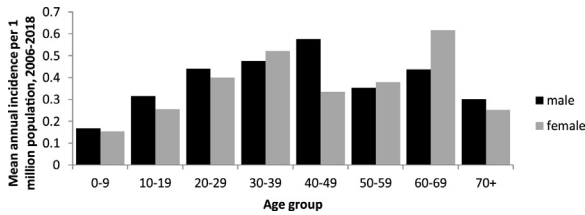


Figure 1. Number of notified human brucellosis cases by year of notification and asylum seeker status (*systematically recorded since September 2015), Germany, 2006–2018.



but started to increase again in 2017 (n = 5), rising further in 2018 (n = 10) (see Figure 3).

In 2015, Middle East countries other than Turkey became the most important region of exposure, mainly due to cases among newly arriving AS from Syria and Iraq, but were superseded again by Turkey in 2018. European countries have been increasingly reported as place of exposure since 2017 and reached the highest number in the study period in 2018 (n = 9, range 2006–2017: 2–6).

Type of travel was not routinely recorded, but information was available for 69 (25%) cases: 31 were migrating AS, 28 stayed with locals (visiting friends and relatives (VFR, n = 26), host family (n = 1), nomads (n = 1)), two were backpacking/hiking and eight were on holidays in hotels and travel groups. For an additional 22 (8%) cases a non-German nationality or a significant language barrier was reported.

Median travel duration was 5 weeks (range 0.4–60 weeks, available for n = 138) and was significantly longer in cases that travelled to Turkey (7 weeks, p = 0.002, available for n = 69).

For 136 (49%) cases at least one likely source of infection was identified in addition to foreign travel. 104 had consumed unpasteurized milk products. Cheese (75 entries) most commonly originated from Turkey (n = 39), Italy (n = 5), Iraq (n = 4), Portugal (n = 4) and Spain (n = 3). Milk (49 entries) most commonly originated from Turkey (n = 18), Iraq (n = 4), Lebanon (n = 4), Syria and Saudi Arabia (each n = 3). All 3 cases exposed in Saudi-Arabia with information had consumed camel milk. 47 cases had contact to livestock (especially sheep, goats), of these two mentioned participating in ritual slaughtering in Turkey. 11 cases had consumed or prepared “fresh” meat (mainly lamb). 26 travel-associated cases occurred in clusters with a maximum of 5 cases; 18 reported consumption of unpasteurized dairy products during travel.

Autochthonous cases (exposure in Germany)

Of 94 cases that reportedly acquired brucellosis in Germany, 29 (31%) indicated at least one likely source of infection. Twelve cases

had consumed imported food (all 10 with information: unpasteurized cheese from Iraq, Italy, Turkey), including one AS that had arrived in Germany more than a year before symptom onset. Imported cheese led to two clusters with a total of five reported autochthonous infections. Three cases had consumed unpasteurized cheese purchased in Germany; for two this was the only identified source of infection. Eleven cases were occupationally exposed; most commonly laboratory workers (n = 6, most recently in 2015), but also military personnel (n = 2), a veterinarian (n = 1), a butcher (n = 1) and an abattoir worker (n = 1). Six cases reported non-occupational contact to livestock: sheep (n = 3), cattle (n = 2), pigs and game through hunting (n = 1). The single identified *B. suis* infection was acquired in rural Germany.

Place of exposure unknown

Of 37 cases with unknown place of exposure, 30 were notified since 2014. Three were AS that had reached Germany in 2015 and were diagnosed with brucellosis in 2017, but symptom onset was unknown. At least one likely source of infection was identified for 13 (39%) cases, most commonly consumption of unpasteurized milk products (n = 10, 6/7 with information from abroad). One case had received a blood transfusion in Iraq in previous years.

Regional variation

All states in Germany reported at least one human brucellosis case between 2006 and 2018. The highest mean annual incidences in 2006–2018 were observed in the city-states Hamburg (0.78/1,000,000 population) and Berlin (0.66/1,000,000 population).

Higher mean annual incidences in 2006–2018 were observed in “Old West German states” including Berlin, where the proportion of inhabitants with foreign nationality is also markedly higher (0.42 vs 0.17/1,000,000 population in “New German states”, RR: 2.5, 95%-CI: 1.7–3.7) (see Figure 4).

Clinical information

Fever was the most commonly reported symptom (n = 343, 84%), followed by arthralgia and exhaustion (each n = 202, 50%), headache (n = 148, 36%), loss of appetite (n = 131, 32%), night sweats (n = 109, 27%) and other symptoms (n = 68, 17%). Other symptoms (specified for n = 29) affected a variety of organ systems, most commonly the gastrointestinal tract (n = 10) and the spine (n = 9). Neurobrucellosis was reported for three and endocarditis for one case. Of 393 cases with information, 272 (69%) were hospitalized.

Comparing infection with *B. abortus* and *B. melitensis* and adjusting for age and sex, *B. melitensis* infection was associated

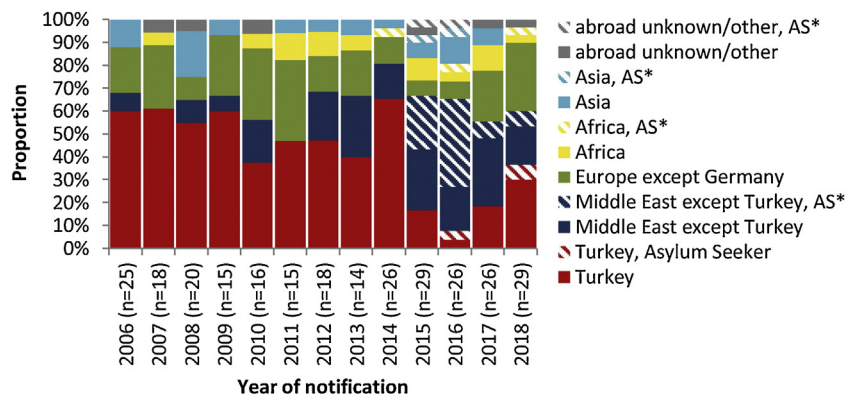


Figure 3. Imported cases of brucellosis by year of notification, region of exposure (%) and asylum seeker status (*systematically recorded since September 2015), 2006–2018 (n = 277).

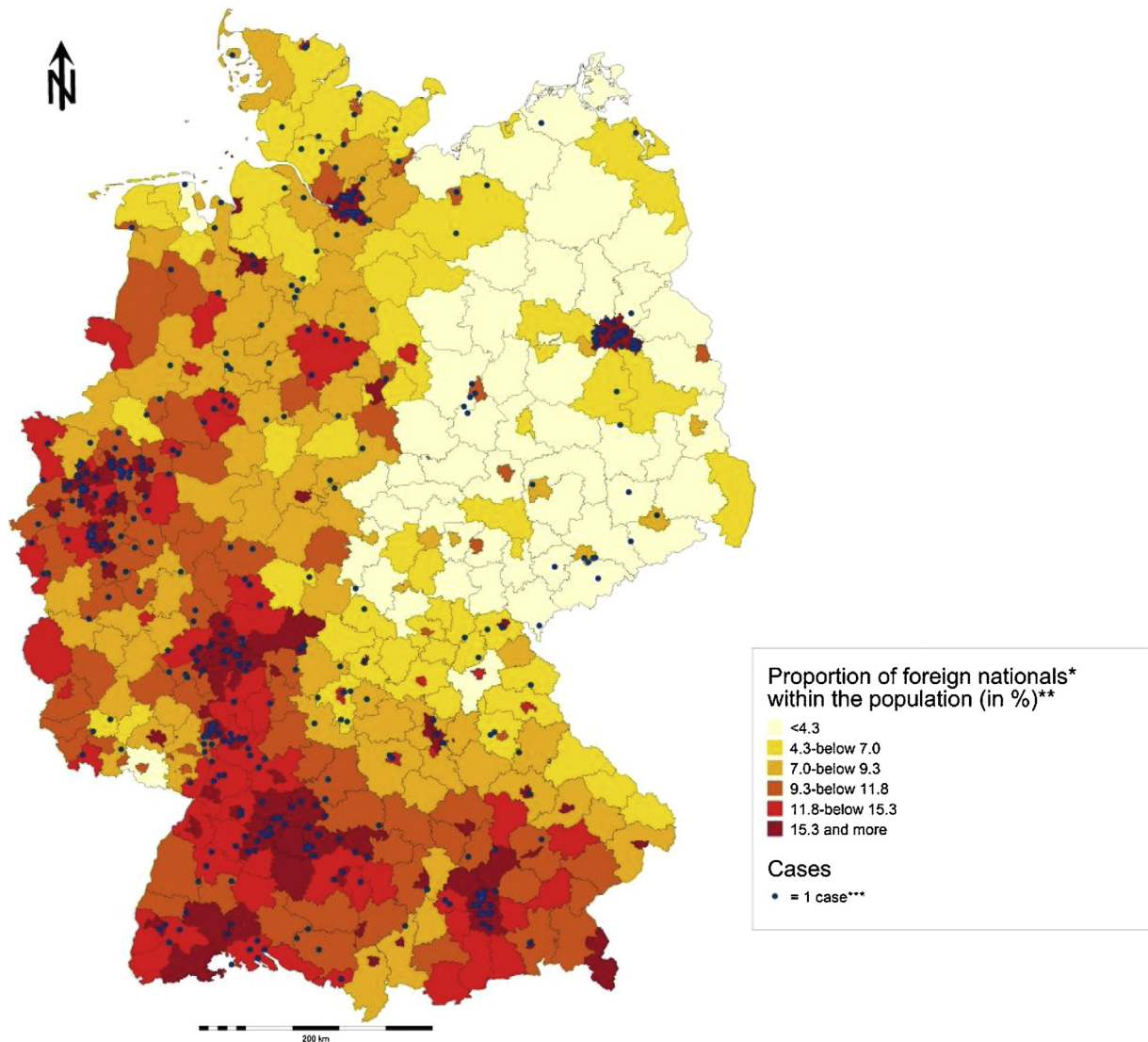


Figure 4. Notified cases of brucellosis by district of residence (dots) and proportion of foreign nationals* within the population, 2006–2018 (shades).

*Defined as a people without German nationality.

**As of 31.12.2018, according to data from the German Federal Statistical Office (DESTATIS Statistisches Bundesamt, 2019).

***Dots randomly positioned in district of notification.

with hospitalization (OR: 71.4, 95%-CI: 14.0–364.7) and fever (OR: 4.1, 95%-CI: 1.3–12.5) while *B. abortus* infection was associated with arthralgia (OR: 3.3, 95%-CI: 1.03–10.8).

The mean time between symptom onset and notification (proxy for diagnostic delay) was 7.5 weeks (available for $n = 311$, median: 4, range: 0–65). It was significantly longer in females (mean 8.8 versus 6.4 weeks, $p = 0.004$) and in cases exposed abroad (mean 8.1 versus 7.3 weeks if autochthonous, $p = 0.02$) and significantly shorter in cases among the often overlapping groups of AS (mean 4.5 versus 7.8 weeks, $p = 0.01$), cases with exposure in Middle East countries other than Turkey (mean 5.3 versus 8.9 weeks, $p = 0.0005$), and hospitalized cases (mean 6.5 versus 9.9 weeks, $p = 0.008$).

While no death due to brucellosis was notified through national surveillance, 13 deaths were attributed to brucellosis in the mortality statistic of the Information System of the Federal Health Monitoring 2006–2016 (data for 2018 not yet available). Using notified cases as the denominator, this would indicate a case-fatality-rate in 2006–2017 of 3.5% (95%-CI: 1.6–5.4). This result needs to be interpreted with caution as there is no accounting for

underreporting of brucellosis and figures were extracted from two different data-sources that could not be matched.

Discussion

We found a marked increase in brucellosis notifications in Germany since 2014. The majority of cases were associated with foreign travel, with indications that VFR-travel might play an important role. The most commonly identified source of infection was consumption of unpasteurized milk products. Fever was the most frequently reported symptom and a high proportion of patients were hospitalized. Most infections were caused by *B. melitensis*. Mean duration between onset of symptoms and notification was 7.5 weeks. For the majority of autochthonous infections no source of infection was recorded; consumption of imported milk products and occupational exposure were the most commonly mentioned, but locally purchased cheese was also reported.

Cases among newly arriving AS contributed to the observed increase and explained all excess notifications in 2016 and most

excess notifications in 2015, even though AS status was only systematically collected since September 2015. The highest increase in brucellosis notifications was observed in young males, most commonly with exposure in Syria and Iraq. Armed conflicts in the Middle East have led to displacement of people and migration to other countries. Between 2014 and 2017 the Federal Office for Migration and Refugees recorded 1.8 million arriving AS in Germany. Most first time applicants for asylum were young males (66% male, 83% <35 years) that had migrated from Syria, Afghanistan and Iraq (BAMF, 2014, 2015, 2016, 2017), countries with high brucellosis prevalence (OIE, 2019; Pappas et al., 2006; Yacoub et al., 2006).

Reasons for the notification peak in 2014 are not fully understood. Despite overall decreasing numbers of cases exposed in Turkey since 2006 and a 50% reduction of annual brucellosis cases in Turkey since the introduction of a new eradication program for animal brucellosis in 2009 (Gul et al., 2014), compared to 2013, the number of cases with exposure in Turkey in 2014 almost tripled and contributed substantially to the peak. This can be partially explained by two clusters associated with consumption of unpasteurized milk products in Turkey. Additionally, a higher proportion of males and a younger age of cases ex-Turkey 2014 compared to 2006–2013 support the possibility that migration of AS through Turkey may have contributed already.

Despite a substantial decrease of migration to Germany, brucellosis notifications remained high in 2017–2018. Interestingly, two of three AS with notified brucellosis in 2017 had already been in Germany for more than 12 months, suggesting either diagnosis or reporting was severely delayed or infection was acquired in Germany. Imported food was the suspected source in one case, which could indicate that AS living in Germany potentially remain at higher risk for brucellosis after migration. This has been previously observed among Turkish immigrants in Germany, the Hispanic population in the U.S., immigrants from Middle East countries in Denmark and the UK, and immigrants in Spain with VFR-travel, and in the absence of travel importation of food products from their home countries being continued risk factors (Al Dahouk et al., 2007; Brough et al., 2011; Eckman, 1975; Eriksen et al., 2002; Norman et al., 2016). As in previous German studies (Al Dahouk et al., 2007), current data indicate that brucellosis often affected VFR-travelers (reported or suggested by long travel duration), that are more likely to live as part of the local community and are also at higher risk for many other travel-associated infections (Angell and Cetron, 2005; Health Protection Agency, 2008; Leder et al., 2006). Few cases among non-VFR travelers were also reported, but as the type of travel was not systematically captured, these results have to be interpreted with caution.

Since 2017 cases exposed in Turkey have increased again, mirroring changes in travel patterns and local brucellosis epidemiology. OIE reported annual brucellosis cases in Turkey have increased again each year after the lowest recorded level in 2015 (OIE, 2019). At the same time air travel from Germany to Turkey has picked up again in 2018 and further in 2019, after it had slumped due to political unrest in 2016 (DESTATIS Statistisches Bundesamt, 2020).

A specific source of infection was only reported for 45% of cases; it was particularly low if brucellosis was acquired in Germany. While laboratory workers in Germany were still occasionally infected with brucellosis, the last case was reported in 2015. In recent years, imported food (especially unpasteurized cheese) was the most commonly mentioned source in autochthonous brucellosis and led to two small clusters in Germany. It is estimated that more than 2,800 tons of illegal food products from non-EU countries reach Germany every year via Frankfurt airport alone. A study found *Brucella*-DNA in 3.6% of all confiscated food at German

airports; in 7% if food originated from Turkey. As only a small subset of passengers is subject to luggage inspection and individual travellers are often carrying large quantities, it has to be assumed that “illegal imports” contribute to infections in Germany (Beutlich et al., 2015). To investigate the potential threat of cheese bought in Germany, 200 cheese samples purchased online and on markets in Berlin were microbiologically tested. Although no viable *Brucellae* were detected using classical culture methods (which are inherently difficult and often unsuccessful), 20.5% were *Brucella*-DNA positive and 7% of those were produced from raw milk with a short ripening period, potentially posing an infection risk (Jansen et al., 2019). The authors suspected organized trade of illegal imports from brucellosis endemic countries, stating often false information was provided to customers. Whole genome sequencing (WGS) was recently described as a useful tool for “trace-back analysis of *B. melitensis* suggesting the potential geographic origin of the strain” (Georgi et al., 2017).

While *B. melitensis* today is the most commonly identified species in human cases as well as in surveyed food items, more exotic species may also play a role: The only notified human case due to *B. suis* was initially misidentified as *B. melitensis* by MALDI-TOF due to a lack of *B. suis* spectra in the database (Zange et al., 2019). The patient had not travelled abroad and was living in a rural area. While *B. suis* biovar 2 is occasionally detected in domestic pigs and wild boars and hares in Germany (Friedrich-Loeffler-Institut, 2018; LGL, 2018; Melzer et al., 2006), this human case was caused by *B. suis* biovar 1 with closest proximity to strains originating from Argentina. Investigations revealed infection might have been acquired through imported meat (Zange et al., 2019).

Patients infected with *B. abortus* more commonly reported arthralgia. This was also observed in studies in Turkey and USA. While the Turkish study found no evidence suggesting that *B. melitensis* was more virulent than *B. abortus*, the American study reported *B. melitensis* “presented more acutely as fevers of unknown origin” (Dokuzoguz et al., 2005; Troy et al., 2005).

Limitations

Underreporting has to be assumed: cases that remained undiagnosed, were not reported or did not fulfill the case definition were not considered in this analysis. Only clinical symptoms included in the case definition were systematically collected, leading to underestimation of other symptoms. Typical complications and treatment outcome were not captured, so we cannot comment on those or the association of diagnostic delay and unfavorable outcomes. Results on exposure can—in the absence of control groups—only indicate possible risk factors. As the exact number of AS was unknown, we used the highest available estimation to avoid overestimation of RRs.

Conclusions and recommendations

In the study period brucellosis notifications increased and epidemiology in Germany has changed in response to migration from brucellosis endemic countries, change in travel patterns and changing brucellosis epidemiology in countries that are frequently visited by people living in Germany. Although it is rare in Germany, physicians should consider brucellosis as a relevant differential diagnosis in AS and people with travel to endemic regions with compatible symptoms to reduce diagnostic delay and complications. Physicians should inform the laboratory if they suspect brucellosis, so that protective measures can be taken to prevent occupational infections. People travelling to endemic countries (especially VFR-travelers) should be advised about risk factors for and symptoms of the disease. As it is known that VFR-travelers often do not seek travel advice, opportunistic inquiry about travel

plans and information during routine medical visits have been suggested by some authors. In patients without foreign travel, physicians and public health officers should inquire about consumption of imported meat and unpasteurized milk products. If identified as a potential source, other people that might have been exposed should be included in the investigation.

Imported milk products seem to play a role in autochthonous brucellosis, but risk factors in the absence of travel are incompletely understood and need to be investigated further. WGS may provide valuable information on the probable origin of the strains causing autochthonous brucellosis.

Declaration of interests

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Ethical approval

Not required.

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