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ZOONOTIC DISEASES IN NORTHEN CYPRUS: CURRENT AND FUTURE THREATS

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Abstract. Diseases transmitted naturally between animals and humans are referred to as zoonoses. Zoonotic diseases are responsible for many pathogenic infections in humans, especially in endemic regions. In recent years, emerging and re-emerging zoonotic infections have become widespread and pose a threat worldwide. Transmitted such bacterial, viral and parasitic infections have been detected in Northen Cyprus over the years. Climate change and human migration are increasing essentially, making such infections potentially more dangerous. To quickly detect these pathogens and limit their spread, it is crucial for the island to control their animal reservoirs. In addition, continued and expanded research is essential for global surveillance.
This review aimed to provide an overview of the etiology of the most recorded zoonotic diseases in Northen Cyprus, their impact on human health, and measures to control their spread better.

Keywords: bacterial zoonosis, viral zoonosis, parasitic zoonosis, northern Cyprus, control of diseases/outbreaks

1. Introduction

The word zoonosis was first used by Rudolph Virchow (1821–1902) in his "Handbook of Communicable Diseases" in 1855 (Singh *et al.* 2023). Zoonoses have been significant among infectious diseases since ancient times and have caused various public health problems. "Zoonotic diseases" or "zoonoses" are terms commonly used to refer to infectious diseases transmitted from animals to humans. Many microorganisms such as bacteria, viruses, parasites, fungi and prions, whose original hosts were animals, are responsible for human zoonoses (https://www.emro.who.int/about-who/rc61/zoonotic-diseases.html). It is estimated that there are one billion cases of disease and millions of deaths caused by zoonoses worldwide each year. Zoonoses account for about 60% of emerging infectious diseases. In the last three decades, 30 new human pathogens have been discovered, 75% of which were transmitted from animals (Jones *et al.* 2008). According to the World Health Organization, the threat of zoonoses is increasing in the eastern Mediterranean region due to increased global interactions and international trade (Malik *et al.* 2013). Some endemic zoonoses, including brucellosis, anthrax and rabies, have not been eliminated. Increasing problems result from infections with viruses causing yellow fever, chikungunya, West Nile fever, Q fever, Cream-Congo hemorrhagic fever, Ebola hemorrhagic fever, Rift Valley fever, highly pathogenic H1N1 influenza virus, monkeypox, sand fever, MERS-CoV. Infections occur in various countries, including Sudan, Yemen, Tunisia, Afghanistan, Iraq, Pakistan, sub-Saharan Africa, Saudi Arabia, Egypt, Iran, Jordan, the Kingdom of Saudi Arabia, Kuwait, Lebanon, Oman, Qatar and the United Arab Emirates. They pose a threat there due to their epidemiological potential, high mortality risk and lack of treatment and vaccines to control their spread (https://www.emro.who.int/about-who/rc61/zoonotic-diseases.html)

According to the 2022 report of the European Centre for Disease Prevention and Control on zoonoses, many pathogens including *Yersinia* spp., *Toxoplasma gondii*,

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rabies, *Coxiella burnetii* (Q fever), West Nile virus, tularemia, *Bacillus* spp., *Chlamydia* spp., *Clostridium* spp., *Cronobacter* spp., *Klebsiella* spp., *Enterococcus* spp., pathogenic *Escherichia coli*, *Proteus* spp., *Staphylococcus* spp., *Streptococcus* spp., *Vibrio* spp., *Leptospira* spp. Caliciviruses, Flaviviruses, Hepatitis virus, *Cysticercus* spp. and Sarcocystis spp. were monitored according to the epidemiological situation in the European Union countries in 2022 (EFSA and ECDC 2023). While the most commonly reported infections are campylobacteriosis, salmonellosis, yersiniosis, infections of Shiga toxin-producing *Escherichia coli* (STEC) and *Listeria monocytogenes*, the highest hospitalizations and mortality rates were due to listeriosis and West Nile virus infections (EFSA and ECDC 2023). Cyprus is located in the eastern part of the Mediterranean Sea and is part of Western Asia. The island is divided into two parts: northern and southern. Turkish Cypriots live in the northern part, while Greek Cypriots live in the southern part of the island. Legally, citizens of both countries can travel across the border after passing security checks. Therefore, there is interaction between citizens living in Cyprus and global connectivity with other countries. There is a problem of cross-border disease outbreaks, including those of animal origin. In Northern Cyprus, the country's economy is based on agriculture and small-scale farming, which also increases the risk of human infections spread from animals. This review presents zoonotic infections detected in Northern e that are dangerous to the island citizens in three sections: bacterial, viral, and parasitic.

2. Bacterial zoonoses

The brucellosis affects livestock and humans worldwide and causes economic losses. The genus *Brucella* includes three highly virulent species that have become endemic in many countries, especially those with low economic levels. These species are *Brucella abortus*, which infects mainly cattle; *Brucella melitensis,* which infects sheep and goats; and *Brucella suis*, which infects mainly pigs (Laine *et al*. 2023). Infection of humans by *Brucella canis* can occur through contact with infected dogs' contaminated secretions or improper laboratory handling (Krueger *et al*. 2014). It is estimated that in 2021, 29 EU/EEA countries reported 0.04 cases per 100,000 people. According to the annual epidemiological report (ECDC 2023a), no cases of brucellosis were reported in 2017, 2018, 2019, 2020 and 2021.

Due to various eradication programs in Cyprus, animal brucellosis has remained at the level of 0.1% since 2007 (Sayı 2013). A study by Süer showed that the seroprevalence was 3.6% with RSAT *B. canis* M (–), 4.4% with RSAT *B. abortus* S99, 5.3% with ELISA *B. canis* M (–) and 9.8% with ELISA *B. abortus* S99 in healthy individuals without brucellosis. These studies are insufficient to present the current situation of *B. canis* infections in Cyprus, but the seropositivity rates can help assess the risk (Süer *et al*. 2023).

Despite the endemic nature of brucellosis in livestock in Northern Cyprus, there is a lack of published scientific data on the disease. Özdoğaç et al. (2018) published the only available information on brucellosis. He found that seropositivity in humans ranged from 3.1% to 6.5% among professionals such as veterinarians, animal breeders and butchers. Regardless of the causative agent, these numbers are consistent with the low to moderate seroprevalence data in livestock reported earlier (Özdoğaç *et al*. 2018).

Francisella tularensis, which causes tularemia, is spread through direct animal-human contact and via vectors, food, water or infected aerosols (Kosker *et al*. 2013). The incubation phase usually lasts three to five days, although it can extend up to 21 days (Gurcan *et al*. 2014). The first case of tularemia in Northen Cyprus was reported in a 5-year-old girl by Uncu M. et al. in 2017. Symptoms included fever, pharyngitis, bilateral periorbital swelling and congestion, cervical and mesenteric lymphadenopathy (LAP), liver and spleen enlargement, and diarrhea. In this case, it was reported that the patient recovered without complications within two weeks of antibiotic treatment (Uncu *et al.* 2017).

Rickettsiae are Gram-negative, obligate intracellular bacteria that include several zoonotic pathogens that are widespread worldwide. The host of *Rickettsiae* typhi infection is rats (*Rattus rattus* and *R. norvegicus*), and the vector is the oriental rat flea (*Xenops cheopis*) (Güvenir *et al.* 2022). According to the study, three species of *Rickettsia* have been found in Southern Cyprus: *Rickettsia conorii*, *R. typhi* and *R. felis* (Psaroulaki *et al*. 2006; Koliou *et al.* 2007). The results of this study show that the geographical distribution of fleas coexists with the geographical distribution of the pathogens they may carry, indicating a potential risk of flea-borne infections in Southern Cyprus (Christou *et al*. 2010). Güvenir et al. reported that although there is not enough information about rickettsiae infections in Northen Cyprus, they are aware of the increase in rickettsiae infections during the SARS-CoV-2 pandemic (Güvenir *et al*. 2022).

Listeriosis is a disease caused by *Listeria monocytogenes*. It mainly causes infections in pregnant women, infants and adults with weakened immune systems. Healthy adults do not develop any symptoms except pregnant women. According to the Annual Epidemiological Report for 2021 distribution of confirmed listeriosis, there were no cases in Cyprus in 2017, one case in 2018, one case in 2019, two cases in 2020 and one case in 2021 (ECDC 2022).

The Shiga toxin-producing strains of *Escherichia coli* can produce toxins that are virtually analogous to those produced by *Shigella dysenteriae* type 1. Two types of these toxins have been described: Shiga 1 (Stx1), which differs from the true Shiga toxin by one to seven amino acids, and Shiga toxin 2 (Stx2), which has about 60% homologies to Stx1. Both Stx1 and Stx2 toxins belong to the Shiga toxin family. Shiga toxin-producing *Escherichia coli* are called STEC. Functionally active Shiga toxins can be detected by the Vero cell toxin test. Therefore, these bacteria are also called verotoxin-producing *Escherichia coli* (VTEC). According to the ECDC/EFSA joint technical report, only two cases were reported in 2008 (ECDC 2011).

3. Viral zoonotic infections

A significant percentage of disease-causing pathogens (70%) known to cause human infections are viruses. Viral zoonoses are a severe problem due to high mortality and morbidity (Marie *et al*. 2023). These agents are transmitted mainly from vertebrate animals, including domestic and wild animals, by insects and arthropods. They can be transmitted by direct contact, aerosols, congenital routes and, in some cases, from person to person (Glud *et al*. 2021; Socha *et al*. 2022). Environmental changes resulting from, among others, the combustion of fossil fuels, increased deforestation and livestock farming may cause the spread of vectors from different geographical regions and contribute to the increase in the number of viral zoonotic infections (Arikan *et al.* 2023). Although there are no scientific publications on the presence of vectors in the island's northern part, various studies on mosquitoes have been conducted in the southern part since 1946. According to these studies, *Aedes* mosquitoes, including *Aedes aegypti*, *Aedes detritus*, *Aedes m*ariae, and *Aedes caspius*, have been detected in the Republic of Cyprus (Violaris *et al.* 2009; Abushoufa *et al*. 2021). Therefore, Northern Cyprus may also be exposed to infections with dengue, yellow fever, chikungunya, and Zika viruses, which are transmitted by *Aedes* mosquitoes. Considering that people from many countries and regions migrate to the island for various purposes, such as education, tourism, and work, the need to consider these diseases is revealed. Moreover, due to the arrival of many foreigners from endemic countries, other significant vector-borne infections, including Ebola virus, West Nile virus, Rift Valley fever, and Cream-Congo hemorrhagic fever, should also be considered in Northern Cyprus. Therefore, this part of the review will discuss some of the main critical viral zoonoses that may pose a high risk to Northen Cyprus.

Currently, it is estimated that half of the world's population is exposed to dengue fever, and about 100–400 million dengue infections occur each year, as it is one of the fastest-spreading arboviral diseases (Sah *et al.* 2023). The disease is transmitted by Aegypti mosquitoes and can cause clinical conditions ranging from asymptomatic/mild infections to life-threatening severe conditions such as dengue hemorrhagic fever and dengue shock syndrome (Sah *et al.* 2023). Dengue virus (DENV) infections are endemic in tropical and subtropical regions worldwide. Still, infections have been reported in many countries, including the Americas, Africa, the Middle East, Asia, and the Pacific Islands (CDC 2023). The European Centre for Disease Prevention and Control (ECDC) reported more than 2 million cases of dengue and more than 500 deaths worldwide between December 2023 and February 2024. This represents a 249% increase compared to the same period in 2023 and a 354% increase compared to the average of the last five years (ECDC 2024). In Southern Cyprus, only two sporadic cases of dengue fever have been reported so far, while in the northern part of the island, no cases have been reported.

Chikungunya is another disease transmitted by vectors, mainly through the bites of mosquitoes, mainly *Aedes aegypti* and *Aedes albopictus*. The disease occurs primarily in Africa and Asia, but cases imported from abroad have also been reported. Since 2005, more than two million cases have been reported in more than 110 countries in Asia, Africa, Europe and America (WHO 2022). Only by February 2024, 70,000 cases and 15 deaths have been reported worldwide. These cases have been detected most frequently in Brazil, Paraguay, Argentina and Bolivia. Although Cyprus has not reported any data for 2017–2021 (ECDC, 2024a), chikungunya fever may pose a significant future threat to Northern Cyprus.

Another emerging infectious disease transmitted mainly by *Aedes* mosquitoes is Zika virus (ZIKV). Since the first human outbreak on Yap Island in 2007, Zika virus outbreaks have occurred in French Polynesia, Easter Island, Cook Islands, New Caledonia, and Brazil from 2013 to 2015 (ECDC 2021). As a link between ZIKV infections and microcephaly and other neurological disorders was demonstrated, WHO declared a public health emergency of international concern in 2016 (WHO, 2016). Mosquito-borne Zika virus infections have been reported in 86 countries to date, but global surveillance is insufficient. As a result of the projection studies, the potential spread of *Aedes* mosquitoes and the risk of ZIKV infection in South Africa, Africa, Oceania, Asia and Northen America was estimated at 16.6% of the land area or 78.6% of the world's population. The study predicts that people living in the risk area, especially in South Asia, tropical Africa, Southern America, North America and the Mediterranean, are at risk. Still, climate change may change these projections

(Xu *et al*. 2022). Another modelling study predicted that global warming could expose more than 1.3 billion new people to ZIKV by 2050 (Ryan *et al*. 2021). In Northern Cyprus, the first and only study presented by Fathi et al. showed no Zika virus infections (Abushoufa *et al*. 2021). However, the increased risk of mosquito spread indicates that ZIKV infections will also occur on the island, and necessary precautions should be taken in advance. Although everyone is at risk for this infection, people with weakened immune systems, people who have close contact with mosquito or tick habitats, and healthcare workers who have direct contact with infected individuals should be trained and educated on the measurements (CDC 2024).

Although none of the above vector-borne diseases have been reported in Cyprus, West Nile virus (WNV) has spread here. The first WNV infection in humans in the Republic of Cyprus was detected in 2016, while the first three cases in Northern Cyprus were described in 2019 (Paphitou *et al*. 2017; Balaman *et al*. 2020). As of December 13, 2023, 707 human cases of WNV have been reported. These infections occurred in Italy (n = 336), Greece (n = 162), Romania (n = 103), France (n = 43), Hungary (n = 29), Spain (n = 17), Germany (n = 6), Croatia (n = 6) and Cyprus (n = 5) (ECDC 2023). The detection of a new case in the capital of Nicosia in Northern Cyprus in October 2023 and the presence of *Culex pipiens*, *Culex perexiguus* and *Culex torrentium* (Orshan *et al*. 2008; Benbetka *et al*. 2018; Vilibic-Cavlek *et al*. 2019) demonstrate the need for vector management and continuous monitoring of all arboviruses in Cyprus (Ministry of Health TRNC 2023; Yetismis *et al*. 2022).

4. Parasitic zoonoses

It was estimated that in 2022, 249 million cases of malaria worldwide caused 608,000 deaths. An infected female *Anopheles* mosquito transmits malaria to humans by biting. Malaria can also be transmitted through blood transfusions and contaminated needles. A person can become seriously ill and die within 24 hours of contracting *Plasmodium falciparum* malaria if left untreated. Five species of *Plasmodium* cause human malaria. Two of them – *P. falciparum* and *P. vivax* are the most dangerous. *P. falciparum* is prevalent on the African continent. Outside of sub-Saharan Africa, *P. vivax* infections predominate. Three other malaria species can also infect humans: *P. malariae*, *P. ovale* and *P. knowlesi* (WHO 2023a). The island of Cyprus was one of the most malaria-affected areas for centuries. However, between 1946 and 1950, the island underwent a "Malaria Eradication Project" that successfully eradicated malaria by eliminating *Anopheles* mosquitoes, which are carriers of *Plasmodium* parasites, and by draining marshlands. There are currently no local cases of malaria in Northern Cyprus. However, imported cases have begun to be observed. This is due to the increased number of people coming to the island to study or to work from regions where the disease is endemic. These patients already bring antimalarial drugs from home (Güler *et al*., 2023). According to the data of the Ministry of Health of the TRNC, 56 cases of imported malaria were reported in Northern Cyprus between 2014 and 2022 (Ministry of Health of the TRNC, 2023). Güler *et al*. link this to the fact that since 2011, the number of students in higher education institutions in Northern Cyprus has increased significantly. Due to these population changes in Northern Cyprus, the Ministry of Health has modified malaria control strategies, increasing the supply of antimalarial drugs (Güler *et al*., 2023).

Leishmaniasis is another significant vector-borne disease affecting about one million people annually (WHO 2023). Female flies of the *Phlebotomidae* family transmit the disease. It affects people living in low-income countries worldwide, mainly in Africa, Asia and Latin America, and is associated with malnutrition, population displacement, poor housing conditions, and weak immune systems. In 2022, more than 5,000 cases of cutaneous leishmaniasis were reported in eight countries, including Afghanistan, Algeria, Brazil, Colombia, Iran (Islamic Republic), Iraq, Peru and the Syrian Arab Republic. Of these cases, 337 were imported. Globally, 69 imported cases of visceral leishmaniasis were also reported in 2022 (WHO 2023). In Cyprus, cases in humans and dogs have been reported since 1990. They are becoming a severe threat as sand flies and dogs have also been reported as vectors and main reservoirs (Demir *et al*. 2010; Ergunay et al. 2014, Ruh *et al*. 2019). Emrah et al. revealed that the rate of positive canine leishmaniasis (canL) and borderline positive results were 3.61% and 15.66%, respectively, in 2004 in Northern Cyprus. In 2012, Tözel et al. reported three more cases of canL in the northern part of the island (Töz *et al*. 2013). In 2016, two different studies were conducted, and the seropositivity of canL was 1.9% and 3.55%, respectively (Beyhan *et al*. 2016). Cases of CanL were also detected in the southern part of Cyprus. The overall seropositivity among dogs in the south part of the island was 1.7% in 1996 (Deplazes *et al*. 1998). However, this rate increased compared to 10 years ago and was 14.9% in the following years (Mazeris *et al*. 2010). Cases of human infection with *Leishmania donovani* and *L. infantum* have been reported in both parts of Cyprus. The first cases in humans in the northern part of Cyprus were detected in 1935. In 1990, 10% and 35% of people tested positive for the parasite in the Kyrenia and Lapithos provinces (Deplazes *et al*.

1998). In the following years, in 2016, three cases of visceral leishmaniasis in children were reported (Sayılı *et al.* 2016). Emrah et al. (Ruh *et al.* 2017) also published that the seropositivity rate for leishmaniasis was 1.2% in 2017. Three human cases were reported in Southern Cyprus in 2006 (Antoniou *et al.* 2008). Furthermore, CL was reported in a family of four in 2014 (Koliou *et al.* 2014). Over the years, zoonotic bacterial, viral and parasitic infections have been detected in Northern Cyprus. Factors such as vectorial mobility due to the effects of global warming and human migrations indicate that such infections may become increasingly dangerous. Vector and reservoir management should be implemented on the island to detect possible agents and limit their spread rapidly. Additionally, continuous and extended studies should be conducted for global surveillance. It may also benefit countries by creating infrastructure for diagnosis and treatment, effective control programs for such infections, and community education programs in case of natural disasters such as earthquakes, floods, etc.

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Conflict of interest

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