

## REVIEW ARTICLE

# Rabies epidemiology and control in Turkey: past and present

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## SUMMARY

Turkey is the only country in Europe where urban dog-mediated rabies persists. Control measures in recent decades have reduced the burden of rabies to relatively low levels but foci of disease still persist, particularly in urban areas. Occasional human cases result from this persistence although the source of these appears to be both dog and wildlife reservoirs. This review considers the current state of rabies in Turkey including current control measures, the varying epidemiology of the disease throughout this country and the prospects for rabies elimination.

**Key words:** Epidemiology, rabies (animal), rabies (human).

## INTRODUCTION

Rabies is one of the most significant zoonotic diseases in the world and is found in many of the countries of the eastern Mediterranean [1]. It is caused by a negative-sense, single-stranded RNA virus (family Rhabdoviridae, genus *Lyssavirus*) that is transmitted by the bite of an infected animal. Since ancient times descriptions of rabies have been made on the land-mass of modern Turkey. A series of authors, both physicians and veterinarians, through the Byzantium period have described the disease [2]. Between the 4th and 14th centuries their works generally describe the disease in man and domestic animals, and propose

various cures, all of which were ineffectual. Table 1 gives examples of some of these authors. One of the earliest records comes from Apsyrto who may have acted as a veterinarian to the armies of Constantine the Great around the time of the emperor's campaigns against the Sarmatians (A.D. 324). In the *Hippiatrica*, a compilation of letters on veterinary subjects, he described rabies in horses and suggested a number of cures such as the root of wild cucumber cooked in wine or bloodletting.

Towards the later years of the Ottoman Empire, Turkey rapidly adopted Pasteur's vaccination method in the late 19th century for the prevention of rabies in humans. The first recorded treatment was in 1887 and during the following 11 years, over 2300 people were treated [3]. Modern Turkey was formed in 1923 under the leadership of Mustafa Kemal Atatürk and established its current borders with Bulgaria and Greece in the west and with Azerbaijan, Armenia, Georgia,

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Table 1. *Byzantine authors who make reference to the disease rabies* [2]

Author	Dates, all A.D. (Emperor)	Occupation	Book
Philumenos	180 (Commodus)	Physician	<i>Corpus Medicorum Graecorum</i>
Oribasios	361 (Julian the apostate)	Physician	<i>Synopsis</i>
Apsyrtos	334 (Constantine)	Veterinarian	<i>Hippiatrica</i>
Aetios of Amida	502–575	Physician	<i>Tetrabiblos</i>
Caelius Aurelianus	5th century	Physician	<i>Acute diseases</i>
Paulos of Aegina	640	Physician	<i>Poisonous animals</i>
Nicholas Myrepsos	13th century	Physician	<i>Dynameron</i>

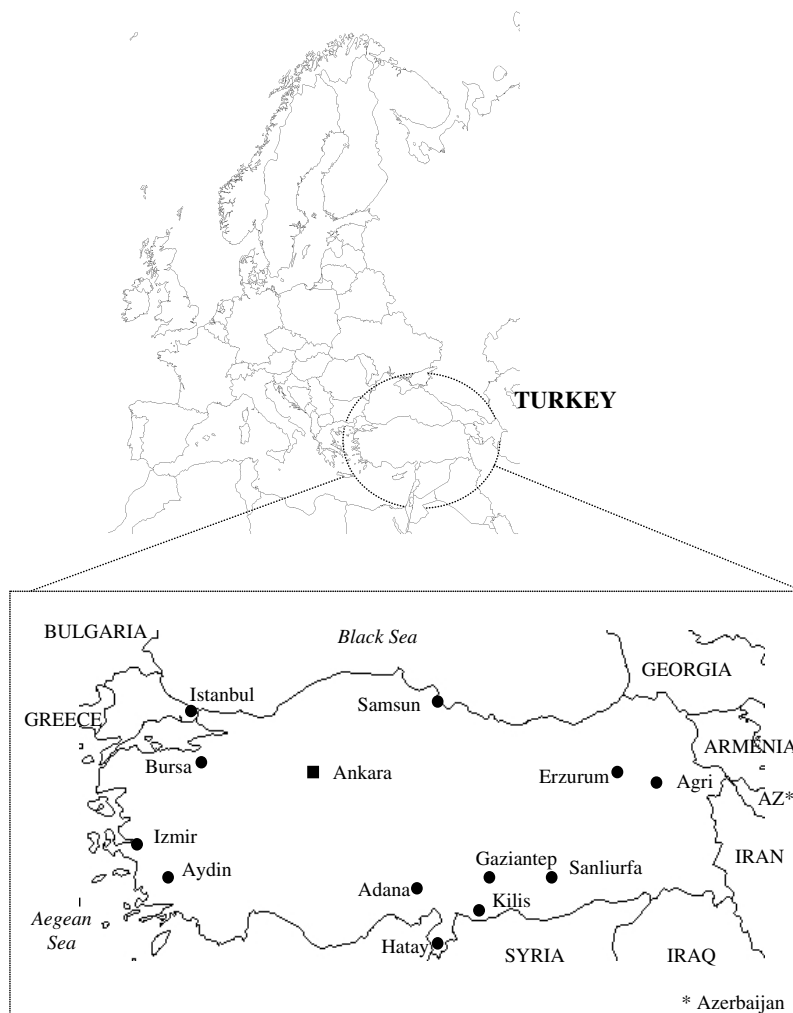


Fig. 1. Map of Europe with a detailed map of Turkey shown inset with major cities marked.

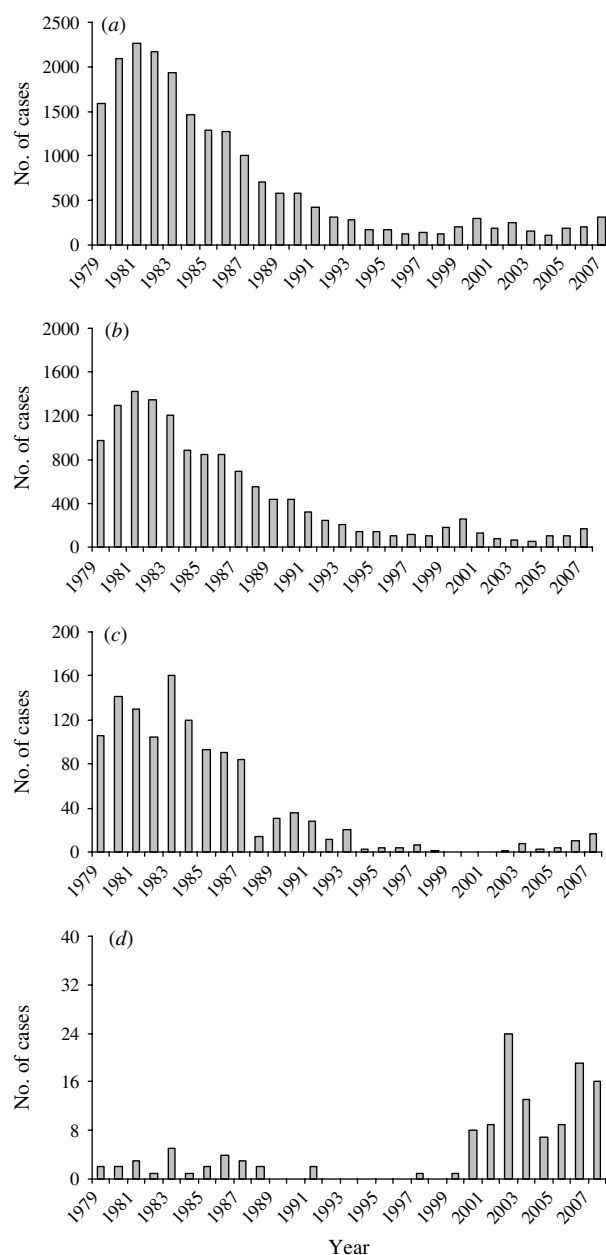
Iran, Iraq and Syria to the east and south (Fig. 1). Little progress was made during the 20th century in controlling dog rabies. Between 1949 and 1969, over 407 000 people were given the Semple rabies vaccine (inactivated nerve tissue-derived) or vaccine plus anti-rabies serum ( $n = 1990$ ) [3]. During this time 120 people were reported to have died of the disease although

this is likely to be an underestimate of the total number of rabies cases during this time. A further 36 suffered complications from treatment. The World Health Organization (WHO) no longer recommends this type of vaccine. Domestic animals were routinely immunized with a modified live rabies vaccine (Kelev strain) and inactivated cell culture vaccines.

During the modern era Turkey has undergone a dramatic urbanization. The country contains 81 provinces with 18 having populations greater than 1 million people. The total human population was in excess of 70 million in 2007 with over 70% living in urban areas. The state capital, Ankara, is a thriving city of over 4 million people. This has been associated with a continual increase in the dog population although there are little firm data on how large this population has become [4] being composed of owned dogs and feral animals. This also increases the risk of exposure of the human population to dog bites and in 1974, 52 deaths due to rabies were reported in Turkey. Turkey has also recorded the only report of transplacental transmission of rabies [5]. The increasing problem of rabies in dogs prompted intensive control of the disease with a corresponding decline in both human and animal rabies by the mid-1990s. Currently, about 200 cases of rabies are reported in animals in Turkey each year. Extensive use of post-exposure prophylaxis (PEP) is made in response to animal bites and human rabies is rare [6].

### Surveillance and control

Rabies is a notifiable disease in Turkey and the country has strong links with the WHO, the World Organization for Animal Health (OIE) and the European Union (EU). Within Turkey, veterinary control and research institutes provide rabies surveillance and diagnosis [7]. A network of eight centres based in Ankara, Istanbul, Samsun, Izmir, Adana, Elazig, Erzurum and Konya provide regional laboratories that deliver routine diagnostic services. The data presented within this review arise from passive surveillance from submissions to these laboratories. The fluorescent antibody test (FAT) and the mouse inoculation test (MIT) are used for routine diagnosis following WHO and the OIE recommended protocols. The Etlik Central Veterinary Control and Research Institute (ECVCRI) in Ankara acts as the national rabies reference centre and producer of a modified live attenuated rabies vaccine based on the Kelev virus for vaccination of dogs. Occasionally, histology and the detection of Negri bodies have been used to diagnose rabies in humans [8]. For molecular tests, particularly for ante-mortem diagnosis in humans, and for confirmation, samples must be transported to the ECVCRI where the standard diagnostic tests are complemented by virus isolation in cell culture and sensitive reverse-transcriptase polymerase

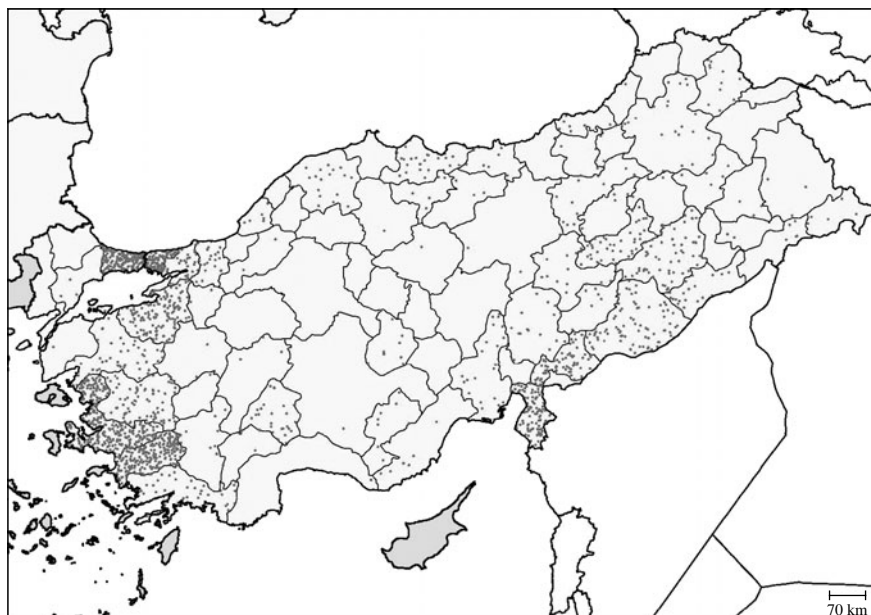


**Fig. 2.** Incidence of rabies cases within animals in Turkey between 1979 and 2007. The total annual number of (a) cases, (b) cases in dogs, (c) cats and (d) foxes are shown (source: *Rabies Bulletin Europe*).

chain reaction (RT-PCR). Efforts are currently being made to make these tests available throughout the network of diagnostic laboratories.

### Rabies in domestic animals

Surveillance for rabies demonstrates that the disease has been in decline within the country since a peak of 2260 cases in 1981 (Fig. 2a). Cases are primarily associated with urban areas with foci in the Istanbul



**Fig. 3.** Distribution of rabies cases ( $n = 1884$ ) in Turkey between 1997 and 2006. Each dot represents a reported rabies case (source: *Rabies Bulletin Europe*).

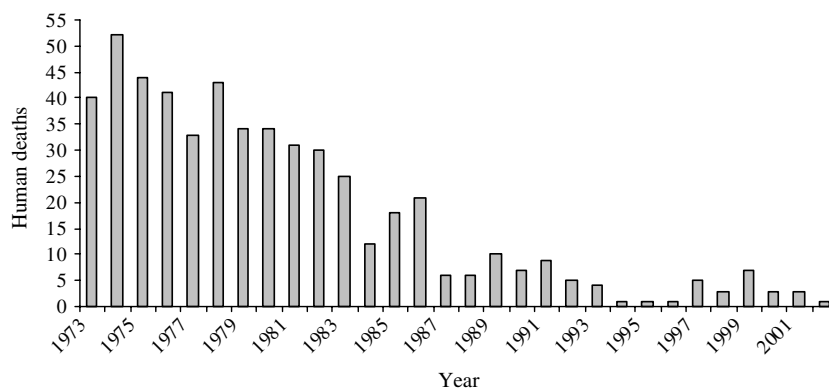
area, provinces on the Aegean coast and in the south of the country, specifically in the provinces of Adana, Hatay and Gaziantep (Fig. 3). Surveillance for rabies is weaker in the eastern provinces, in part due to the remoteness of many areas limiting access to veterinary services, which may account for the low numbers of reports in those areas. The domestic dog is the principal reservoir for rabies in Turkey that until recently accounted for over 60% of cases. The dynamics of the rabies situation in Turkey is shown in Table 2 where comparison of the number of cases at 5-year intervals clearly shows the decline of the disease since 1982, but also confirms its persistence, and possible resurgence, to the present day. The urbanization during the 20th century has led to an expansion of the dog population and provided a large pool of susceptible animals for the disease to persist. Efforts to control dog-mediated rabies gradually reduced the number of rabid dogs, reaching a trough in 1997 at 125 (Fig. 2*b*). The number of positive submissions has remained around this level despite further attempts to eliminate the disease completely. The dog is critical to bringing the disease into contact with humans and most instances of disease are the result of a dog bite. Cats although unable to act a reservoir for the disease were often responsible for human exposures to the virus. Although cats were responsible for a significant number of rabies cases until the late 1990s, no rabid cats were reported in this species between 1999 and 2001 (Fig. 2*c*). The

**Table 2.** *The evolution of rabies virus epidemiology in Turkey between 1982 and 2007*

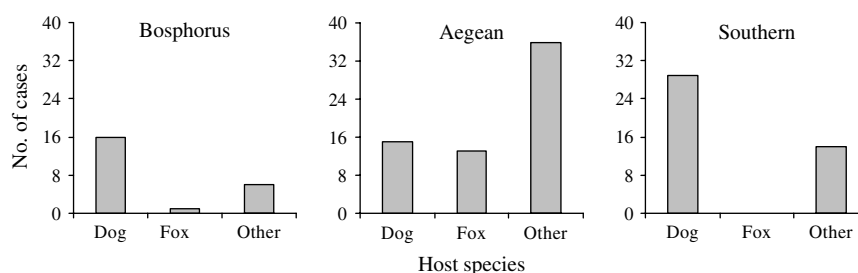
Year	Dog	Cat	Domestic livestock	Fox	Other
1982	1342	104	657	1	68
1987	695	84	190	3	33
1992	239	11	59	0	11
1997	117	6	14	1	4
2002	75	1	141	24	8
2007	165	16	106	16	4

recent reappearance of the disease in this species is a concern, therefore educating the public that cats transmit rabies is important.

Control measures are the responsibility of local administrators within municipalities and in the provinces, provincial veterinary authorities act to control animal diseases. Measures include voluntary vaccination of dogs, quarantine and the provision of public information. Small-scale oral vaccination trials in dogs have been attempted [9–11], but no large-scale national or provincial campaigns have been financed and with limited efforts to control the stray dog population within urban centres, the possibility of rabies elimination in the immediate future seems unlikely. A further issue is that of animal welfare legislation that is poorly implemented in many areas and limits local authorities to housing stray dogs and the



**Fig. 4.** Annual incidence of human deaths due to rabies in Turkey between the years 1973 and 2002 (Turkish Government statistics).



**Fig. 5.** Variation in epidemiological characteristics of animal rabies in different regions of Turkey in 2006 (source: *Rabies Bulletin Europe*).

introduction of neutering schemes, both of which are expensive to maintain.

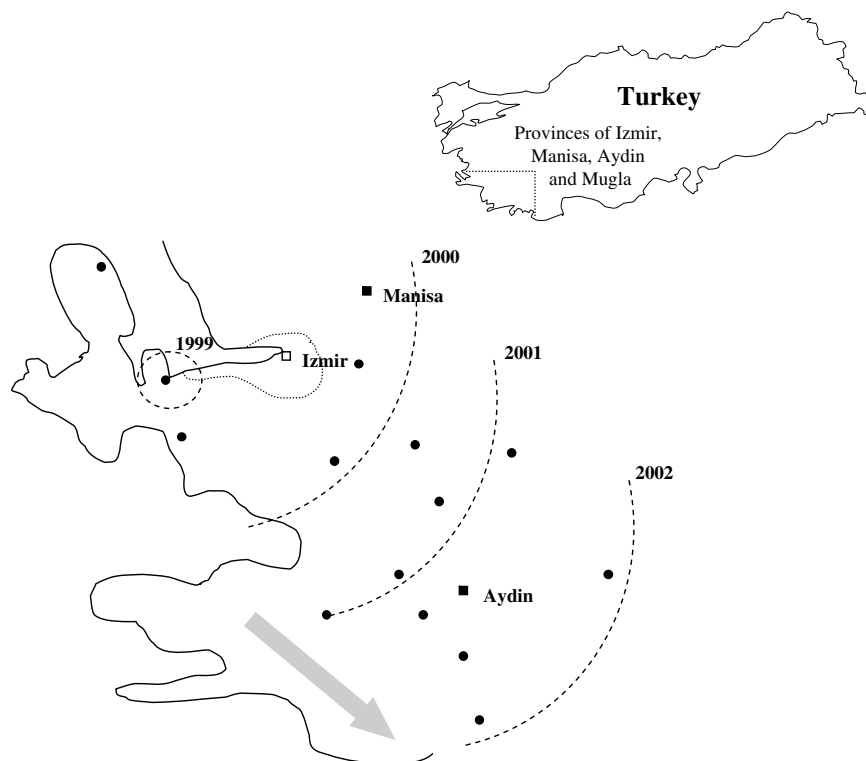
#### Rabies in humans

As recently as the early 1970s, between 40 and 50 people each year died from rabies. This figure has declined, in parallel with the reduction in rabies in dogs (Fig. 4). Unfortunately, reporting of human cases has been sporadic, either within the scientific literature [12] or in the national press. A report in the *Turkish Daily News* from 6 October 2007, documented the death of a 5-year-old boy from rabies in Istanbul. In 2003, over 100 000 animal bites were recorded by the Turkish Ministry of Health. Most were treated with a five-dose intra-muscular course of vaccine (human diploid cell vaccine or VERO cell vaccine) and rabies immunoglobulin following WHO guidelines [13]. A case study of four deaths resulting from rabies in Turkish nationals [14] demonstrates the importance of reacting rapidly to an animal bite whether from a domestic animal or wildlife as two of the cases resulted from bites by wild animals, in one case a fox. In two cases diagnosis of rabies was

confirmed ante-mortem. The epidemiological observations of these cases are discussed below.

#### Rabies in wildlife

A further trend has been the recent emergence of fox rabies. Occasional cases of rabies have always been reported in the red fox (*Vulpes vulpes*). However, in 2000, eight cases were reported and this number continued to increase (Fig. 2d) and appears to be associated with an increase in the number of domestic animals infected with rabies, now in excess of the number of dog cases. Of significance is the regional focus for these cases in provinces on the Aegean coast. This is clearly demonstrated when the cumulative cases for three regions of Turkey affected by rabies are compared (Fig. 5). In the Bosphorus region of the country, including Istanbul, dog submissions dominate the number of animals reported positive for rabies. This is also the situation found in the southern provinces along the Syrian border. This contrasts with the Aegean provinces where an equal number of dog and fox cases are reported, but where both are dominated by the number of submissions from domestic



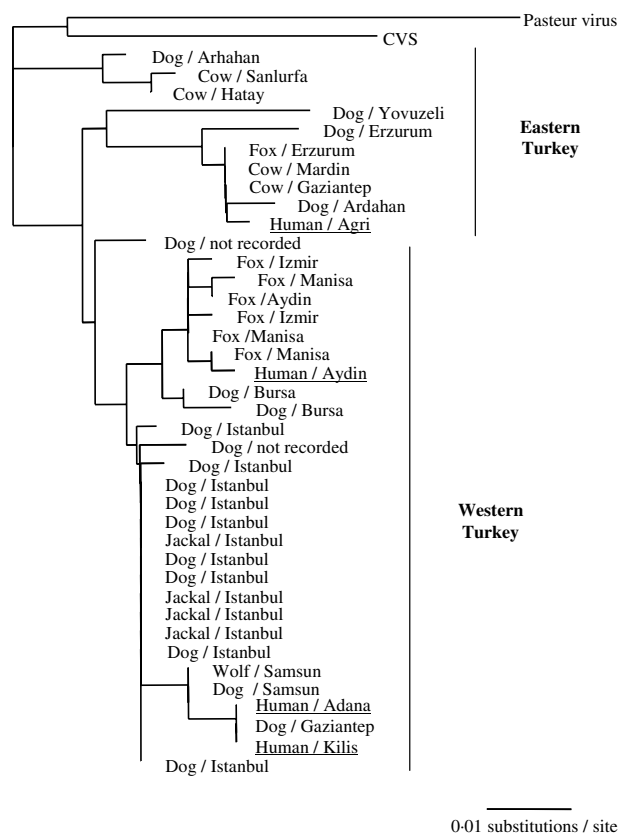
**Fig. 6.** Map of western Turkey showing the spread of fox rabies cases through the provinces of Izmir, Manisa, Aydin and Mugla. The wave front of each year between 1999 and 2002 is indicated.

animals, mainly cattle. Most of the fox cases have been reported in the provinces of Izmir and Aydin. Whilst dog rabies is found predominantly in the large urban centre and provincial capital (also called Izmir) the total numbers of rabid dogs and foxes reported in the Aegean region is approximately equal, a situation unique in Turkey. Careful mapping of the appearance of fox cases [15] has suggested that there was spread of the disease from a site to the west of the city of Izmir in 1999, eastwards into the province of Manisa and south into the province of Aydin (Fig. 6). By 2003, rabid foxes had been reported in the province of Mugla (south of Aydin). During subsequent years, rabies spread to the provinces of Denizli and Usak. By 2008, the disease had reached Burdur, Isparta and Afyonkarahisar. The increase in rabid foxes, the steady spread of the disease, cases of the disease in domestic cattle and a late winter peak of cases all point to the likelihood that an endemic cycle of rabies has become established in the fox population [16]. This has prompted the European Union to fund attempts to improve rabies control in Turkey, including an attempt to eliminate rabies in the fox using aerial distribution of a live-attenuated vaccine enclosed in an edible bait in the Aegean provinces.

This is the first attempt at aerial vaccine delivery in Turkey.

Occasional rabies cases are observed in the jackal (*Canis aureus*), particularly around Istanbul. Phylogenetic analysis of these cases suggests that they have resulted from transmission or spillover from the endemic reservoir in dogs (Fig. 7). Rabies cases in wolves (*Canis lupus*) are also reported in Turkey, mainly from the eastern provinces of the country. Although an incidental host, and rare in Turkey, the wolf is capable of inflicting severe bites to humans.

In 1956, a rabid bat was reported from Turkey. Of 71 bats (including *Rhinolophus* and *Plecotus* spp.) from Diyarbakir and Bergama (western Turkey) examined for the presence of negri bodies one Greater horseshoe bat (*Rhinolophus ferrumequinum*) was positive [17]. Following this early report no further bats have been identified as rabid although there is little in the way of surveillance in bat species. Bat rabies has been reported from European countries to the north of Turkey. In 1956, three noctule bats (*Nyctalus nyctalula*) infected with a lyssavirus were reported [18]. Subsequent reports have demonstrated that Eastern European bats are a reservoir for European bat lyssavirus type 1 [19]. However, a



**Fig. 7.** Molecular phylogeny of rabies in Turkey based on a 322 base-pair region of the rabies virus nucleoprotein-coding gene. The infected host and location from which the sample was found are given for each virus sequence. This phylogeny was derived using the neighbour-joining method. The Pasteur virus (PV) and Challenge Virus Standard (CVS) fixed rabies isolates were used as outgroups.

recently isolated lyssavirus named West Caucasian bat lyssavirus, was isolated from a Common bent-winged bat (*Minopterus schreibersi*) 100 km south-east of the city of Krasnodar in Russia, and a similar distance from the Turkish border to the south [20]. These reports suggest that it would not be unusual to find lyssaviruses in Turkish bats. However, the elusive nature of bats means that unless specifically looked for through surveillance it is unlikely to be detected, provided that diagnostics currently in use are capable of detecting bat-associated lyssaviruses.

**Molecular epidemiology**

Molecular techniques have made a major contribution to further understanding the epidemiology of rabies virus throughout the world [21]. The first report to include Turkish isolates within a phylogenetic

study included two isolates (TU93100 and TU93201) within an investigation of both the ecology and evolution of rabies virus throughout Europe [22]. From the perspective of Turkey, this placed Turkish rabies viruses at an intermediate position between eastern European and Middle-eastern viral populations. This prompted further investigation of rabies virus isolates from within Turkey with the result that two major populations were identified (Fig. 7). These are a western clade composed of groups recovered from the urban centres of Istanbul, Bursa and Izmir, and an eastern clade composed of disparate isolates found throughout the eastern provinces of Turkey [21]. The dominant reservoir in both clades is the domestic dog and quite rightly, the majority of control measures have been focused on this host. However, in recent years the western clade has spread south and east entering provinces that had previously been free of the disease such as Aydin, Manisa, Mugla and Denizli [15]. In 2008, the infected area was further enlarged to include provinces to the east.

A recent publication [23] and an investigation [14], triggered by a series of human cases, have suggested that the western clade has moved from Samsun province in the north, through Hatay province and south to the Israeli border. The speed of this movement implies that human intervention such as illegal movement of animals may have contributed to this translocation.

**CONCLUSIONS**

The rabies situation in Turkey remains balanced between near elimination and sporadic outbreaks. This dynamic situation has led to the emergence of rabies in a second reservoir species, the fox, and the possible movement of a distinct strain of rabies from Western Turkey to the southern border and its appearance in a northern province of Israel. Occasional cases of human rabies occur and act as a tragic reminder that only total elimination will remove this threat to public health. Challenges include continued political support for rabies control measures, continual improvement of surveillance and diagnosis and methods for controlling trans-border movement with rabies-endemic neighbouring countries. Indeed, most countries on the southern and eastern borders of Turkey have reported cases of rabies in humans, domestic animals and occasionally wildlife [1]. Terrestrial rabies elimination from much of Turkey is a possibility but will require renewed efforts to succeed over the coming years.

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## DECLARATION OF INTEREST

None.

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