



T.C. SAĞLIK BAKANLIĞI
HALK SAĞLIĞI
GENEL MÜDÜRLÜĞÜ

Tatarcık Humması Virüsleri

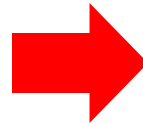
Uzm. Dr. Dilek MENEMENLİOĞLU

Halk Sağlığı Genel Müdürlüğü

Mikrobiyoloji Referans Laboratuvarları ve Biyolojik Ürünler Dairesi

Ulusal Arbovirüs ve Viral Zoonotik Hastalıklar Laboratuvarı

Phleboviruses



SSS Enfeksiyonları

Effects of sandfly fever on isometric muscular strength, endurance, and recovery¹

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Summary head: EFFECTS OF SANDFLY FEVER ON MUSCULAR PERFORMANCE

Approved for public release: Distribution unlimited

22 April 1977

U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland 21701

Phlebovirus: Sınıflama:

Cins

- *Bunyavirus*
- *Hantavirus*
- *Nairovirus*
- *Phlebovirus*
- *Tospovirus*



BUNYAVIRIDAE

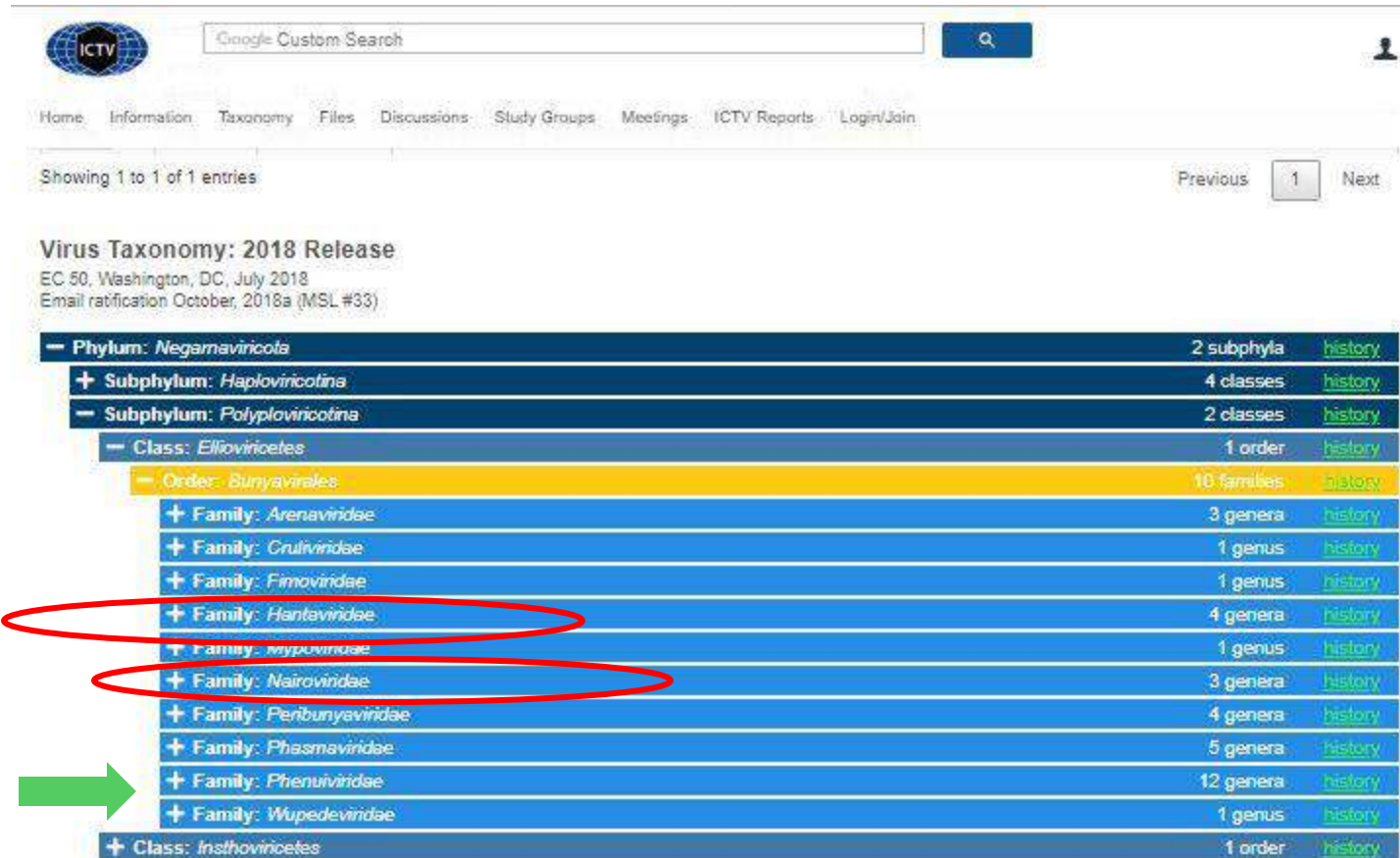
ailəsi

Uluslararası Virüs Taksonomi Komitesi (ICTV)

– 9. rapor (2011)

Phlebovirus: Sınıflama:

<https://talk.ictvonline.org/taxonomy/>



ICTV

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Previous 1 Next

Virus Taxonomy: 2018 Release

EC 50, Washington, DC, July 2018
Email ratification October, 2018a (MSL #93)

– Phylum: <i>Negamaviricota</i>	2 subphyla	history
+ Subphylum: <i>Haplovinicotina</i>	4 classes	history
– Subphylum: <i>Polyplovinicotina</i>	2 classes	history
– Class: <i>Elioviricetes</i>	1 order	history
– Order: <i>Bunyvirales</i>	10 families	history
+ Family: <i>Arenaviridae</i>	3 genera	history
+ Family: <i>Crulviridae</i>	1 genus	history
+ Family: <i>Fimoviridae</i>	1 genus	history
+ Family: <i>Hantaviridae</i>	4 genera	history
+ Family: <i>Mypoviridae</i>	1 genus	history
+ Family: <i>Nairoviridae</i>	3 genera	history
+ Family: <i>Peribunyaviridae</i>	4 genera	history
+ Family: <i>Phasmaviridae</i>	5 genera	history
+ Family: <i>Phenuiviridae</i>	12 genera	history
+ Family: <i>Wupedeviridae</i>	1 genus	history
+ Class: <i>Insthoviricetes</i>	1 order	history

Uluslararası Virüs Taksonomi Komitesi (ICTV)
– 10. rapor (2018)



— Class: <i>Elioviricetes</i>	1 order	history
— Order: <i>Bunyavirales</i>	10 families	history
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+ Family: <i>Nairoviridae</i>	3 genera	history
+ Family: <i>Peribunyaviridae</i>	4 genera	history
+ Family: <i>Phasmaviridae</i>	5 genera	history
— Family: <i>Phenuiviridae</i>	12 genera	history
+ Genus: <i>Banyangvirus</i>	1 species	history
+ Genus: <i>Beidivirus</i>	1 species	history
+ Genus: <i>Goukivirus</i>	3 species	history
+ Genus: <i>Honwivirus</i>	1 species	history
+ Genus: <i>Hudivirus</i>	1 species	history
+ Genus: <i>Hudovirus</i>	1 species	history
+ Genus: <i>Mobuvirus</i>	1 species	history
+ Genus: <i>Phasivirus</i>	4 species	history
— Genus: <i>Phlebovirus</i>	9 species	history
Species: <i>Bujaru phlebovirus</i>		history
Species: <i>Candiru phlebovirus</i>		history
Species: <i>Chilibre phlebovirus</i>		history
Species: <i>Frijoles phlebovirus</i>		history
Species: <i>Punta Toro phlebovirus</i>		history
★ Species: <i>Rift Valley fever phlebovirus</i>		history
Species: <i>Salehabad phlebovirus</i>		history
Species: <i>Sandfly fever Naples phlebovirus</i>		history
Species: <i>Ukuniemi phlebovirus</i>		history
+ Genus: <i>Picchovirus</i>	1 species	history
+ Genus: <i>Tenuivirus</i>	7 species	history
+ Genus: <i>Wubeivirus</i>	2 species	history

<https://talk.ictvonline.org/taxonomy/>

Phlebovirus: Sınıflama:

Phenuiviridae ailesi *Phlebovirus* cinsi
sınıflandırılabilmiş 9 tür /serotip

› 50 serotip

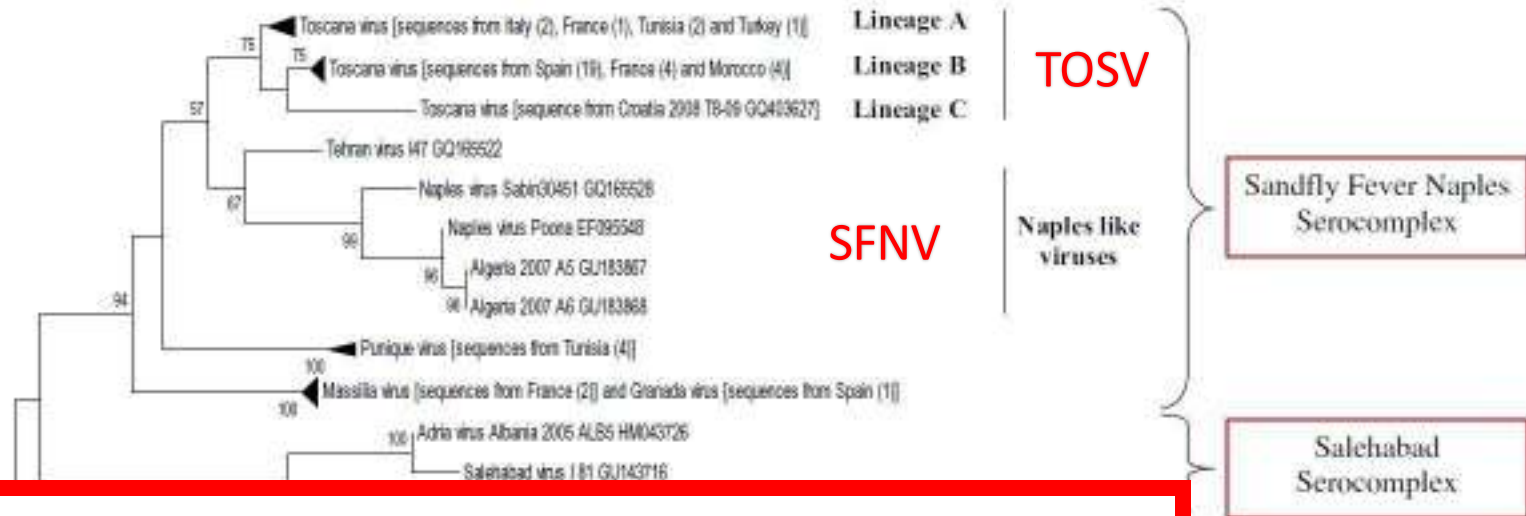
- *Bujaru phlebovirus*
- *Candiru phlebovirus*
- *Chilibre phlebovirus*
- *Frijoles phlebovirus*
- *Punta Toro phlebovirus*
- *Rift Valley fever phlebovirus*
- *Salehabad phlebovirus*
- *Sandfly fever Naples phlebovirus*
- *Uukiniemi phlebovirus*

Phlebovirus cinsi

Tür/Serotip Virüs

	Maldonado virus (MLOV) Mombi virus (MR/MBV) Mucuna virus (MCRV/MRAV) Nique virus (NIQV) Orizimã virus (ORXV) Serra Norte virus (SRNV) Turana virus (TUAV) Cacao virus (CACV) Chilibe virus (CHIV) Frijoles virus (FRIV) Joã virus (JOAV) Buena Ventura virus (BUEV) Campana virus (CMAV) Capira virus (CAPIV) Cocã virus (CCLV) Luzia virus (LUZV)
<i>Chilibe phlebovirus</i>	
<i>Frijoles phlebovirus</i>	
<i>Punta Toro phlebovirus</i>	
<i>Salehabad phlebovirus</i>	Adana virus (ADAV) Adria virus (ADRV) Alcube virus Arbia virus (ARBV) Arumowot virus (AMTV) Medjerda Valley virus (MVV) Odrénisrou virus (ODRV) Olbia virus (OLBV) Salehabad virus (SALV) Bogalaka virus (BREV) Zaba virus (ZABAV) Arrabida virus (ARRV) Baikan virus (BALKV) Fermo virus (FERV) Gordil virus (GORV) Granada virus (GRV – GRAV) Massilia virus (MASV) Panique virus (PUNV) Saddaguia virus (SADV) Saint-Floris virus (SAFV) sandfly fever Naples virus (SFNV) Tehran virus (THEV) Toscana virus (TOSV) Zendali virus (ZHRV)
<i>Sandfly fever Naples phlebovirus</i>	

Phlebovirus: Serotip:



«Toscana virus» (TOSV)
 «sandfly fever Naples virus» (SFNV)
 «sandfly fever Turkey virus» (SFTV)
 «sandfly fever Sicily virus» (SFSV)
 «sandfly fever Cyprus virus» (SFCV)

amino-acid sequences of the L protein.

***BUNYAVIRALES* takımı**

Bunyaviridae - Schematischer Aufbau

ORTAK ÖZELLİKLER

Zarflı

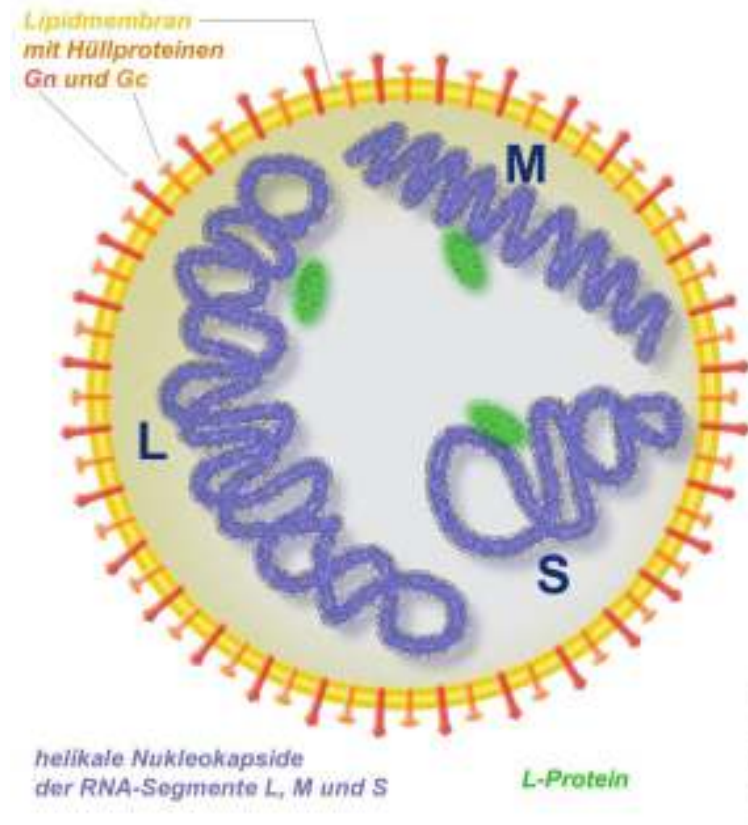
Tek iplikli negatif polariteli RNA

3 segmentli

S Segment (1.7-1.9kb)

M Segment (3.2-4.2kb)

L Segment (6.4kb)



BUNYAVIRALES takımı

ORTAK ÖZELLİKLER

S segmenti nükleokapsid proteinini, NS proteinini
M segmenti zarf glikoproteinleri G1 ve G2'yi,
L segmenti RNA polimeraz enzimini
kodlamaktadır.

- G1 ve G2 proteinler;
viral nötralizasyon, füzyon ve hemaglütinasyon
- nükleokapsid proteini;
çapraz reaksiyonlar

VEKTÖR: Tatarcık - Kum Sineği:

Diptera takımı,

Psychodidae ailesi,

Phlebotominae alt ailesinde



SPECIES NAME/CLASSIFICATION: Phlebotomus spp. (Diptera: Psychodidae)

- ✓ *Lutzomyia* cinsi – Yeni Dünya
- ✓ *Sergentomyia* cinsi – Eski Dünya
- ✓ *Phlebotomus* cinsi – Eski Dünya

P. papatasi – Ana vektör
(SFNV-SFSV)

P. ariasi

P. major s.l. (SFTV)

P. longicuspis

P. perniciosus (TOSV)

P. neglectus

P. perfiliewi (TOSV)

S. minuta

VEKTÖR: Tatarcık - Kum Sineği:

- ✓ sarımsı renkte (tamamen beyaz - tamamen siyah)
- ✓ 1,5-3 mm büyüklük
- ✓ tüylü, dinlenirken kanatlarını gövdelerinden yukarda tutan, avlarına yaklaşınca zıplayıcı hareketleri ile tipik sinekler
- ✓ oldukça sessiz - “pappataci”
- ✓ genellikle dış ortamda bulunup yumurtlar
- ✓ 25 - 28°C de aktif / nem
- ✓ açık havada rüzgara duyarlı – yere yakın
- ✓ dişiler yumurtaları geliştirebilmek için kan emerler
- ✓ gece ve şafakta kan emerler – gündüz rahatsız edilirse
- ✓ 35-69 günde erişkin – 2hafta
- ✓ 4. evre larvaları soğuğa dayanıklıdır



VEKTÖR: Tatarcık - Kum Sineği:

- ✓ tatarcıklar virüsü enfekte kişiyi ısırırken alıyorlar
ateş başlangıcından 48 st önce ve 24 st sonra
- ✓ sinekte 7-10 gün IP, hayatı boyunca enfekte kalıyor
- ✓ vertikal, venereal, transstadiyal yolla yavrulara aktarıyor
- ✓ rezervuar konak???
- ✓ oldukça kaşıntılı lezyonlar (%1)
tükrük enjekte ederler-antijenik

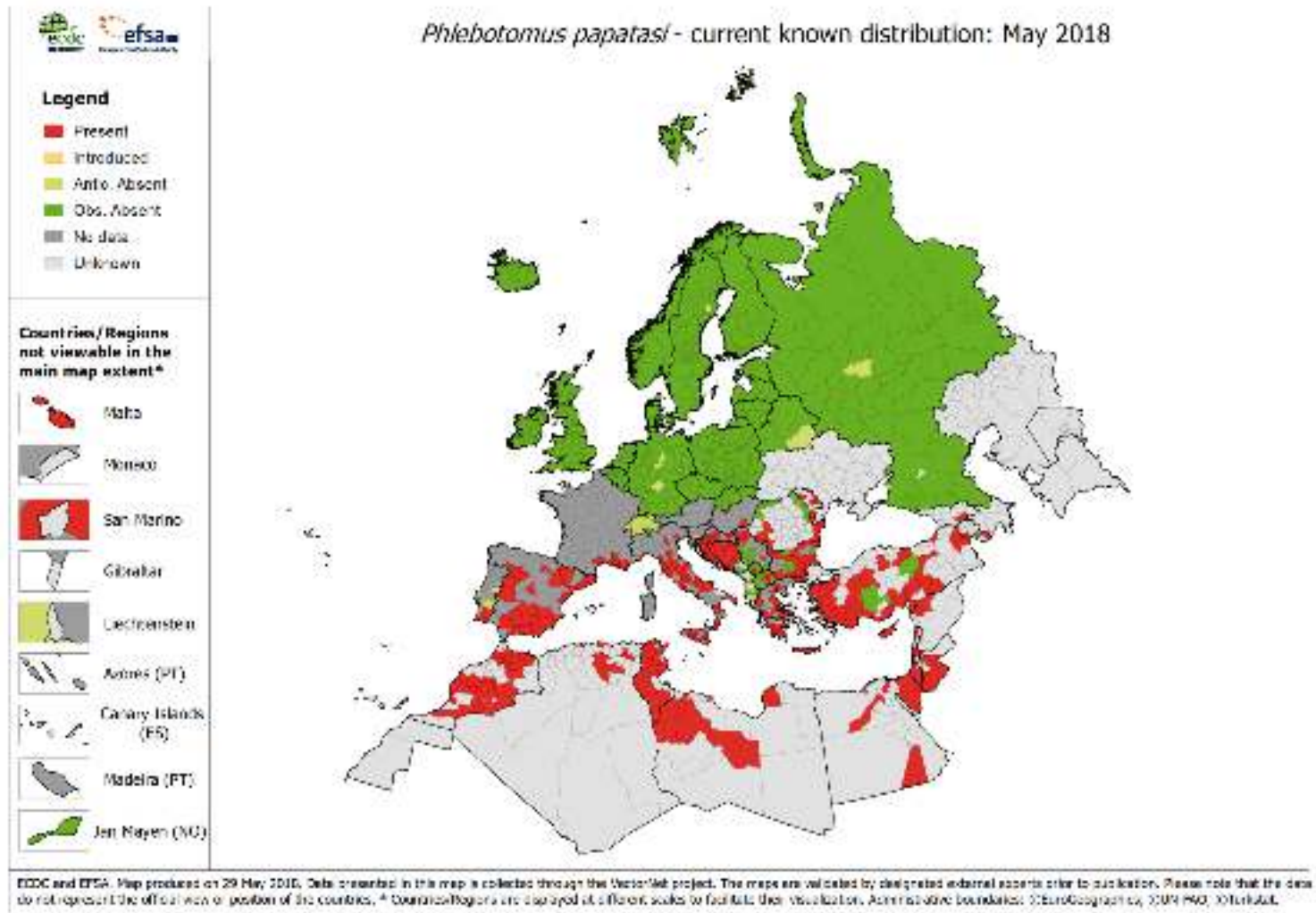


Epidemiyoloji: vektörün yayılımı



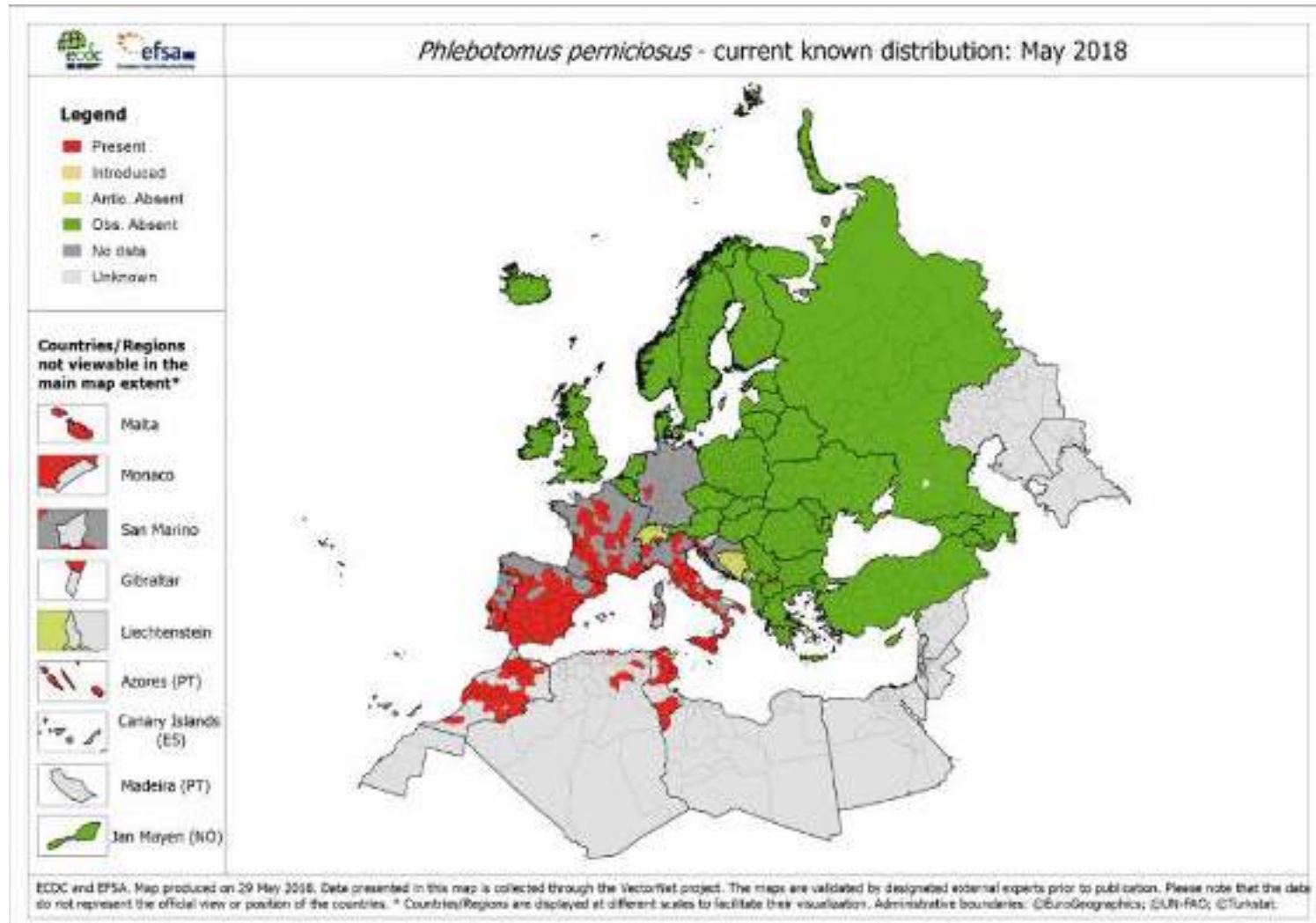
özellikle Akdeniz çevresi, Orta Doğu ve Batı Hindistan
Asya, Afrika, Avustralya, Güney Avrupa, Amerika
N20° - N49°
3300m yüksekliğe kadar farklı habitatlar
nisan – ekim ayları arası

Epidemiyoloji: ECDC vector maps



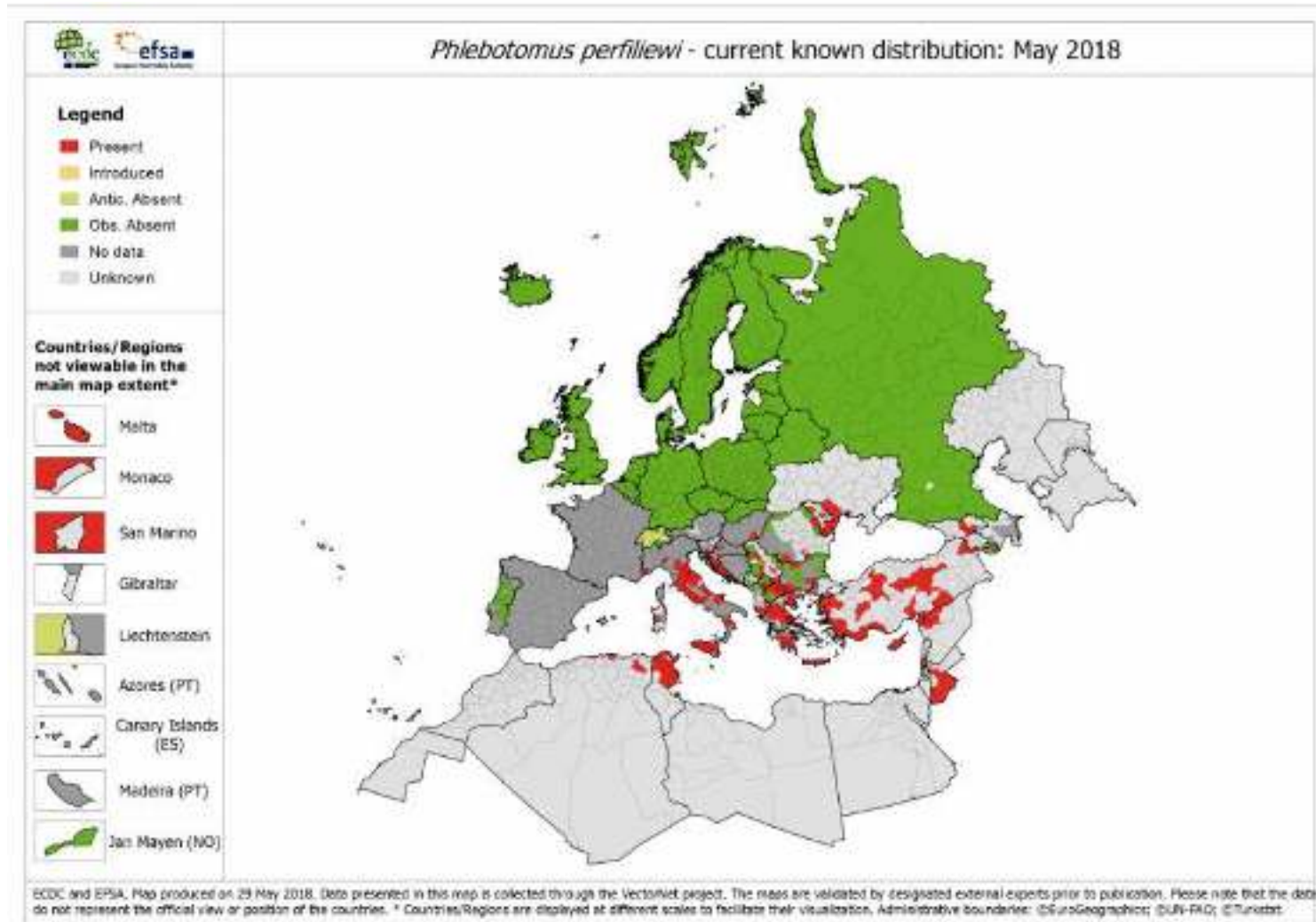
<https://ecdc.europa.eu/en/search?s=phlebotomus>

Epidemiyoloji: ECDC vector maps



<https://ecdc.europa.eu/en/search?s=phlebotomus>

Epidemiyoloji: ECDC vector maps

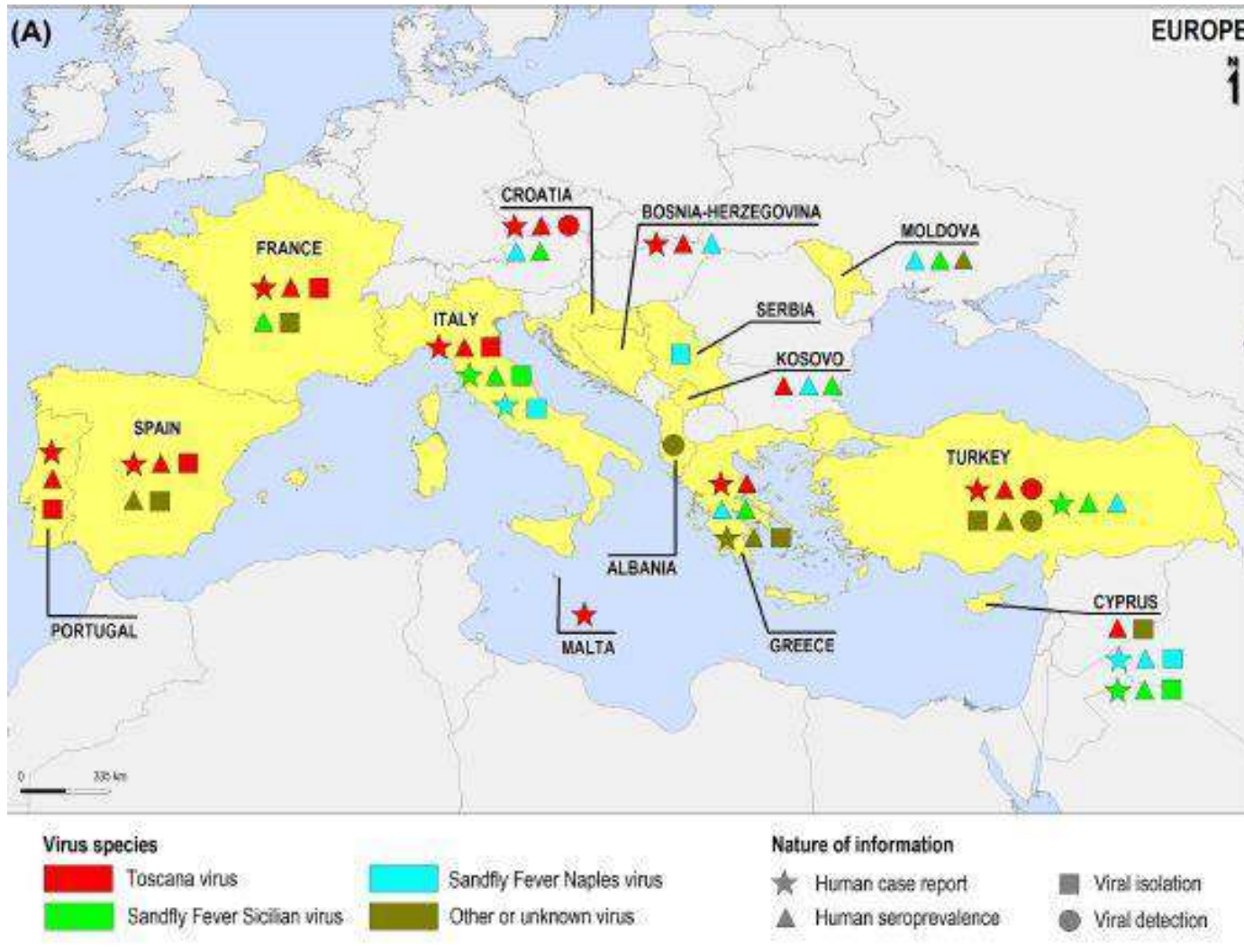


<https://ecdc.europa.eu/en/search?s=phlebotomus>

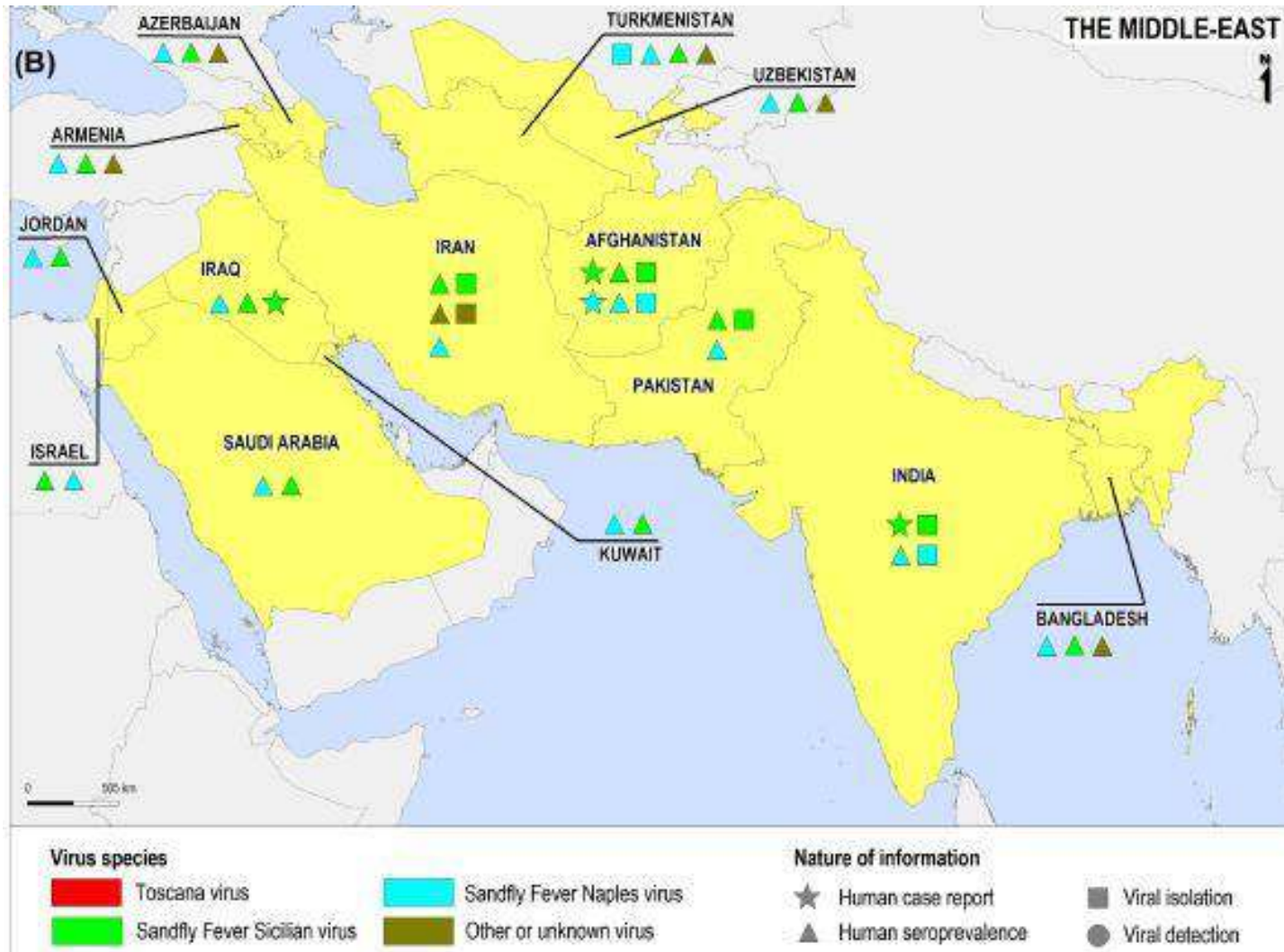
Epidemiyoloji:

- ✓ Hastalık tanımı: 1886 - Alois Pick Balkanlarda
1905 - Tatarcık
1909 - Tatarcıklar tarafından
bulaştırılan filtre edilebilir ajan
- ✓ II. Dünya Savaşı'nda görev yapan askerlerde salgın
Sabin
1943 – SFSV izolasyonu (Mısır&Sicilya)
1944 - SFNV izolasyonu (Napoli)
- ✓ Toskana virüs 1971 P. perniciosus'dan izole ediliyor
1985&1987 SSS enfeksiyonlarından
(Portekiz ve İtalya'dan dönen turist)

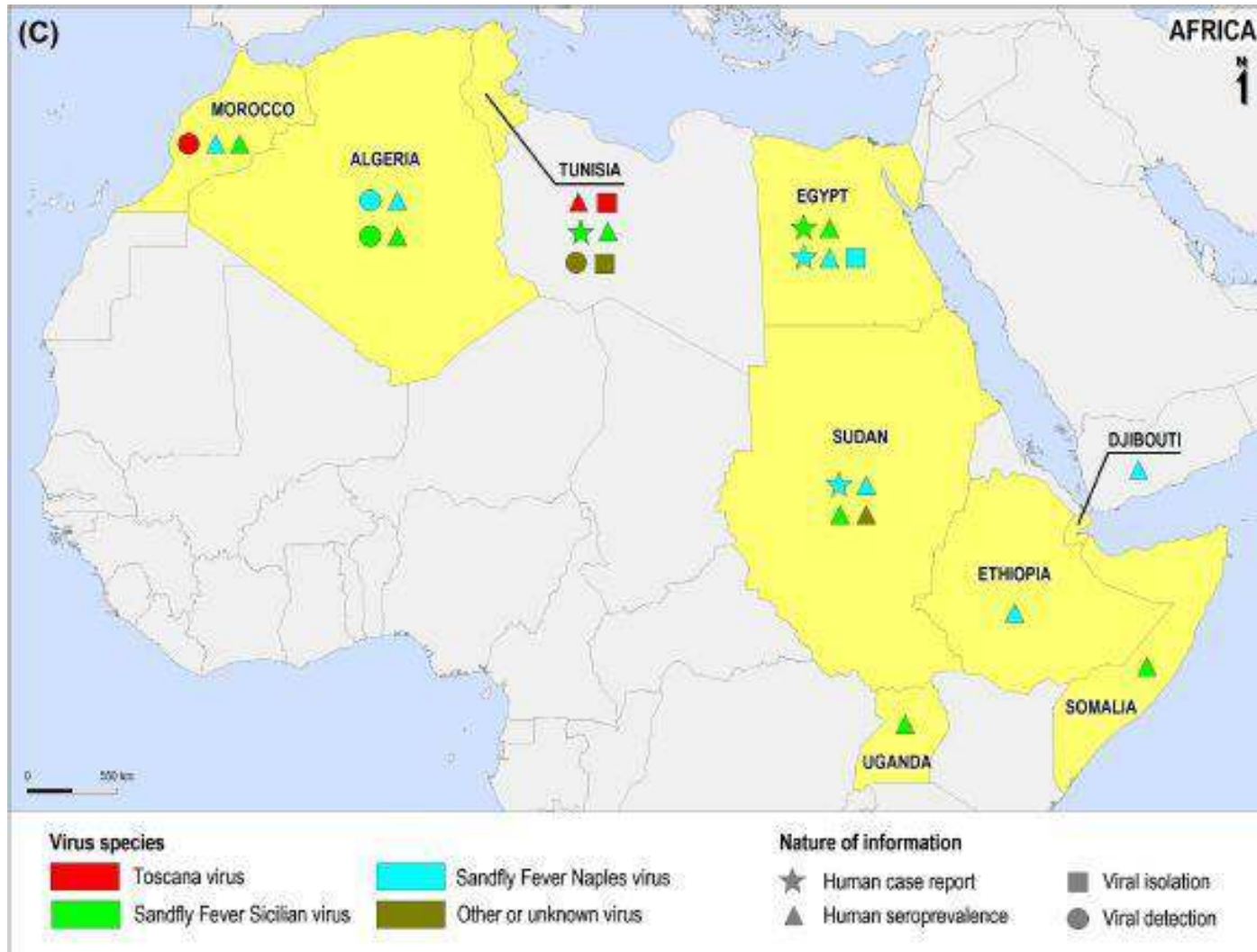
Epidemiyoloji: Avrupa



Epidemiyoloji: Orta Doğu



Epidemiyoloji: Afrika



Epidemiyoloji: Türkiye

- ✓ Seroprevalans : 1976 – Tesh
Akdeniz bölgesinde SFSV % 22
SFNV % 62
PRNT testi ile doğrulanmış

1980 - Serter – Sağlıklı gönüllülerde
Ege bölgesinde SFSV % 0.8
SFNV % 13.9
- ✓ Serolojik tanı: 1997 - Becker Almanya'ya
dönen bir turiste
menenjit etkeni olarak SFSV???

Epidemiyoloji: Türkiye

- ✓ Salgınlar :
 - 2010 – Çarhan
(2007-2008) İzmir, Kozan, Ankara
SFSV % 38
SFSV / SFCV % 12
SFCV % 4 (IgM +) IFA testi
İlk SFTV izolasyonu
 - 2010 – Torun Edis
Kırıkkale salgını SFSV % 27.27
(2009) SFNV %45.45
 - 2012 – Güler
Kahramanmaraş salgını (2010)
SFSV PCR +9/19hasta
SFSV IgM + 19 hasta

Sandfly fever Turkey virus - izolasyon

Journal of Clinical Virology 48 (2010) 264–269



Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv



Characterization of a sandfly fever Sicilian virus isolated during a sandfly fever epidemic in Turkey

Ahmet Çarhan^{a,1}, Yavuz Uyar^{a,1}, Etem Özkaya^a, Mustafa Ertek^a, Gerhard Dobler^b, Meik Dilcher^c, Yongjie Wang^c, Martin Spiegel^c, Frank Hufert^c, Manfred Weidmann^{c,*}

^aReplikasyon National Public Health Agency (RSNPH), Ankara, Turkey

^bInstitute for Microbiology of the Armed Forces, München, Germany

^cUniversity Medical Center, Institute of Virology, Krauszbergstr. 57, Göttingen 37075, Germany

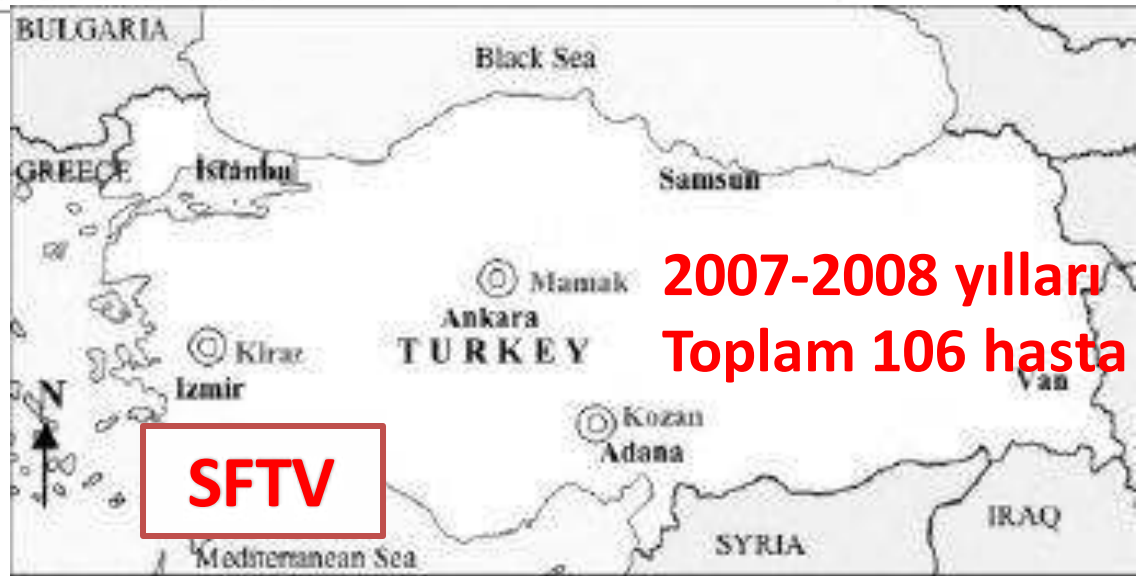
PCR: NEGATİF

Seroloji: IgM

%38 SFSV

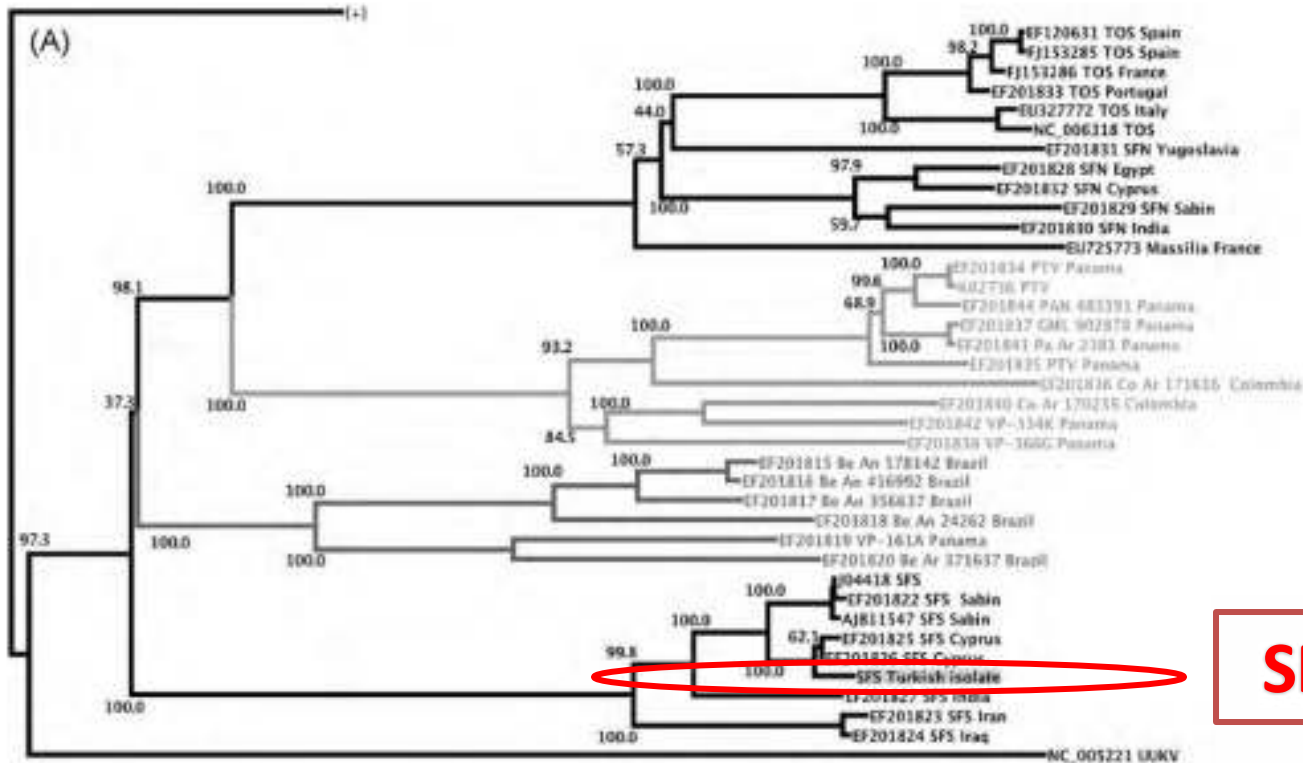
%12 SFSV / SFCV

%4 SFCV



Sandfly fever Turkey virus - izolasyon

A. Çarhan et al. / Journal of Clinical Virology 48 (2010) 264–269



S segment filogenetik analiz sonuçlarına göre
SFSV Sabin izolatı ile %91,8
SFCV sekansları ile %97,8 ve 97,9 homoloji

Epidemiyoloji: Türkiye

✓ SFTV virüs

2011 – Koçak Tufan

Ankara Salgını (2007-2008)

SFTV 10 PCR +

12 IgM + 50 hasta

2012 – Ergünay

Diyarbakır 63y SSS enfeksiyonu

BOS PCR +/sekans analizi

SFTV ilk kez ensefalit etkeni olarak

tanımlanıyor

Epidemiyoloji: Türkiye

✓ Toskana virüs

2003 – Özbel Ege bölgesi
SFNV ve TOSV (ELISA VNT)
Sağlıklı gönüllülerde

2011 – Ergünay 16/102 hasta %15.7
a. PCR +/- sekans (Ankara, Konya, Eskişehir)
ilk TOSV pozitifliği
b. %32.5 /1533 donörde SFV IgG +
(Ankara, Konya, Eskişehir, Zonguldak)

2015 – Dinçer
Adana ve Mersin
Evcil köpeklerde TOSV IgG+ % 40,4



Epidemiyoloji: Türkiye - yeni virüsler

TABLE 2 Features of the novel and previously known sandfly-borne phleboviruses with confirmed circulation in Asia Minor

Virus	Taxonomy ^a	Source	Virus Isolation	Distribution	Probable Vector	Human/Animal Infections ^b
Sandfly fever Turkey virus	Sandfly fever Sicilian virus species ^c	Human plasma, CSF	Yes (plasma)	Aegean, Mediterranean, and Central Anatolia	<i>Phlebotomus major</i> sl	Yes/probable
Adana virus	Salehabad virus species ^c	Field-collected sandflies	Yes (sandfly pool)	Mediterranean Anatolia	<i>Phlebotomus tobbi</i>	Yes/yes
Toros virus	Sandfly fever Sicilian virus species ^c	Field-collected sandflies	Yes (sandfly pools)	Mediterranean Anatolia	<i>P tobbi</i> / <i>Phlebotomus perfiliewi</i> sl	Not known
Zerdali virus	Sandfly fever Naples virus species	Field-collected sandflies	Yes (sandfly pools)	Mediterranean Anatolia	<i>P tobbi</i> / <i>P perfiliewi</i> sl	Not known
Edirne virus	Salehabad virus species ^c	Field-collected sandflies	No (partial sequences available)	Eastern Thrace	<i>P perfiliewi</i> sl	Not known
Toscana virus	Sandfly fever Naples virus species	Human plasma, CSF, urine	No (partial sequences available)	Aegean, Mediterranean, Central, and Northern Anatolia	Not known	Yes/yes

Abbreviation: CSF, cerebrospinal fluid.

^aGenus *Phlebovirus*, Family *Bunyaviridae*.

^bDefined by RNA and/or neutralizing antibody detection.

^cAs proposed.

Klinik Bulgular:

- SFSV;SFNV klinik olarak birbirinden ayırt edilememektedir
- IP 3-6 gün (50st - 9 gün)
- ani başlangıçlı yüksek ateş
(39-40°C) 2 - 4 gün sürer (%85) -11 gün
- ateşin ilk gününde taşikardi
- baş ağrısı
- halsizlik
- kas ağrısı
- fotofobi
- retroorbital ağrı
- karın ağrısı, diyare/kabızlık
- asteni (yorgunluk, güçsüzlük – bradikardi, kan basıncı↓)
- SFTV – SFCV; gastrointestinal semptomlar↑↑↑

Klinik Bulgular:

Toskana virüs enfeksiyonları:

- menenjit, meningoensefalit
- ani başlangıçlı baş ağrısı
- yüksek ateş
- bulantı kusma
- kas ağrısı

Son dönemdeki enfeksiyonlarda;

- sağırılık
- kişilik değişiklikleri
- konuşma bozuklukları
- parezi

Tanı: Laboratuvar bulguları

Table 3 Laboratory findings of patients on admission.^a

Variable ^b	Value
Leukocyte count	
Mean count — $\times 10^3/\mu\text{L}$ (min-max)	3.8 \pm 2.4 (1.3–12.8)
<4.0 $\times 10^3/\mu\text{L}$ — no/total no (%)	34/49 (69)
>10 $\times 10^3/\mu\text{L}$ — no/total no (%)	2/49 (4)
Mean hemoglobin — g/L	14
Platelet count — $\times 10^3/\mu\text{L}$	
Mean count (min-max)	119 \pm 49 (21–268)
≥ 150 — no/total no (%)	9/49 (18)
<150 — no/total no (%)	40/49 (82)
Creatine kinase	
Mean, U/L (min-max)	712 (55–5559)
Above normal >145, U/L — no/total no (%)	34/44 (77)
Lactate dehydrogenase	
Mean, U/L (min-max)	308 \pm 133 (137–694)
Above normal >248, U/L — no/total no (%)	30/47 (64)
Alanine aminotransferase	
Mean, U/L (min-max)	106 \pm 84 (12–322)
Above normal >35, U/L — no/total no (%)	41/49 (84)
Aspartate aminotransferase	
Mean, U/L (min-max)	110 \pm 77 (17–407)
Above normal >35, U/L — no/total no (%)	41/48 (85)
Alkaline phosphatase	
Mean, U/L (min-max)	78 \pm 41 (21–269)
Gamma-glutamyl transpeptidase	
Mean, U/L (min-max)	62 \pm 63 (14–261)
INR— Mean, (min-max)	1.18 \pm 0.22 (0.89–1.9)
aPTT— Mean, (min-max)	38.6 \pm 7.4 (27.5–55.3)
PT1— Mean, (min-max)	13.2 \pm 2.9 (7.1–22.5)

^a Plus-minus values are means \pm SD. Range and clinically important limits are implicated.

^b All the variables' mean counts point out the first visit to the outpatient department of infectious diseases. The laboratory parameters were changed over time (see text).

- ✓ lökopeni
- başvuru anında mevcut
- en düşük düzeyler ateş düştükten
- hemen sonra
- ✓ trombositopeni
- ✓ KC enzimleri \uparrow
- ALT, AST
- ALP
- GGT
- LDH
- ✓ CK yüksekliği

2008 – 2009 SFTV Mamak salgını verileri:

Hastaların özellikleri

Table 1 Characteristics of the patients June–July 2008 and June–July 2009^a.

Characteristic	Value
Male/Female, n (%)	35/15 (70/30)
Age, years (min-max)	33.4 (17–58)
Sandfly exposure, n (%) ^b	
Positive	7/8 (88)
Negative	1/8 (12)
Similar symptoms in family or neighbourhood, n (%) ^c	
Positive	8/11 (73)
Negative	3/11 (27)
Outcomes-days	
Duration of fever	
Median (min-max)	5 (3–6)
Complete recovery-days	
Median (min-max)	15 (5–30)

^a Plus–minus values are means \pm SD. Characteristics were noted retrospectively from the records.

^b Only 8 patients were reported sandfly exposure when they applied to outpatient department. Others were either not asked or not reported any vector exposure.

^c Family or neighbourhood data were noted only for 11 patients.

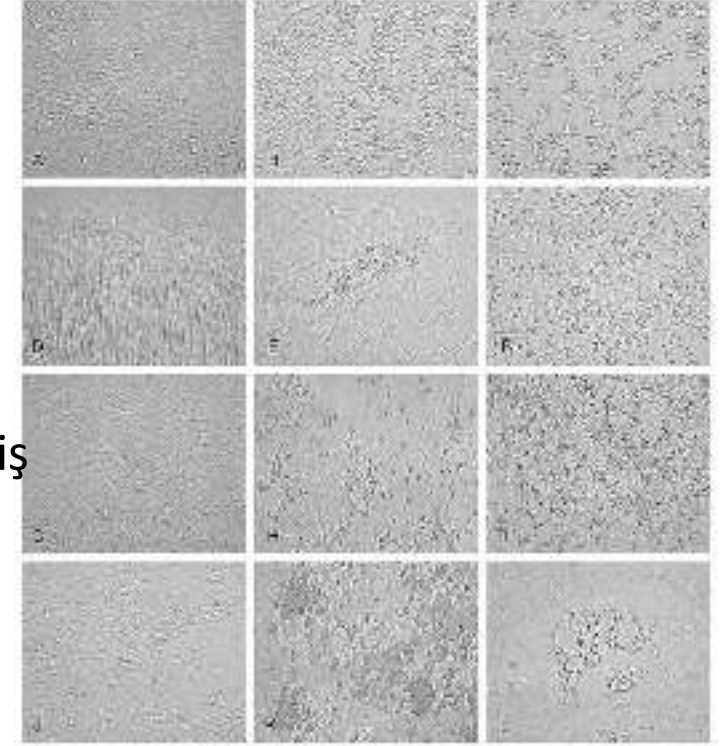
Table 2 Clinical features of the patients.

Symptoms or signs	n/total no (%)
Fever	50/50 (100)
Headache	33/50 (66)
Photophobia and/ or conjunctival congestion	28/50 (56)
Fatigue	48/50 (96)
Myalgia and/or arthralgia	40/50 (80)
Nausea/vomiting	16/50 (32)
Anorexia	22/50 (44)
Diarrhoea	11/50 (22)
Abdominal pain	9/50 (18)

Klinik bulgular

Tanı:

- Virüs izolasyonu:
serum, plazma veya BOS ilk 2-4 gün
Vero → sitosidal ve plak oluşturuyor
BHK-21; LLC-MK2; C6/36; SW13
Duyarlılığı düşük PCR + TOSV %14'ü üretilebilmiş



- Moleküler Testler:
*r*RT-PCR
serum, plazma, BOS
idrar

★ ilk 2-4 gün



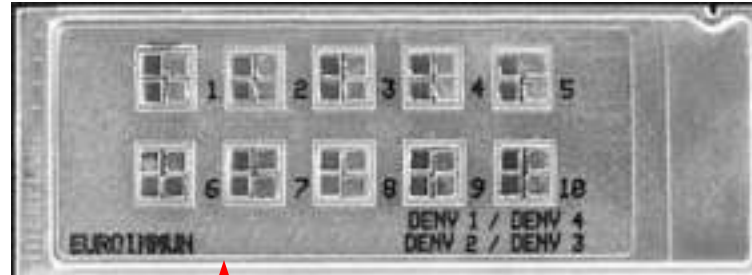
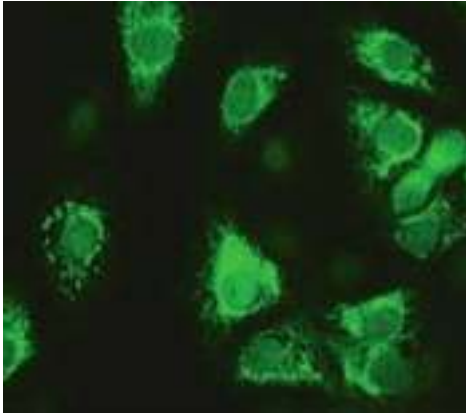
Tanı:

Serolojik tanı:

Serum veya BOS IgM/IgG

ELISA (IgM capture/IgG Sandwich)

IFA (BOS için valide değil)



ÇAPRAZ REAKSİYON

Altın Standart Tanı:

Nötralizasyon testleri (VNT)

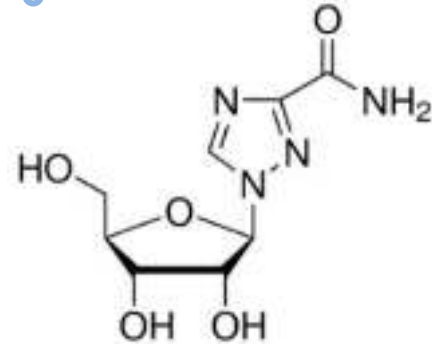
(Yüksek özgüllük ve Antikor titresi)

Tedavi:

- semptomatik tedavi
hepatotoksik ilaçlardan kaçınılmalı
(aspirin, ibuprofen, ketoprofen...)

primum non nocere!!!

- ribavirin 400mg/8st oral dozda etkili
- ribavirin +IFN- α *in vitro* aktivite



- 6- azaüridin, IFN- α , glisirrizin, süramin sodyum, dekstran sülfat, pentozan polisülfat, MxA protein, selenazol

- pirazin türevleri



favipiravir (T-705), T-1106 SFNV *in vitro* aktivite

Korunma:

- aşı; koruyuculuk???
- korunma - vektör aktivitesinin engellenmesi ile mümkün
 - ✓ habitat tahribi
 - ✓ insektisitlerin sürekli olarak uygulanması
 - ✓ uzun pantolon uzun kollu kıyafetler
 - kıyafet üzerinden kan ememez
 - ✓ sineklik & cibinlik – oldukça küçük etkili değil
 - insektisit emdirmek
 - ✓ gece dış mekan aktivitelerinin sınırlandırılması
 - ✓ repellentlerin kullanımı