

In the name of God



# The current CCHF situation in Iran

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# **Crimean-Congo Hemorrhagic Fever (CCHF)**

- » **A tick-borne disease caused by a virus in the genus Nairovirus, family Bunyaviridae**
- » **Endemic in many regions such as Africa, Southeastern Europe and Asia.**

# History

**.1944**

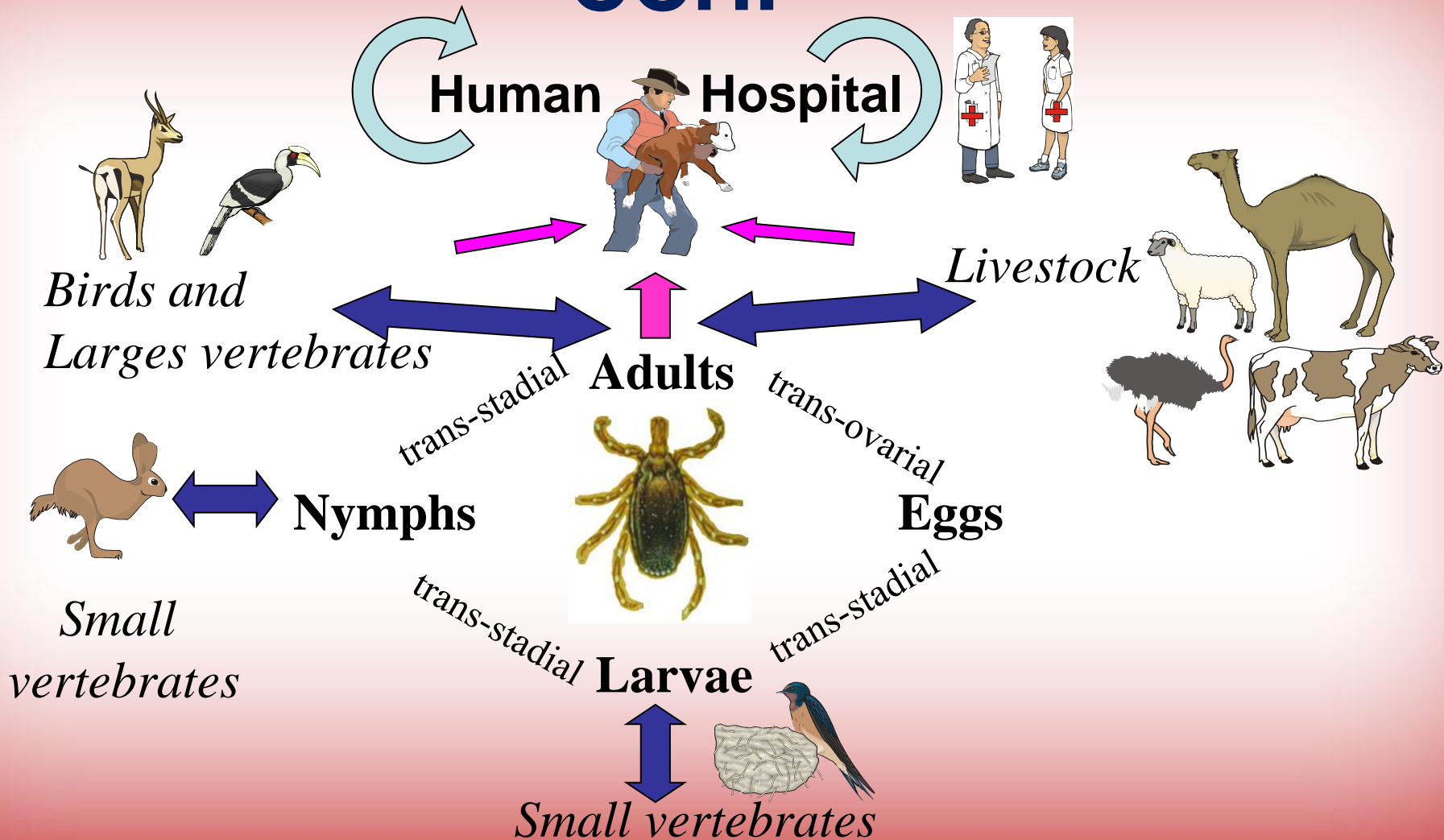
- **First described in Crimea**
- **Soviet military personnel**

**.1969**

- **Also detected in Congo**
- » **Outbreaks continue to occur**
- » **Potential bioterrorist agent..?**
- **CDC/NIAID Category C pathogen**



# Transmission of CCHF



## Crimean-Congo hemorrhagic fever in Iran

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### Abstract

The presence of Crimean-Congo hemorrhagic fever virus (CCHFV) in Iran was first identified in studies of livestock sera and ticks in the 1970s, but the first human infection was not diagnosed until 1999. Since that time, the number of cases of CCHF in Iran has markedly increased. Through January 2012, articles in the published literature have reported a total of 870 confirmed cases, with 126 deaths, for a case fatality rate (CFR) of 17.6%. The disease has been seen in 26 of the country's 31 provinces, with the greatest number of cases in Sistan and Baluchestan, Isfahan, Fars, Tehran, Khorasan, and Khuzestan provinces. The increase in CCHF in Iran has paralleled that in neighboring Turkey, though the number of cases in Turkey has been much larger, with an overall CFR of around 5%. In this article, we review the features of CCHF in Iran, including its history, epidemiology, animal and tick reservoirs, current surveillance and control programs, diagnostic methods, clinical features and experience with ribavirin therapy, and consider possible explanations for the difference in the CFR of CCHF between Iran and Turkey. The emergence of CCHF in Iran calls for countermeasures at many levels to protect the population, but also provides opportunities for studying the epidemiology, diagnosis and management of the disease.

### 1. Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne disease caused by a virus in the genus *Nairovirus*, family *Bunyaviridae*, which is endemic in many countries in Africa, southeastern Europe and Asia. The disease was first described in the Crimea in 1944 and given the name Crimean hemorrhagic fever. In 1969, it was recognized that the same

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# Tick



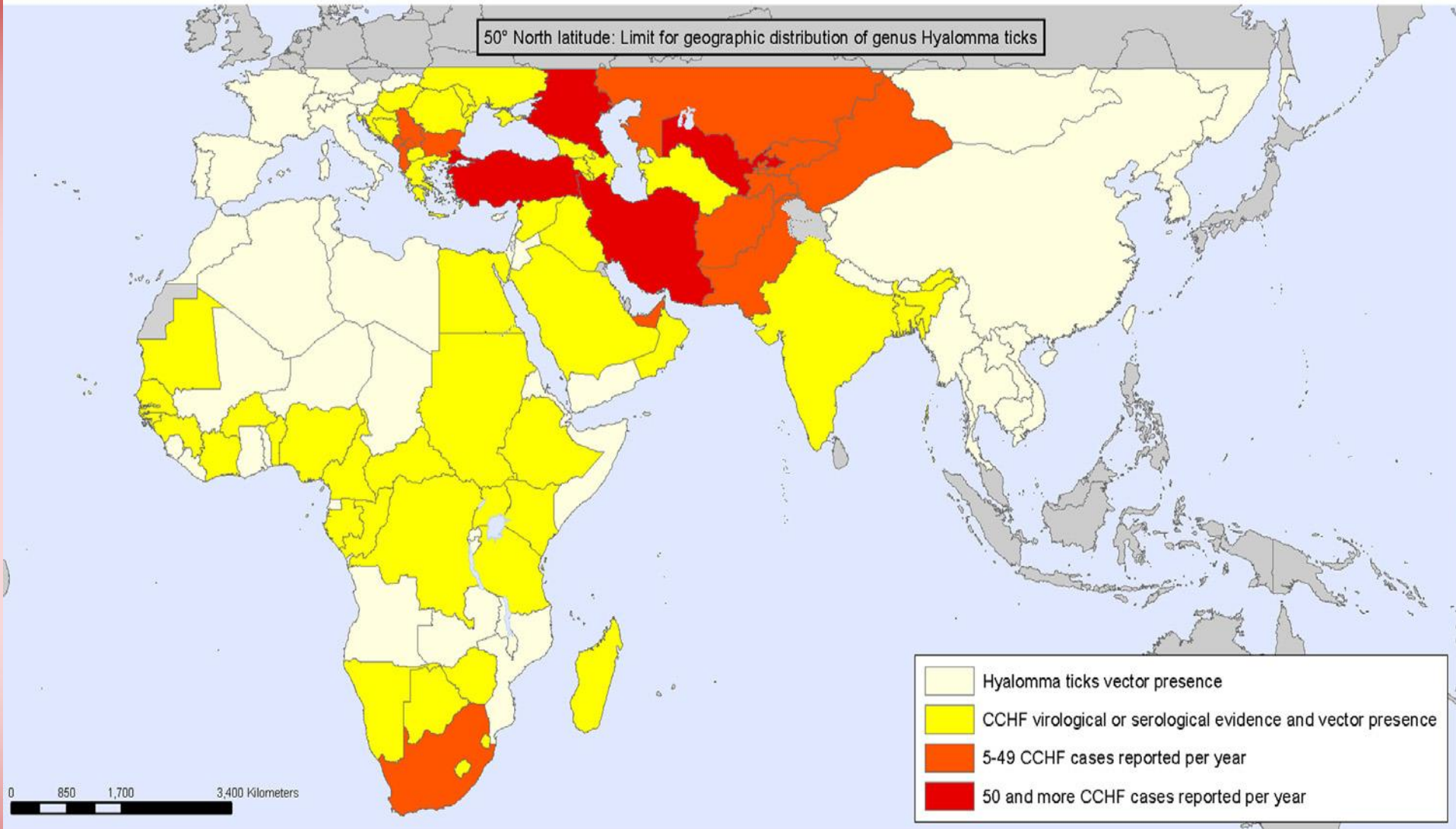
**Table 4**

Species of ticks from which CCHFV has been recovered in Iran. As discussed in the text, only *Hyalomma* spp. and certain other species of ixodid (hard) ticks are considered to be competent vectors for the virus.

Tick	Location	Virus detection	Reference
<i>Ornithodoros lahorensis</i>	Khorasan	Virus isolated for the first time in ticks in Iran	(Sureau and Kluge 1972)
<i>Rhipicephalus bursa</i> <i>Hyalomma</i> genus <i>Ornithodoros lahorensis</i>	Ardabil	Ticks were tested by RT-PCR	(Telmadarraiy et al. 2005)
<i>Hyalomma</i> genus <i>Rhipicephalus sanguineus</i> <i>Argas reflexus</i>	Hamadan	Tested by RT-PCR	(Tahmasebi et al. 2006)
<i>Hyalomma</i> genus	Kurdistan	Tested by RT-PCR	(Fakoorziba et al. 2007)



# Geographic distribution of Crimean-Congo Haemorrhagic Fever



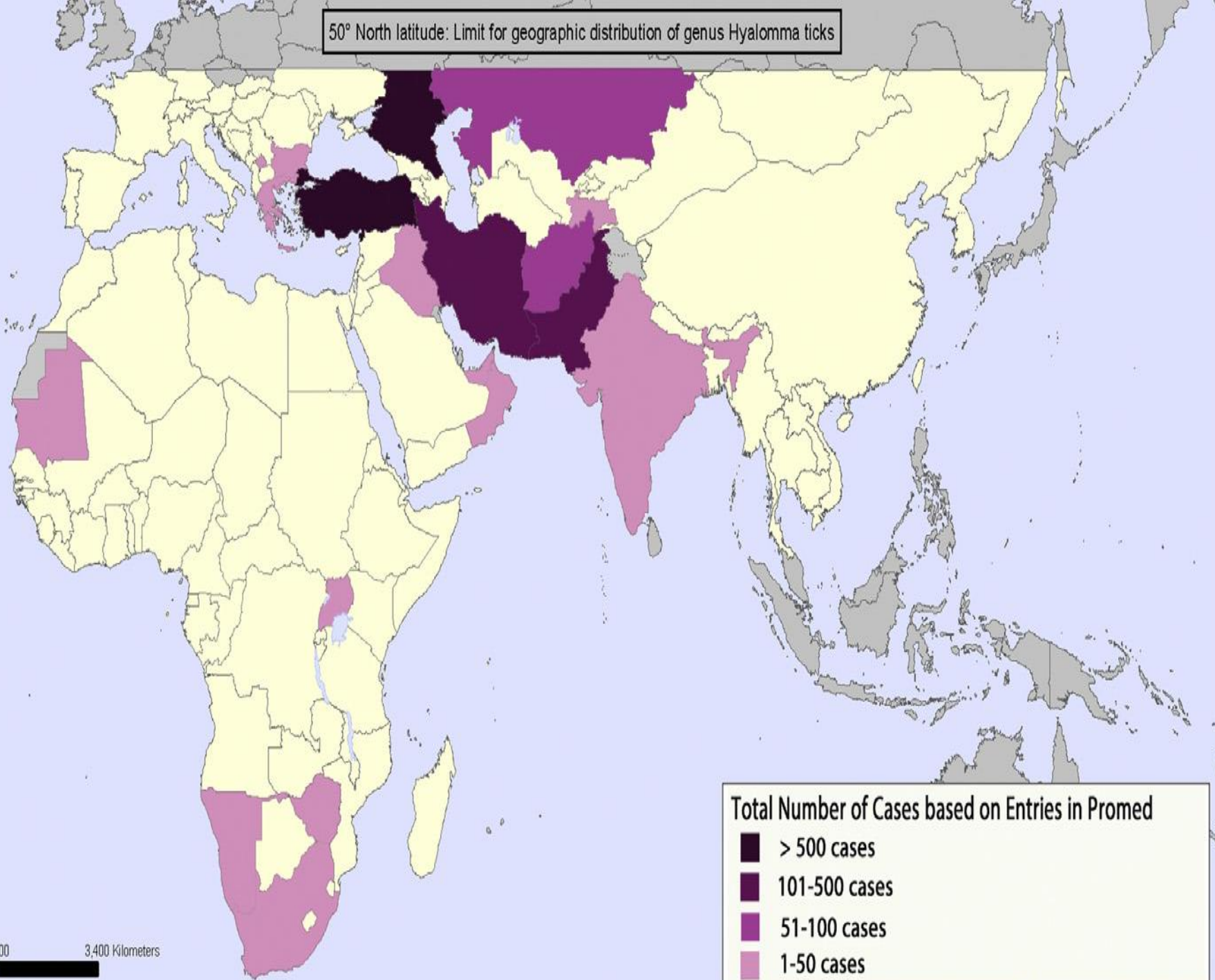
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization  
Map Production: Public Health Information  
and Geographic Information Systems (GIS)  
World Health Organization



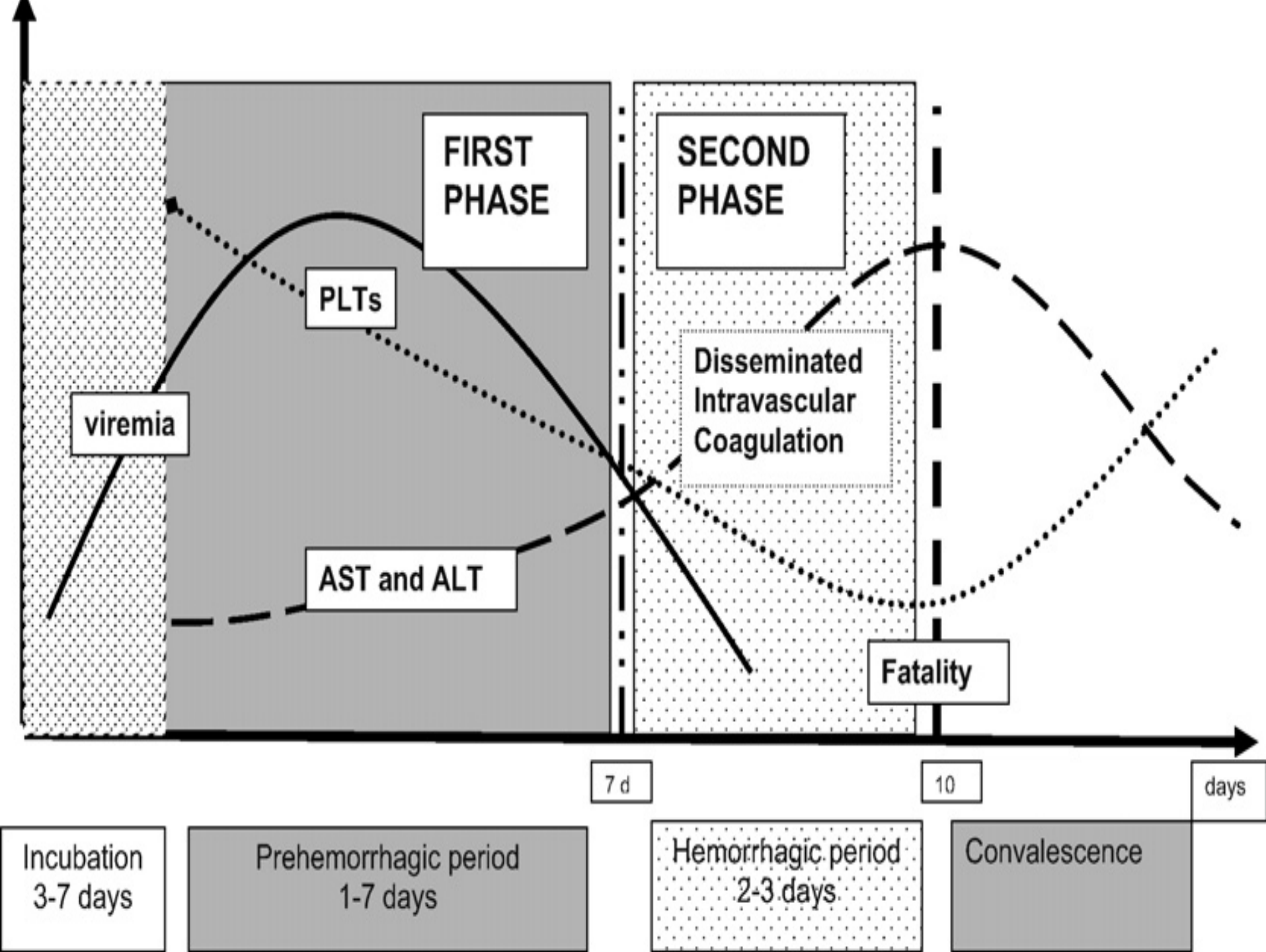
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50° North latitude: Limit for geographic distribution of genus Hyalomma ticks



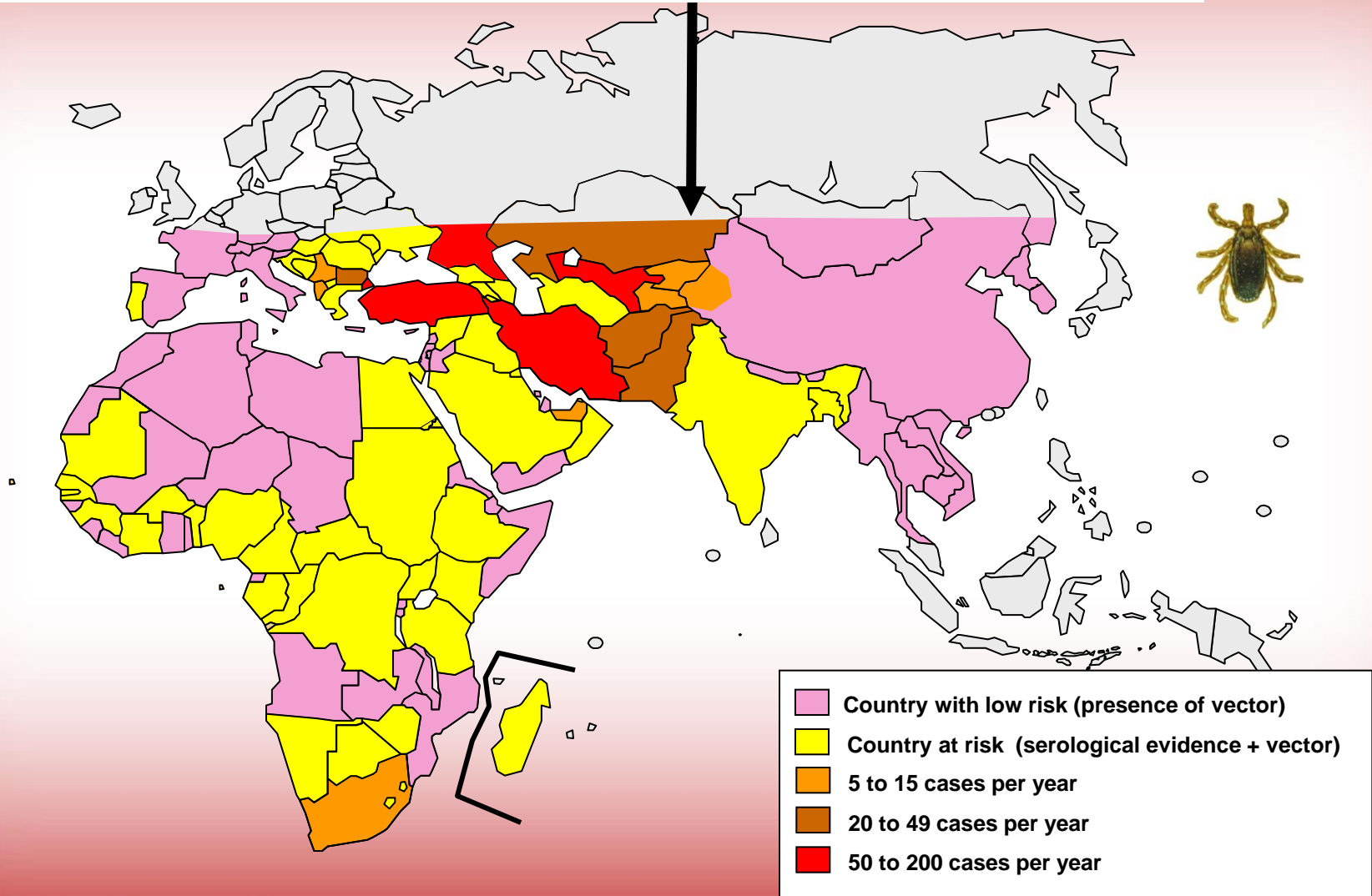
# Crimean-Congo Hemorrhagic Fevers

- **Highly contagious diseases**
- **Differ by geographic occurrence**
- **Potential lethal syndrome**
- **Transmission occurs through contact with blood and tissue of infected human and animals**
- **Tick bite and tick splashing is another route of transmission**
- **Possibility of Nosocomial transmission**
- **Has between 10- 30% mortality**
- **No FDA approved vaccine is available**



# Crimean-Congo Hemorrhagic Fever Geographic Distribution

50° North limit for the geographic distribution of genus *Hyalomma* ticks



# Islamic Republic of Iran

- » **First case was diagnosed in 1999 but it has historical evidence in Persian medical textbooks dates to the Zakhīra-yi Khrāzmshāhī, written by Jurjānī in the late 12th century**
- » **From 1999 till now, CCHF has been reported in most of Iran's provinces, with the most cases in Sistan and Baluchestan, Isfahan, Fars, Tehran, Khorasan, and Khuzestan.**
- » **The most recent cumulative data show a total of 1337 confirmed cases of CCHF in Iran, with 182 deaths from, 1999 through Dec, 2017 .(case fatality rate=13.6)**







# Published studies reporting cases of CCHF in Iran since 1999

Years	Location	Number of cases	Summary	Possible mode of transmission
1999-2004	Sistan and Baluchestan	255 patients	Epidemiologic, laboratory and clinical description	Animal contact, nosocomial, tick bite, slaughtering
2001-2004	Fars, southern Iran	16 patients, 3 deaths	Epidemiologic, clinical and laboratory data are described.	Slaughtering, animal contact, tick bite
1999–2007	Sistan and Baluchestan	123 patients, 19 fatalities		N/A
1999–2001	Shahrekord (central Iran)	3 healthcare workers, 1 death		Nosocomial
2000–2009	All involved provinces	635 patients, 89 fatalities	Risk and geograpfactors hic distribution	Slaughtering, animal contact, nosocomial
2009	Mashhad (north-eastern Iran)	6 healthcare workers, 2 deaths		Nosocomial
2011	Khorasan (north-eastern) Province	Khorasan (north-eastern) Province	A medical student who died within one week of exposure.	Nosocomial

**Table 1**

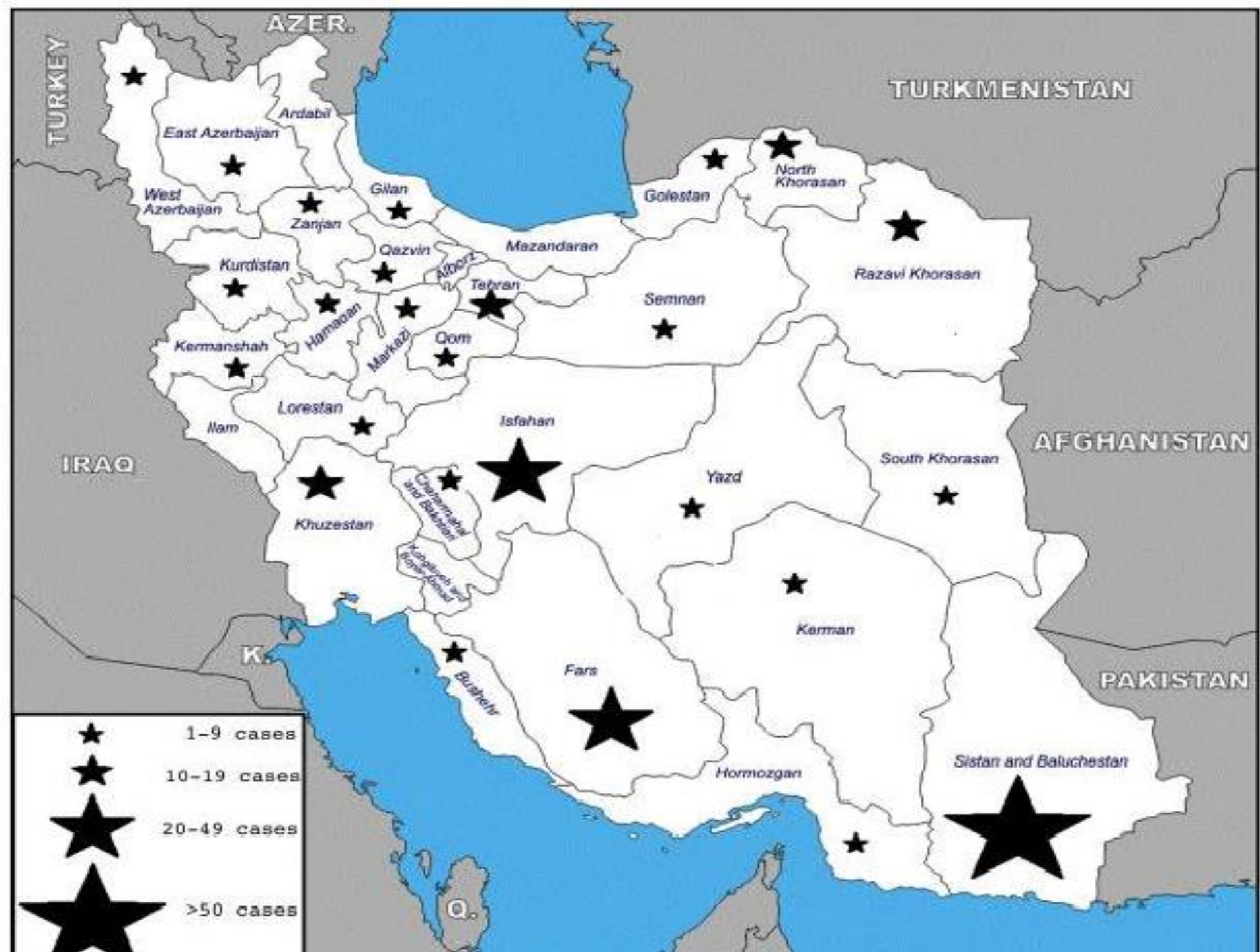
Published studies reporting cases of CCHF in Iran since 1999.

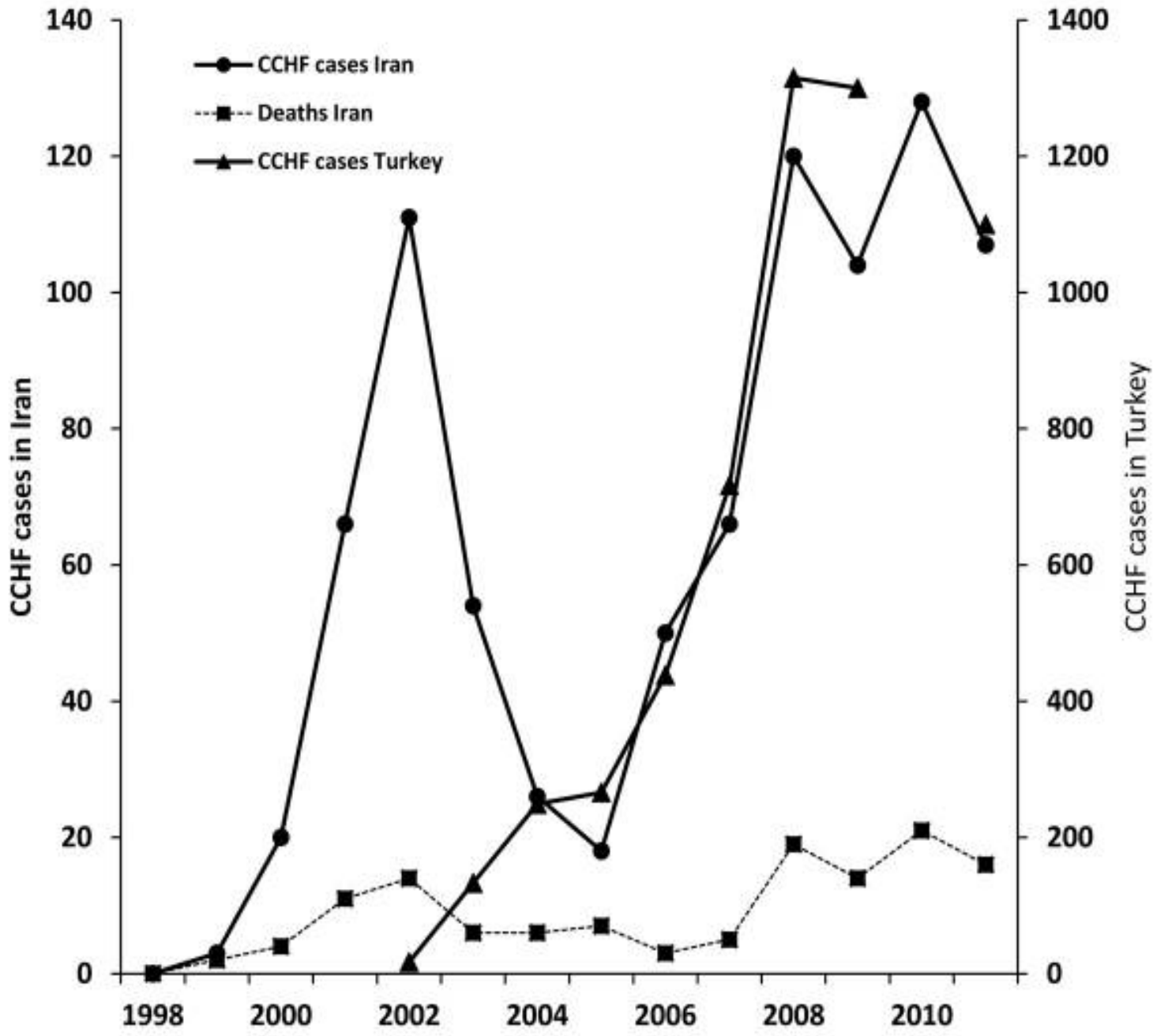
	<b>Number of cases</b>	<b>Summary</b>	<b>Possible mode of transmission</b>
Chaharmahal and Bakhtiari)	255 patients	Epidemiologic, laboratory and clinical description	Animal contact, nosocomial, tick bite, slaughtering
Central Iran)	16 patients, 3 deaths	Epidemiologic, clinical and laboratory data are described.	Slaughtering, animal contact, tick bite
Chaharmahal and Bakhtiari)	123 patients, 19 fatalities		N/A
Central Iran)	3 healthcare workers, 1 death		Nosocomial
Chaharmahal and Bakhtiari)	635 patients, 89 fatalities	Risk factors and geographic distribution	Slaughtering, animal contact, nosocomial
Central Iran)	6 healthcare workers, 2 deaths		Nosocomial
Central Iran)	1 healthcare worker, fatal	A medical student who died within one week of exposure.	Nosocomial

## Table 2

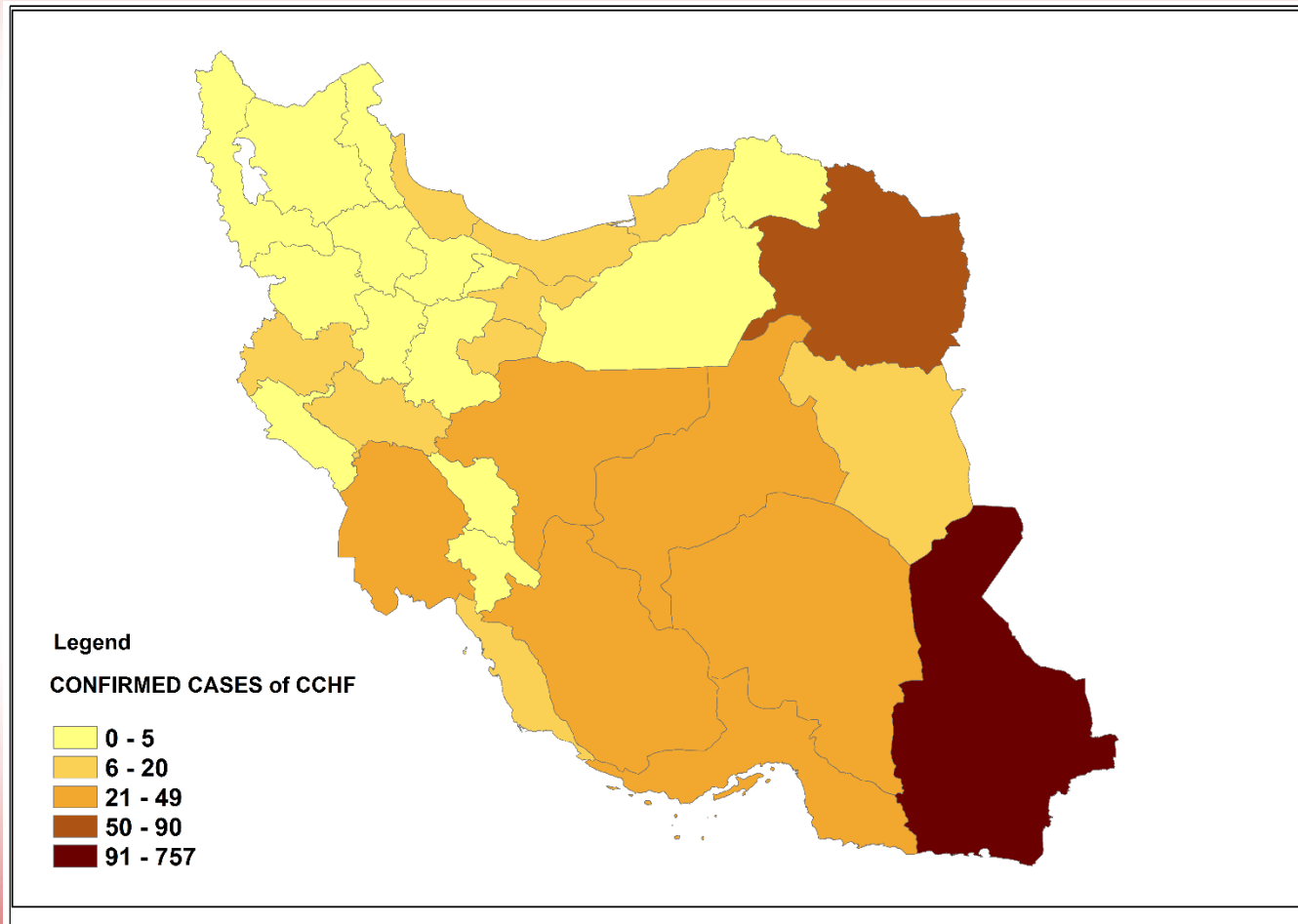
History of Crimean-congo hemorrhagic fever in Persia/ Iran.

	Comment	Reference
on of hemorrhagic fever and its putative causative agent (vulture louse)	Description identical to Galen's, thus may not be specific to CCHF	(Jurjān)
fatal hemorrhagic disease among the nomadic Yomut Turkomen in northern	Likely CCHF, but key details, such as fever and season, are missing	(Brown)
etimes fatal disease though to be caused by <i>Argas persicus</i> in the Mianeh	Unlikely to be CCHF, though some clinical features suggestive	(Nuttall)
etimes fatal hemorrhagic fever known locally as <i>Gara Mikh</i> typhoid fever in Iran.	Clinical and epidemiologic features consistent with CCHF.	(Amin, Noorani)
s of hemorrhagic fever from East Azerbaijan, Iran.	Possible CCHF outbreak	(Amin)
tested positive for CCHFV antibodies.	First documentation of CCHFV in livestock	(Chumakov)
s of hemorrhagic fever from East Azerbaijan, Iran.	First suspected cases of CCHF in humans.	(Asefi)
n northern Iran tested positive for anti-CCHFV antibodies	First documentation of CCHFV infection	(Saïdi)
er epidemic in northern Iran	Suspected CCHF, but not proven	(Ardo)
mission of CCHF	First confirmed cases of CCHF in Iran	(Mard)

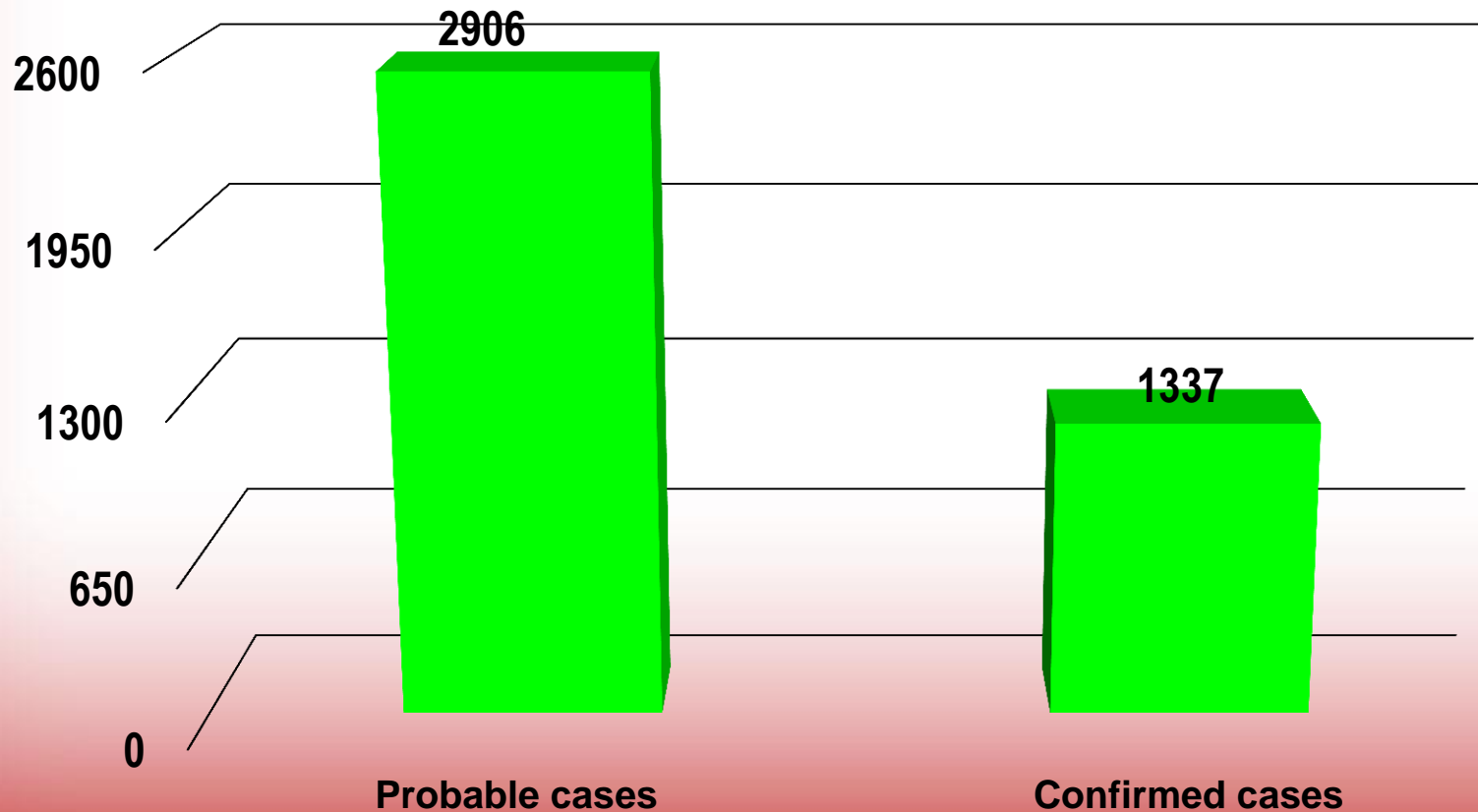




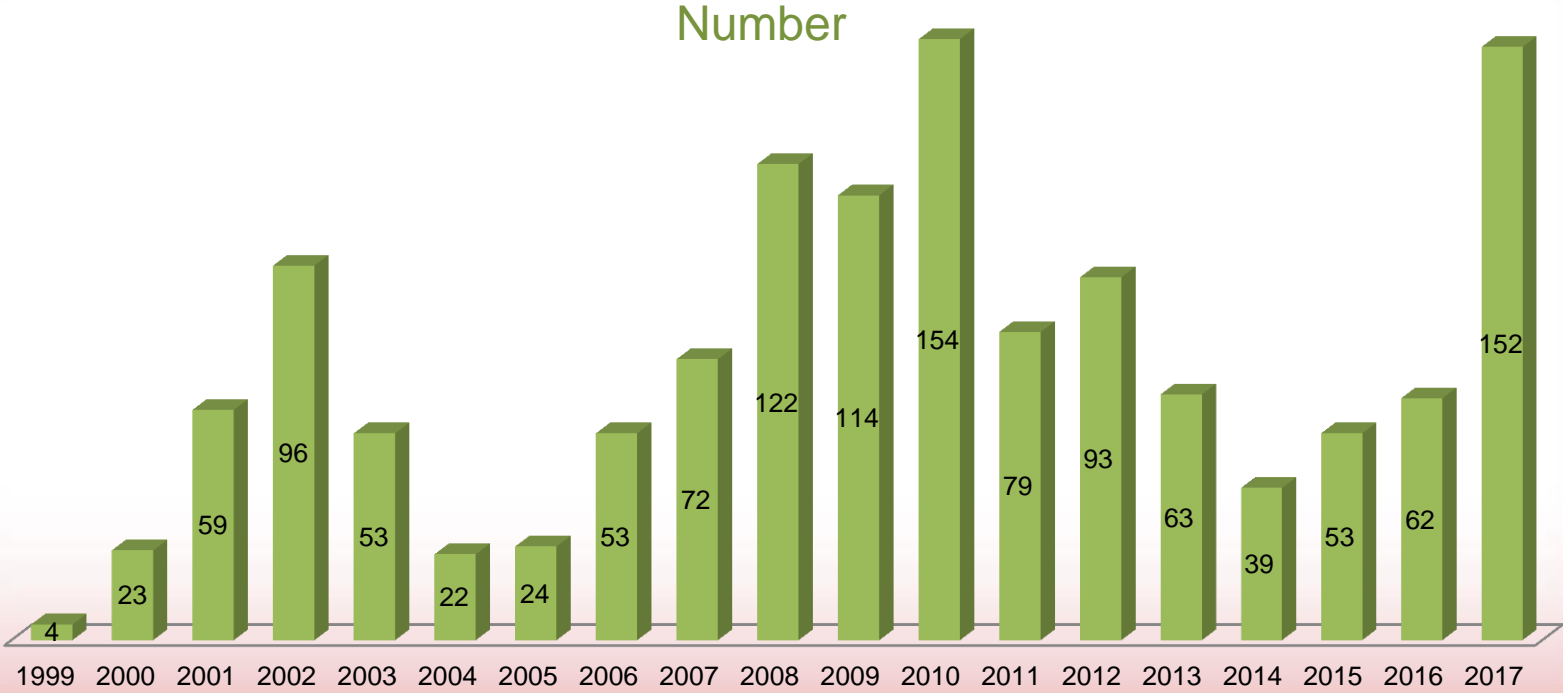
# Geographical distribution of CCHF cases in Iran from 1999 till 2017



# Probable and confirmed cases of CCHF from 1999 till 2017

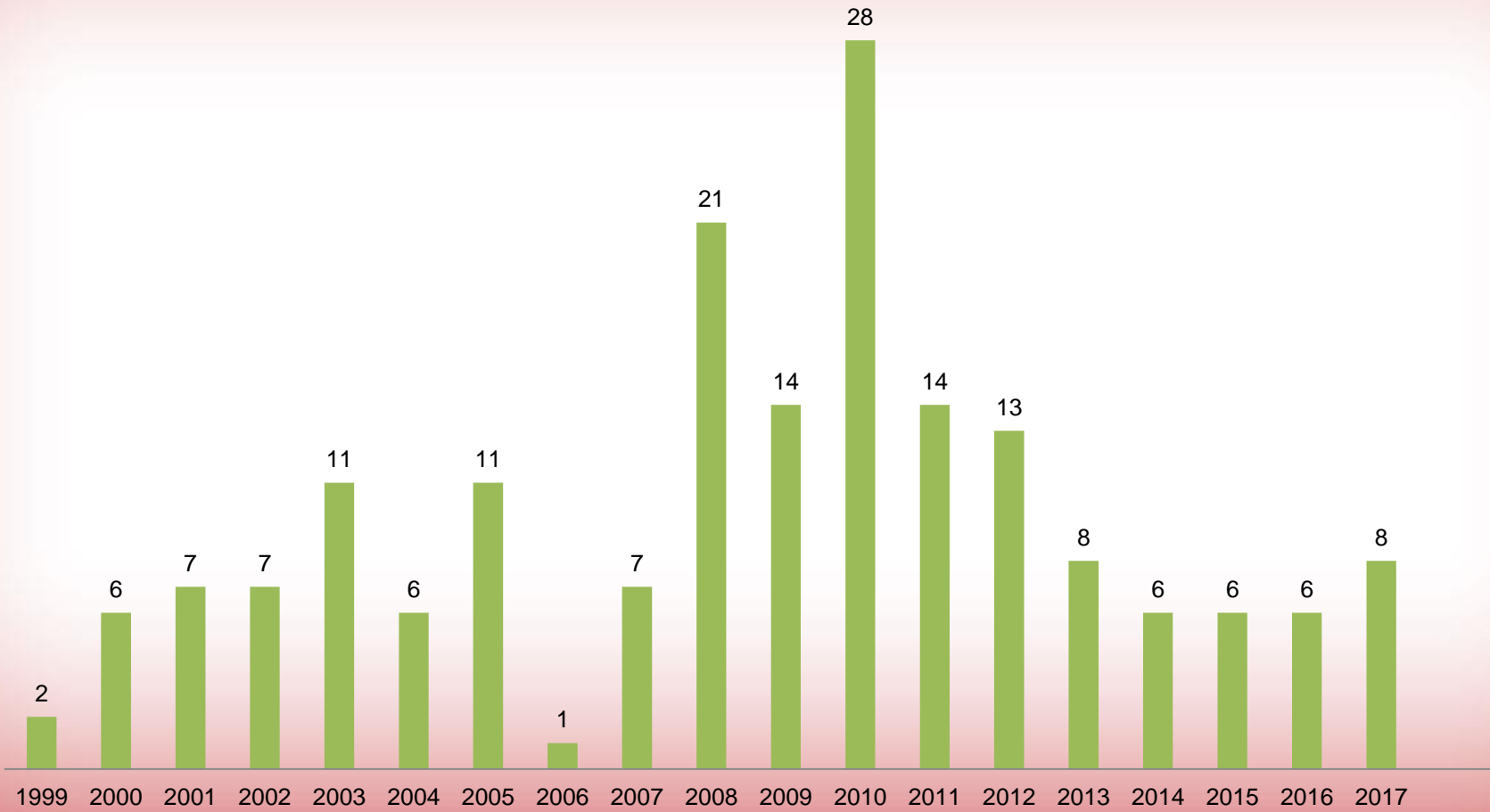


# Trend of CCHF confirmed cases from 1999 till 2017





# Trend of deceased CCHF confirmed cases from 1999 till 2017







# Trend of CCHF case fatality rate from 1999 till 2016



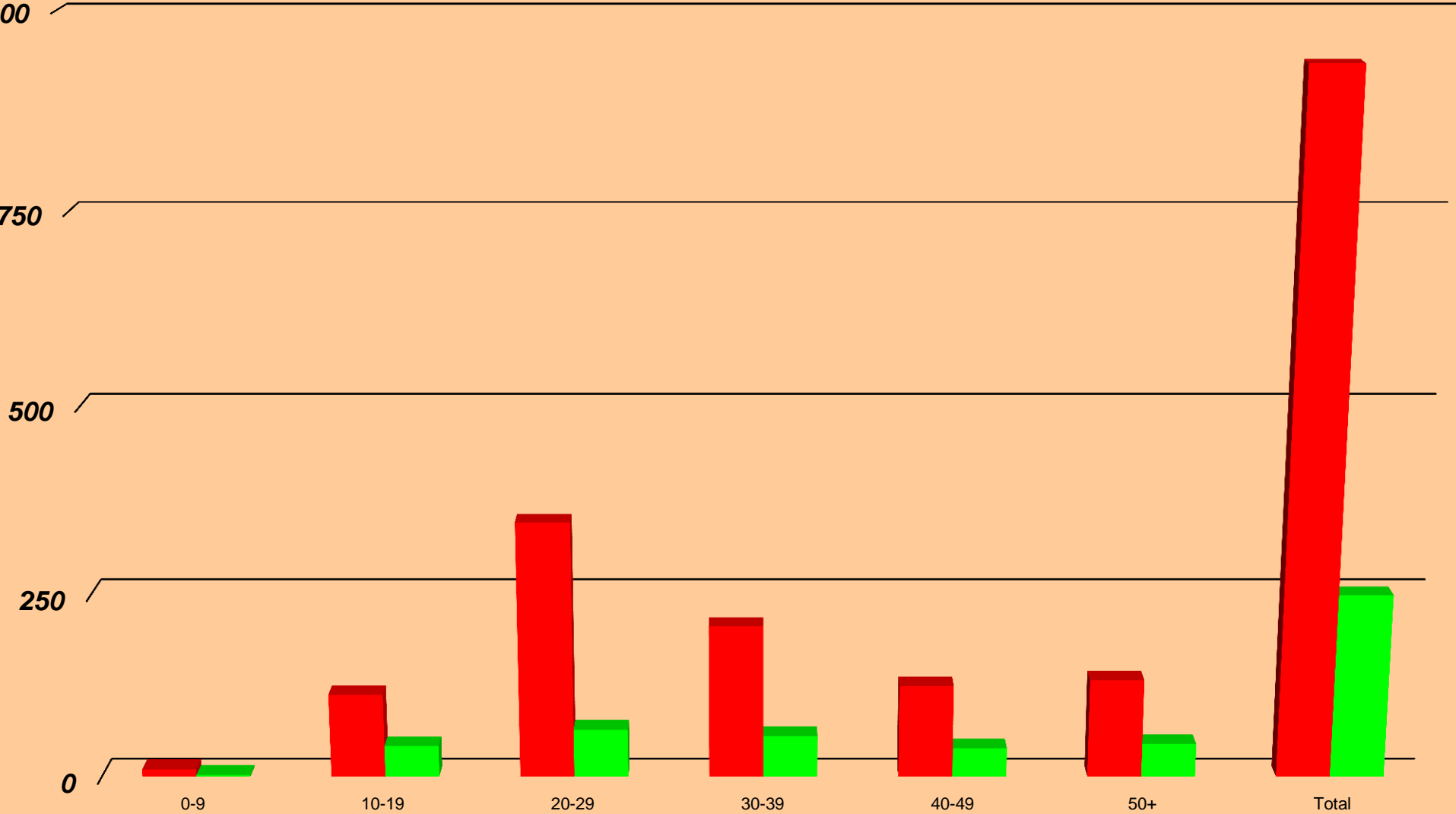
# CCHF confirmed cases by month from 1999 till 2017



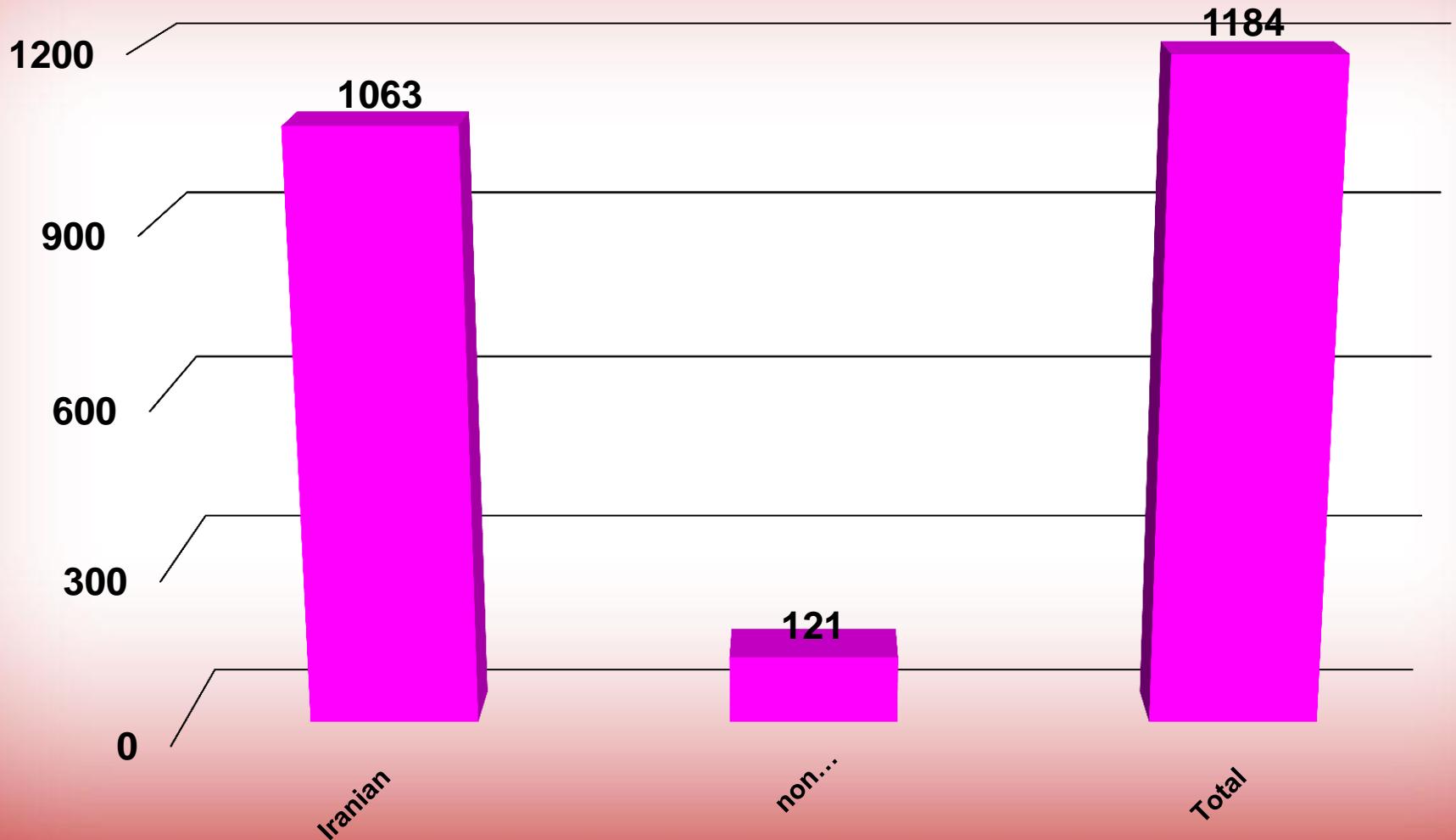
# CCHF confirmed cases by job from 1999 till 2017



# CCHF confirmed cases by age and gender from 1999 till 2017



# CCHF confirmed cases by nationality from 1999 till 2016





## **Definition of CCHF suspected case:**

**Sudden onset of fever, myalgia, bleeding manifestations and an epidemiological history**

## **Epidemiological manifestations:**

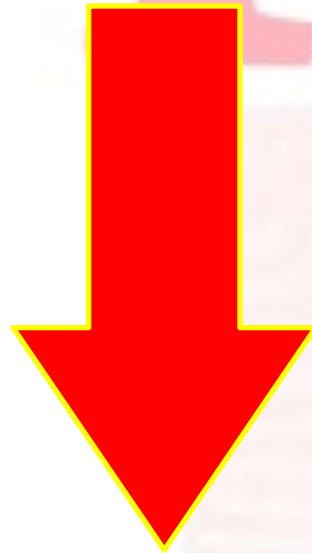
- 1. A history of tick bite or tick squeeze by hand**
- 2. Direct contact with infected animals' fresh blood or tissues**
- 3. Direct contact with blood, secretions or excretions suspected or confirmed cases of CCHF**
- 4. History of travel or accommodation in rural areas with a possibility of contact with cattle or ticks**

# Definition of CCHF probable case:

**A suspected case plus the following results in non-specific lab tests:**

- 1. Thrombocytopenia (Platelets less than 15000 / cubic mm)**
- 2. Leukopenia (WBC less than 3000/ cubic mm) or Leukocytosis (WBC more than 9000/ cubic mm)**

**In case of a probable case  
diagnosis**



**Instant treatment is necessary**



In case of diagnosing a probable case, the sampling guideline is as such, 3 samples:

- First sample: upon clinical diagnosis
- Second sample: 5 days after taking the first sample
- Third sample: 10 days after taking the first sample
  
- All samples are taken under observation of Provincial Health Center and Provincial Reference Lab then are sent to Pasteur Institute of Iran

# Laboratory of Arboviruses and Viral Haemorrhagic Fevers of Iran

## Serological Part

IgM & IgG Detection by ELISA methods



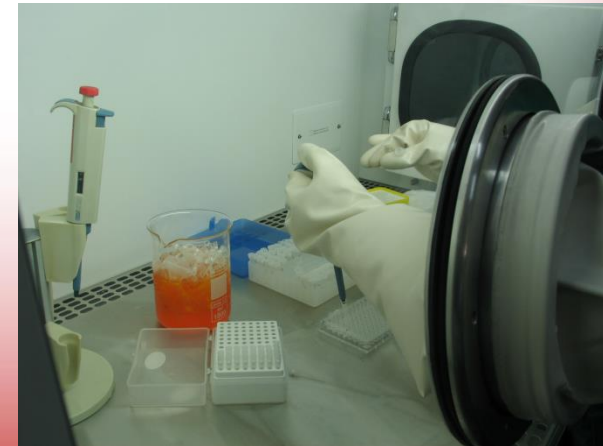
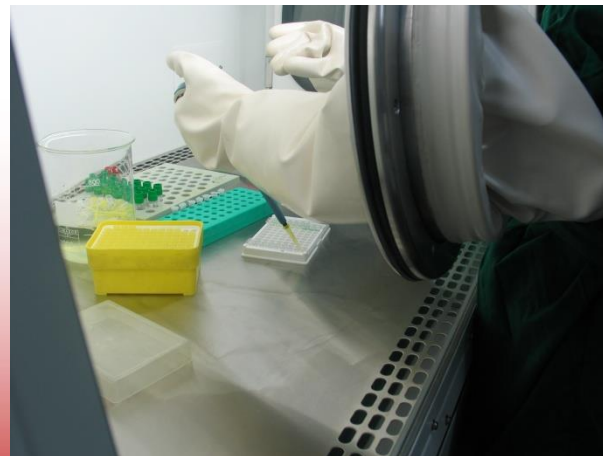
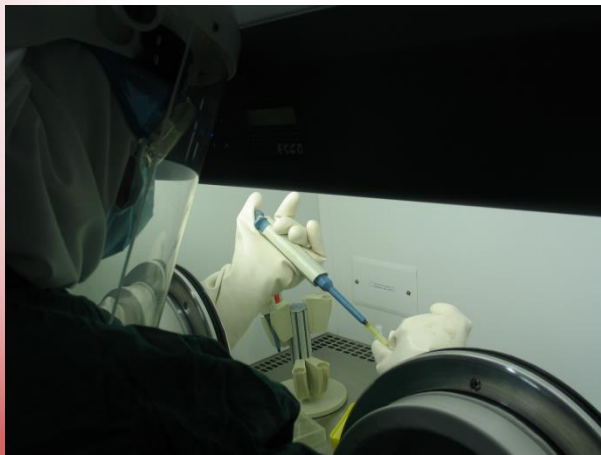
## Molecular Part

Diagnosis of virus genome in Probable Human cases' sera and suspected ticks by RT- PCR assay (Gel-based & Real-Time PCR).





# Biological Safety Cabinets Level 3





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# Negative Pressure Area





Negative Pressure Area

FACE MASKS

**RESTRICTED AREA**

**DO NOT ENTER**  
AUTHORIZED PERSONNEL ONLY



این درب باید بسته بماند

The Door Must be Closed

این درب باید بسته بماند

The Door



توجه  
توجه  
مدکاران گرامی  
OR Timer  
به مدت ۱۰ دقیقه قرار دهید

**NOTICE**  
  
Lab coats must be worn

  
Wear gloves

# Molecular Tests

## » CCHF Virus

- **Simple RT-PCR**
  - Iran F2 / R3 Primers [ 536 bp ]
  - Iran Con 3 / 5 Primers [ 197 bp ]
  - IN 3' / 5' Primers [ 226 bp ]
  - Swanepoel F2 / R3 [ 536 bp ]
- **Nested RT-PCR**
  - F3 / R2 Primers [ 260 bp ]



## » WN Virus

- **Simple RT-PCR**
  - WN233 / WN 640c [ 408 bp ]
- **Multiplex RT-PCR**
  - WN233 / WN 640c [ 408 bp ]
  - WN3' NC F / R [ 103 bp ]
  - WNV F / R [ 445 bp ]



## » RVF Virus

- NSCa / NS2g [800 bp]

**Pumala Virus**  
P1/P2 Primers

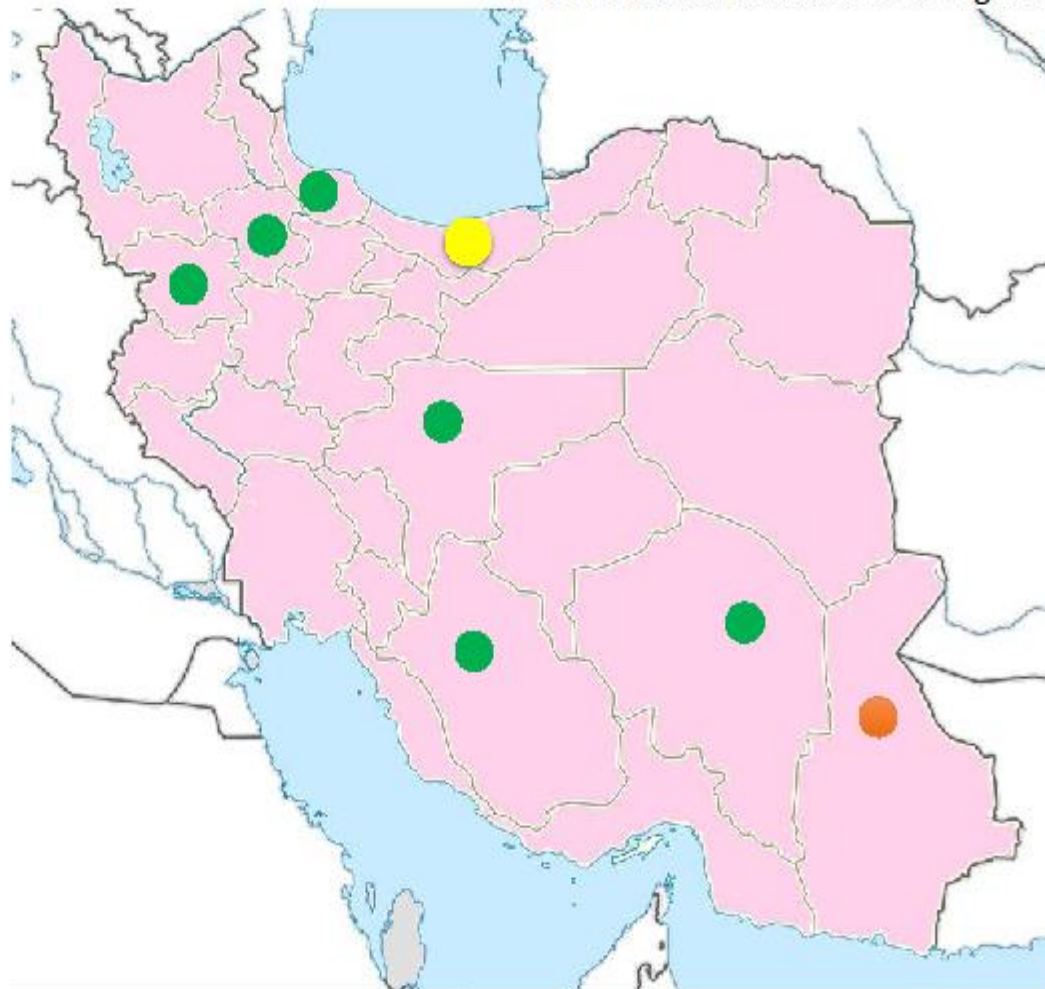
**Dengue Virus ( 1,2,3,4)**

## » Chikungunia Virus (CHK)

• **Ebola Marburg**

Iran has the broadest CCHFV genetic diversity

- Asia-1 (Clade IV)
- Europe 1 (Clade V)
- Asia-2 (Clade IV)
- Europe 2 (Clade VI)



# Ribavirin in Hemorrhagic Fevers

- Ribavirin is the only antiviral drug that has been used to treat viral hemorrhagic fever syndromes, including CCHF and Lassa fever.

The application in 2006 to include ribavirin in the WHO Model List of Essential Medicines as a treatment for CCHF (WHO 2006), was based on evidence from several non-randomized retrospective and observational studies that reported efficacy of oral or intravenous ribavirin for the treatment of CCHF. Some studies suggested that ribavirin treatment needed to be given early in the course of disease for beneficial effects. Later, two systematic reviews regarding the

# Clinical use of Ribavirin

- No randomized clinical trials of the efficacy of ribavirin against CCHF have been performed,
- The efficacy has been described in several observational studies.
- A report published in South Africa in 1985 described the use of intravenous Ribavirin for both therapy and postexposure prophylaxis in a small number of patients in a nosocomial outbreak.

Van Eeden et al., 1985

# CCHF Treatment in Healthcare Workers

In 1994, in Pakistan, Fisher Hoch et al reported three health workers infected with CCHF virus who were treated with oral ribavirin. All the three patients were severely ill. The patients became afebrile within 48 hours of treatment with ribavirin. All the three patients made a complete recovery

Fisher-Hoch et al., 1995



In 1999, in Pakistan, Sheikh AA et al evaluated the efficacy of oral Ribavirin in CCHF cases. CCHF were confirmed in 39 out of the 94 cases by the CDC.

After a mean period of  $2.30 \pm 0.69$  days of starting the 10-day course of treatment with oral Ribavirin, the patients improved and the laboratory parameters returned to normal levels

In a historical cohort study, in Iran, in 2003, we compared the mortality rate among patients suspected of having CCHF who received treatment with oral Ribavirin and those who did not. Ninety-seven (69.8%) of 139 treated patients suspected of having CCHF survived, and 61 (88.9%) of 69 treated patients with confirmed CCHF survived.

**The efficacy of oral ribavirin was 80% among patients with confirmed CCHF and 34% among patients suspected of having CCHF**

Mardani et al, *Clin. Infect. Dis.* 36, 1613–1618.

In another study, for eight critically ill patients with severe hemorrhagic manifestations & GI bleeding, we administered oral Ribavirin by nasogastric tube.

Only one out of the eight patients died.

So it is recommended that  
**in severe and comatose forms of CCHF, Ribavirin  
can be administered via this route**

Mardani M., Clin Mic&Inf: 10 supp 3,2004;661

In 2003, in Turkey, Önder Ergönül et al described the role of ribavirin in treating 35 patients who diagnosed as having CCHF.

All of the eight patients who were given oral ribavirin **survived**, while the overall mortality among the untreated cases was 4.5%.

(Ergonul et al., 2004).

In 2006, in Turkey, [Ozkurt Z](#) et al demonstrated that mean recovery time in the cases treated with Ribavirin was shorter than those of controls. But the need for blood and blood product, mean length of hospital stay, fatality rates, and hospital expenditure values were not significantly different between the group treated with ribavirin and the controls.

Ozkurt et al. (2006).

# Two Systematic Review analyzing Efficacy of Ribavirin

The first (Soares-Weiser et al. 2010), analysed twelve studies from Iran, Pakistan, Turkey and Russia which provided data on mortality outcomes between ribavirin treated and untreated patients [one Randomised Control Trial (RCT) and eleven observational studies]. Results from the single RCT (136 participants; (Koksal et al. 2010)) suggested no benefit from ribavirin treatment, with a mortality risk ratio (treated vs. untreated) of 1.13. Analysis of the pooled observational studies (9955 patients) suggested that ribavirin reduced mortality by 44% when compared to no ribavirin treatment. However, the quality of all the data was judged to be low (RCT) or very low (observational studies) with a high risk of bias and the study concluded that the benefit of ribavirin suggested by the observational study was confounded and these data alone are not reliable.

# The Second Systematic Review

The second systematic review (Ascioglu et al. 2011) included one randomised trial and 7 published observational studies that included an untreated comparison group in the study design. Compiling the data from all 8 studies, survival following ribavirin treatment was found to be only 1.06 times better than no treatment, suggesting no significant benefit from ribavirin

# Crimean-Congo Hemorrhagic Fever in Children and Adolescents

A total of 34 non-adult confirmed CCHF patients were studied. The mean age of the studied subjects was  $13.3 \pm 4.6$  (range: 5.0 – 18.0) years. All the patients except two were received oral Ribavirin for treatment for 10 days.

The case-fatality rate was 26.5% (9/34). Those who survived received treatment with Ribavirin sooner (initial 3 days of illness) than those who did not survived.(85.5% versus 24.8%)



# CCHF in pregnant women

- We report a series of six pregnant women with confirmed CCHF who were admitted to BooAli hospital in a time period of 5 years from 2000 to 2005. Due to the severity of the illness all patients were treated by Ribavirin.
- All the patients except one were survived.(83.3%).
- Abortion was observed in 3 patients and stillbirth in one patient.
- Unfortunately one pregnant woman died due to DIC and multiorgan failure. In fact, 66.6% of pregnant women had fetal loss.

# Observational versus controlled trials

- 1-Limitations: Ethical considerations prevent the performance of placebo-controlled trials.
- 2- Unavailability of IV formulation of Ribavirin in endemic areas.
- 3- No Comparison study between IV and Oral formulation.

**Evidence of efficacy is therefore limited to observational studies, which have been criticized**

**Table 3**

Experience with the treatment of CCHF with ribavirin in Iran from 1999–2011. In Column 2, some studies compared the outcome of cases treated with ribavirin, beginning at different time points in the disease course. Column 3 lists the number of patients in each study who were treated with ribavirin and the total number of confirmed cases of CCHF. Column 4 lists the number of deaths among patients who were treated with ribavirin.

Year	Study type	Treated/confirmed	Deaths among treated cases	Province	Reference
1999–2001	Historical comparison	61/69	8/61 (13.1%)	All involved provinces	(Mardani et al., 2003)
2001–2004	Historical comparison	236/255	37/236 (15.7%)	Sistan and Baluchestan	(Alavi-Naini et al., 2004)
2004–2005	Comparison to evaluate	184/184	38/184 (20.65 %)	Sistan and Baluchestan	(Metanat et al., 2006)
2005–2006	Comparison to evaluate timing	63/63	16/63 (25.4%)	Sistan and Baluchestan	(Izadi et al., 2009)
2006–2006	Observational	6/6	0/6 (00.0%)	Golestan	(Jabbari et al., 2006)
2006–2006	Observational	6/6	2/6 (33.3%)	Khorasan	(Naderi et al., 2011)
	Total of all 7 studies	679/706	120/679 (17.67%)		





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## Ribavirin has a Demonstrable Effect on Crimean-Congo Hemorrhagic Fever Viral Populations and Viral Load during Patient Treatment

Nicole Espy, Unai Pérez-Sautu, Eva Ramírez de Arellano, Anabel Negredo, Michael R Wiley, Sina Bavari, Marta Díaz Menendez, María Paz Sánchez-Seco, Gustavo Palacios 

*The Journal of Infectious Diseases*, jiy163, <https://doi.org/10.1093/infdis/jiy163>

Published: 23 March 2018 Article history ▾

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### Abstract

The use of ribavirin to treat infections of Crimean-Congo Hemorrhagic Fever virus (CCHFV) has been controversial based on uncertainties on its antiviral efficacy in clinical case studies. We studied the effect of ribavirin treatment on viral populations in a recent case by deep sequencing plasma samples taken from a CCHFV-infected patient before, during, and after a five-day regimen of ribavirin. CCHFV viral load dropped during ribavirin treatment and subclonal diversity (transitions) and indels increased in viral genomes during treatment. Although the results are based on a single case, these data demonstrate the mutagenic effect of ribavirin on CCHFV *in vivo*. (Word Count: 100)



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## *Favipiravir (T-705)*

T-705 (6-fluor-3-hydroxy-2-pyrazinecarboxamide) is a pyrazinecarboxamide derivative that inhibits the replication of various RNA viruses. The drug is intracellularly phosphoribosylated to its active form, favipiravir-RTP, which interacts with the viral RNA-dependent RNA polymerase, thus inhibiting viral replication (Furuta et al. 2017). T-705 and other derivatives of pyrazinecarboxamide (T-1105 and T-1106) have demonstrated good activity in treating viral infections in laboratory animals caused by various RNA viruses, including influenza virus, arenaviruses, bunyaviruses, West Nile virus, yellow fever virus and foot-and-mouth disease virus.

In 2014, the efficacy of favipiravir, ribavirin and arbidol (umifenovir) was tested *in vivo* in CCHFV-infected transgenic (IFNAR<sup>-/-</sup>) mice. Results indicated good efficacy of T-705, some beneficial effect from ribavirin (survival time was prolonged but survival rate did not increase) and no effect from arbidol (Oestereich et al. 2014). Favipiravir also shows potential efficacy against other bunyaviruses, notably Severe Fever with Thrombocytopaenia Syndrome virus (SFTSV) inhibiting

## *Intravenous immunoglobulin (IVIg)*

Intravenous immunoglobulin (IVIg) is a non-specific immunoglobulin G preparation that has immunomodulatory activities (Stangel and Pul 2006). It is used to treat various autoimmune, infectious and idiopathic diseases. A study in Iran compared the outcome of 28 lab-confirmed CCHF cases treated with ribavirin alone with that of 12 cases treated with a combination of ribavirin and 30-50g IVIg. No significant differences were found between the groups in terms of mortality rate but the time taken for white blood cell counts and liver function tests to return to normal levels was significantly shorter in the patients who received IGIV (Salehi et al. 2013).

## Steroids

One study demonstrated that the use of steroids was beneficial particularly among patients with severe disease (Dokuzoguz et al. 2013). Among 24 patients with severe CCHF, 16 received steroid treatment. Eight of the case group died (fatality rate 50%) but all 8 patients in the control group died (fatality rate 100%;  $P = .014$ ). Further studies are needed to determine the value of steroid treatment for severe CCHF, specifically to assess whether the anti-inflammatory effect of steroids and their ability to stimulate hematopoiesis in the bone marrow outweigh the negative effects associated with immunosuppression. There may also be a need to investigate the potential to combine corticosteroids such as high-dose methylprednisolone with ribavirin, based on promising findings from two studies (Sharifi-Mood et al. 2013); (Jabbari et al. 2006).



## *Therapeutics: Gap analysis*

The only antiviral available for the treatment of CCHF infection in humans is ribavirin. However, evidence about its efficacy is inconclusive and in some affected countries it is no longer recommended for CCHF treatment. In the absence of ribavirin, supportive care remains the mainstay of CCHF management.

# Measures taken by MOH and provinces:

1. **Technical meetings of the national CCHF committee and revision of national guideline to fight VHF**
2. **Strengthening CCHF surveillance conducted in PHC network according to standard case definition**
3. **Reinforcement of intersectoral coordination especially with Iranian veterinary system in declaring affected areas within the country with an aim to take control measures among cattle and fighting against Hyalomma Tick**
4. **Conducting national and regional seminars in order to raise knowledge of physicians, hospitals' staff and HCWs in public and private sectors**

5. Strengthening CCHF diagnostic lab in Pasteur Institute of Iran which receives samples of suspected cases for confirmation since 2000

6. Supplying the necessary medicine (Ribavirin) according to number of cases in the country and treatment of patients for free

7. Raising public awareness especially among high-risk groups about manifestations, transmission route and preventive measures through posters, pamphlets, public health circulars and mass media

# Main factors of prevalence and incidence of CCHF in Iran:

1. Introduction of infected cattle across illegal points at eastern borders of country
2. Insufficient quarantine posts at country's points of entry (PoEs) and across provincial borders
3. Insufficient tick bath for cattle in different areas (to fight disease reservoir)
4. Insufficient industrial slaughter houses and lacking serious supervision to the quality of existing ones
5. Holding infected cattle in houses especially at suburban areas

# Main factors of prevalence and incidence of CCHF in Iran:

6. Illegal and insanitary slaughtering of cattle
7. Insanitary structure of traditional ranches in rural and suburban areas
8. Slaughtering without taking standard precautionary measures and PPEs
9. Existence of infected ticks as the main disease reservoir in provinces





# An overview of CCHF surveillance

- It has 3 pillars:
  - Virus circulation in human
  - Virus circulation on vectors (ticks and mosquitos)
  - Virus circulation in animals (domestic and wild animals)
- Risk factors for disease prevalence
- Intra- and Inter-sectoral collaboration and sharing information



# Virus circulation studies

- Wild-life surveillance
- Vector surveillance activities
- Domestic animals and veterinary surveillance
- Human surveillance (human cases) including:
  - Early warning surveillance
  - Outbreak surveillance
  - Active case finding and contact tracing (including case definition, definition of contacts , case investigation forms)
- Laboratory surveillance: to confirm cases

# Risk factors surveillance for disease prevalence

- Climate change, rainfall pattern and events of flood comparing historical data
- Environmental changes
- Pathogenicity of disease agent
- Risky behaviors (for social and behavioral interventions)
- Infection prevention and control during health services

# Coordination/collaboration

- Establishment of coordination mechanisms
- Sharing data and information among those responsible for prevention and control of disease
- Communication with media
- Logistical support to sampling, sample transportation, etc(

WHO R&D Blueprint Roadmaps: CCHF Taskforce Face-to-Face  
Meeting, WHO/HQ, Geneva  
March 2018

- » **Vision** To be able to reduce death and morbidity from CCHF through safe and affordable effective treatments informed by rapid, reliable and easily accessible diagnostics by 2023,
- » and To be able to prevent or mitigate CCHF disease through deployment of safe, affordable and effective vaccines and other preventive measures by 2030.

# Strategic objectives/ goals

» (Diagnostics)

Affordable, quality assured nucleic-acid tests for near-patient acute CCHF diagnosis accessible for use in CCHF-affected countries by 2021, and RDT tests for point-of-care use by 2022.

# Point-of-care (POC) tests

can be performed at the patient bedside.

POC tests must be low complexity with minimal sample handling, minimum training requirements and rapid time-to-results.

# Near patient testing

- » Near patient testing refers to tests that are performed in a laboratory setting that is near to the patient i.e. not in a reference laboratory located a travelling distance away but in a community based clinic or field laboratory.
- » Near patient tests require automated, onboard sample processing but can be more complex than POC tests as trained staff and a basic laboratory are available.

# Therapeutics 1

- » Address the need for effective treatment for CCHF by evaluating antivirals with potential activity against CCHF in well-designed multi-centre prospective clinical trials, commencing by 2021. (Therapeutics 1)



# Therapeutics 2

- » Develop and assess new drugs, biologicals and/or their combinations for their efficacy as CCHF therapies in relevant animal models through to early clinical trials by 2023. (Therapeutics 2)

# Vaccines 1

- » Prioritize and progress the best human CCHF vaccine candidates from development to licensure, leveraging novel funding and regulatory mechanisms where necessary, with a lead candidate entering phase I trial by 2019 and phase II trial by 2023. (Vaccines 1).

# Vaccines 2

- » By 2025 evaluate through proof-of-concept studies alternative immunization strategies including animal CCHF vaccines and vaccines for tick-vector control for their ability to limit transmission and spread of CCHF virus and their cost effectiveness.  
(Vaccines 2)

# Therapeutics Landmark goals

By 2019, produce protocols in consultation with national regulatory authorities for dose regimen and subsequent randomised controlled trials to assess the efficacy and safety of existing therapeutic products (e.g. favipiravir), alone or in combination therapy against CCHF.

By 2020, initiate first evaluation of the therapeutic potential of antibody therapy in a relevant preclinical model of CCHFV infection.

By 2021, start patient enrolment to phase II trials of an existing therapeutic (e.g. favipiravir) in 2 or more countries to evaluate efficacy against CCHF disease and establish pharmacokinetic data.

By 2023, take successful therapeutics forward to a phase III randomised controlled trial to establish full efficacy against CCHF disease.

# Research Priorities of CCHF

1- Development of Rapid Diagnostic Test (RDT)

2- Full genome sequencing of CCHF virus isolates in different parts of Iran to determine the circulation of various genotypes (based on all 3 genome segments) in the country.

3-Surveillance of CCHF in wildlife (Ticks and amplifier host like small mammals) to better understand the ecology of the virus

4-Development of monoclonal antibodies for diagnostic and therapeutic purposes.

5- To become a WHO collaborating center to help other endemic countries in the Region.

6-Development of Pseudotyped Lentivirus for CCHF Neutralization test



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