Spatial Analysis of Crimean Congo Hemorrhagic Fever in Iran

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Abstract.

Crimean Congo hemorrhagic fever (CCHF) is a viral zoonotic disease. During 1999–2011, 871 human cases of CCHF were diagnosed in Iran. A history of serologic conversion for CCHF virus was seen in 58.7% of 2,447 sheep samples, 25.0% of 1,091 cattle samples and 24.8% of 987 goat samples from different parts of Iran. Spatial analysis showed that the main foci of this disease in humans during these years were in eastern Iran ($P < 0.01$) and the second most common foci were in northeastern and central Iran. Two livestock foci were detected in the northeastern northwestern Iran. On the basis of the results of this study, infection likely entered Iran from eastern and western neighboring countries.

INTRODUCTION

Crimean Congo hemorrhagic fever (CCHF) virus, family *Bunyaviridae*, genus *Nairovirus*, is an RNA virus that commonly infects domestic livestock and wildlife; such an infection is not accompanied by specific clinical signs in animals. *Hyalomma* spp. ticks are regarded as the main vectors in nature, humans are accidental hosts, and human infection is usually acquired via a tick bite or after contact with infected livestock, their blood, or other secretions.[1,2] Up to 80% of CCHF cases are subclinical and seropositive. The case-fatality rate among clinical patients is reported to be approximately 30%.[3] This disease has been reported in 30 countries in Africa, Asia, and eastern Europe. There have been reports of CCHF outbreaks in some of the neighboring countries of Iran, including Afghanistan, Iran, Iraq, Kuwait, Oman, Pakistan, Saudi Arabia, United Arab Emirates, and Turkey.[4] The emergence of diseases such as CCHF, which is transmitted by ticks in areas where the vector, domestic livestock, and wildlife are present, leads to an endemic situation and is why it is assumed that eradication of such diseases is difficult.[5]

In recent surveillance systems, application of the relationship between environmental and geographic factors and incidence of disease has been extensively applied to predict the status of disease.[6] To demonstrate such relationships and their modeling, it is essential to have complete information about reported cases of a disease over time.[7] Spatial analysis of a disease is defined as a presentation of cases of a disease, taking into respect spatial factors and their related analyses. One of the modern instruments for spatial analysis is the application of the geographic information system (GIS).[8] This system leads to a better understanding of clusters and hot spots of disease and their interpolation.[8,9]

On the basis of various studies conducted in Iran since 1972, virus circulation has been demonstrated in different regions of Iran.[10,11] The first human clinical cases were confirmed in

1999 in western Iran after a nosocomial infection.[12,13] Since then, the disease has been reported in different parts of Iran and a surveillance system has been planned and conducted.

Hyalomma spp. ticks are considered to be the most important and the most common vectors and reservoirs of CCHF in Iran. The virus has also been reported in other genera of ticks such as *Haemaphysalis* spp., *Rhipicephalus* spp., and *Ornithodoros* spp. Soft ticks belonging to the genus *Argas* have been also shown to be another vector of CCHF virus in Iran.[14]

Despite the belief that the disease is more prevalent in the eastern parts of Iran, probably because of importation of infected livestock from neighboring countries, evidence is lacking to confirm this as a source of new infections. Thus, scientific evaluations are needed to investigate this belief. In this regard, having applied data from the Pasteur Institute of Iran and used GIS for spatial analysis of CCHF in human and livestock samples during 1999–2011 in Iran, we conducted this study to evaluate the reporting process of this disease, the distribution of cases and foci, as well as to identify any overlap between human and livestock foci.

MATERIALS AND METHODS

Study areas.

Iran is located in the Middle East, has an area of 1,648,195 km^2, and is the 18th largest country in the world. It has various environmental conditions with respect to wide latitude and longitude ranges, topographic diversity, and an elevation that ranges from 25 to 5,671 meters above sea level. Iran is essentially a mountainous country with an ecologically diverse habitat that is subject to climate fluctuations. Climate in Iran ranges from arid to subtropical. Iran is bordered on the north by Armenia, Azerbaijan and Turkmenistan and to the north across the Caspian Sea by Kazakhstan and Russia, on the east by Afghanistan and Pakistan, on the south by the Persian Gulf and the Gulf of Oman, on the west by Iraq, and on the northwest by Turkey.

Case-patient definition.

In this study, a confirmed case of CCHF in a human was defined as a person with a positive IgM serologic test result for CCHF by enzyme-linked immunosorbent assay, a four-fold increase in IgG against CCHF demonstrated between specimens collected during the acute and convalescent phases of disease, or an isolated causative virus of the disease in serum by reverse transcription polymerase chain reaction. Livestock showed a positive history of CCHF virus infection if IgG against the virus was confirmed by specific enzyme-linked immunosorbent assay.

Study data.

Data for human cases and livestock samples wee obtained from the National Reference Laboratory of Arboviruses and Viral Hemorrhagic Fevers of Pasteur Institute of Iran for a 13-year period (1999–2011) (Figure 1). According to the national disease surveillance system, this laboratory is the only diagnostic laboratory for analysis of viral hemorrhagic fevers in Iran. After detecting a probable human case of CCHF, patient serum are maintained in a cold chain and dispatched to this laboratory for confirmation.

A person is considered as having a probable case of CCHF when he or she shows sudden onset of fever, myalgia, and different hemorrhagic manifestations; has a suggestive epidemiologic pattern, such as a history of tick bite, handling animal or human blood or tissues;

and has thrombocytopenia (platelet count < 150,000/mm^3), leukopenia (leukocyte count < 3,000 cells/mm^3) or leukocytosis (leukocyte count > 9,000 cells/mm^3).

Three blood samples were taken from each probable case-patient. The first sample was taken immediately after clinical diagnosis of the disease had been made, and the second and third samples were taken 5 and 10 days, respectively, after the first clinical symptoms of the disease.

Samples of healthy livestock from all over the country are also collected randomly and sent to this national reference laboratory in cold chain after serum separation.

Data obtained from the files of human cases included the location (county and province) and onset date (year) for CCHF human cases. Information for livestock included type of animal (sheep, cattle, or goat) and location (county and province), and the results of tests. For spatial analysis, information from counties with ≥ 30 livestock samples during the study period was used. The GIS maps at the national, provincial, and county level were collected from the National Geographic Center. Data analysis was performed on county level maps.

Data analysis.

ArcGIS software version 9.3 (ESRI, Redlands CA) was used for description and analysis of spatial information. Statistical Package for the Social Sciences software version 16 (SPSS Inc., Chicago, IL) was used for statistical analysis. Data were imported into ArcGIS, and observations were mapped with the Zone 19 (N) Universal Transverse Mercator projection by using World Geodetic System 1984 data.

A disease cluster is the occurrence of a greater than expected number of cases of a particular disease within a group of persons, a geographic area, or a period of time.[15] There are two ways of assessing spatial patterns in geographic data: global and local measures of spatial association. Global measures of spatial association can analyze patterns on a global scale to show whether data are clustered, dispersed, or randomly distributed in space.[16] Because global measures of spatial association can be used to test general patterns in data, identification of statistically significant patterns of high (hot spots) or low (cold spots) attributed values within the study area is also useful. Local measures of spatial association can quantify spatial autocorrelation at a local scale, which may be masked by global measures.[16,17] In this study the Getis-Ord General G statistic and the Getis-Ord Gi-star statistics was used to assess the global and local measure of spatial association, respectively.

To evaluate the pattern of the distribution of human cases in the population, high/low clustering was used. Such a spatial statistical test presents the results in the form of a *P* value, and a *P* value ≤ 0.05 was regarded as a cluster distribution.

To determine the high risk foci of the disease, Getis Ord's Gi* test and hot spot analysis was used in ArcGIS software. Analysis results were in the form of Z value and in the appearance of different layers on a map. The Z score, as measured in SD units, represents the magnitude of variation from complete spatial randomness. A high positive value is interpreted to represent spatial clustering and a high negative value represents spatial dispersion. The *P* values from this calculation represent the probability of such an event occurring by chance. In this study, a $Z > 2.58$ SD was regarded a hot spot.

Interpolation refers to the estimation of events between sample points and is frequently used in spatial modeling of diseases; interpolation methods are based upon the geospatial principle that areas closer to each other are more similar and correlated compared with areas farther apart from each other.[18] Inverse distance weighting (IDW) is a type of interpolation. In this method, it is believed that the correlation and similarity between neighbors is proportional to the distance between them and such a distance is used as the model's weight.[19] In this study, to determine the suspected livestock foci of the disease in the country, we designed a smoothed map of livestock serum antibody conversion in Iran by IDW. In this method, optimum power and radius were measured by calculating the least root mean square (RMS) prediction error from the regression function of the cross-validation procedure in ArcGIS Geostatistical Analyst.[20] The source of input data into the RMS calculation was the rate of CCHF antibody conversion in districts of the country where animal serum samples were referred for testing. The correlation between human and livestock foci was evaluated visually by comparing the generated maps.

RESULTS

During 1999–2011, 871 patients were confirmed to be infected with CCHF virus in Iran. As shown in Figure 2, the disease had two peaks, one in 2002 and one in 2010. Furthermore, during this period, 126 (14.5%) patients died of this disease.

A total of 67.6% of all human cases were from in Province of Sistan and Baluchistan in southeastern Iran. The Provinces of Razavi Khorasan (northeastern region), Isfahan, and Fars (central and south regions, respectively) with 6.0%, 5.9%, and 4.6% of all human cases, respectively, had the next highest number of reported human cases of the disease. Most human cases were reported in the Counties of Zahedan and Zabol (in northern Sistan and Baluchistan): 43.2% and 23.4% of all confirmed human cases, respectively. With the exception of the Provinces of Ilam, Kohkiluyeh, Boyer-Ahmad, Ardebil, and Ghazvin, the disease was reported in all other provinces of Iran.

Ninety-nine counties in 26 provinces of Iran submitted ≥ 30 livestock blood samples during this study. There were no livestock samples submitted from some of the western provinces (Chaharmahal, Bakhtiari, Lorestan, Ilam) and northern provinces (Semnan and Golestan). During this period, 43.2% of 4,525 livestock samples show seropositive test results. Of 2,447 sheep samples, 58.7% were positive, and 25.0% of 1,091 cattle samples and 24.8% of 987 goat samples were positive.

The pattern of occurrence of the disease during 2002 ($P < 0.05$), 2008 ($P < 0.05$), and 2010 ($P < 0.01$) was clustered, and the high frequency of reported human cases was associated with those counties located near each other; there was a cluster distribution in these regions. As for other years, random distribution was the pattern of distribution for the disease. When such an analysis was conducted for all years, cluster distribution was seen again for all 13 years ($P < 0.01$).

In the analysis of hot spots, the main focus of the disease during these years was in the Counties of Zabol and Zahedan ($P < 0.01$) (Figure 3A). To show other foci of the disease, an analysis was conducted after eliminating information relating to the Counties of Zabol and Zahedan. It was then shown that the second foci of the disease were located in counties in northeastern (Mashhad in Razavi Khorasan Province), southwestern (Kazeroon and Shiraz in Fars Province), central (Golpaygan, Barkhoar, Meimeh, and Isfahan in Isfahan Province), northern (Tehran in Tehran Province and Aliabad Katol in Golestan Province), and southeastern (Saravan in Sistan and Baluchistan Province) Iran (Figure 3B). On the basis of three-dimensional modeling of the distribution of CCHF serum antibody conversion among sheep, cattle, and goats, most infected livestock samples were from northwestern and northeastern regions of Iran.

The IDW results used to designate the smoothed map of CCHF serum antibody conversion in livestock in the country showed that the application of neighborhood status of six points and a power of one accompanies the least amount of RMS error. The smoothed map of CCHF serum antibody conversion in livestock of the country was designed in accordance with this information (Figure 3C). In this map, two probable foci of livestock serum antibody conversion were seen in northeastern Iran in northern Khorasan Razavi Province; this second focus extended towards the Counties of Zabol and Zahedan, which had a lower CCHF serum antibody conversion rate. The other probable focus of the disease was in the northwest region of Iran in Zanjan Province, which also included neighboring Kurdistan Province, which had a lower seroconversion rate. The seroconversion rate for livestock in the southern, northern, northwestern, and some parts of central Iran was lower than for other areas.

To compare and evaluate the correlation between human and livestock foci of the disease, the map of human high risk spots and the smoothed map of livestock CCHF serum antibody conversion (Figure 3B and D) were compared. There was no significant correlation between human and livestock foci of the CCHF serum antibody conversion. The northeastern focus of livestock serum antibody conversion overlapped with the main human focus of the disease, i.e., the Counties of Zabol and Zahedan had approximately 60% of all human case studies of the disease. The County of Mashhad, one of the human foci of the disease, was also located in this area. The northwestern CCHF serum antibody conversion focus showed no overlap with human foci. Other foci of the disease had no overlap with livestock foci.

DISCUSSION

This study showed that the main foci of reported cases of CCHF in humans in Iran are the Counties of Zabol and Zahedan in the Province of Sistan and Baluchistan, which are near Afghanistan. In addition, three foci in northeastern and central Iran are regarded as the other important foci of the disease. Two probable livestock foci were also detected in northeastern and northwestern Iran.

During 1999–2011, 871 patients with CCHF were detected in Iran. Because approximately 80% of CCHF infections are accompanied by no clinical symptoms,[21] this reported number is assumed to be much lower than the actual number of human cases.

Evaluation of the trend of cases of the disease in Iran showed that after a significant increase in the number of patients during 2000–2001 and a subsequent decrease during 2002–2007, the number of human cases started to increase again after 2008. Incidence of the disease in other parts of the world has also shown a similar repeated pattern. For instance, an epidemic of CCHF occurs every six years in Kosovo.[22] To better determine the long-term trend of the disease in Iran, evaluation over a longer period of time and of newly reported human cases is essential.

Except for 2002, 2008, and 2010 when occurrence of the disease showed a cluster distribution pattern, in other years, it has adhered to a pattern of random distribution. In these three years, those counties with a higher number of reported cases when compared with others were located near each other. Thus, most cases of the disease were in Counties of Zabol, Zahedan, Mashhad, Isfahan, Shiraz, and Tehran, and surrounding areas. The clustering pattern of the disease in these years could be related to an increased number of reports of the disease in these years versus other years. The distribution pattern of the disease in Iran is generally random, but where occurrence of the disease increases in a year, such a pattern changed to a cluster and new human cases in that particular year were mostly concentrated in counties with a high level of reports and their surrounding areas.

When all reports of the disease during the 13-year study period were evaluated together, a cluster distribution pattern was prominent. Such information also shows that there is a correlation between reported human cases in different years, i.e., that where a disease occurs in one county, the probability of reports of the disease in the same county or in neighboring ones in the following years would increase. Thus, it is essential that the health system in Iran designs a plan to fight against and evaluate any type of clusters of the disease in a scientific way. Such programs help policy makers and those authorities involved in the health care system to make decisions based upon scientific evidence.[23]

As expected, the two main human foci of this disease during these years in Iran were the counties of Zabol and Zahedan. Other major foci are in Mashhad County in northeastern Iran and in Saravan and Khash in eastern Counties of Sistan and Baluchistan Province. These counties are near the border with Afghanistan and Pakistan. Because more than 60% of all human cases of CCHF in Iran have been reported in Sistan and Baluchistan Province, excessive livestock importing and high frequency of Afghani traveling to this area can be a source of human infection reported from this region. Annually, approximately 300,000 livestock are imported illegally from Afghanistan into Iran.[24]

Other human foci of this disease included some western counties of Isfahan Province, which are located near each other. In this study, another human focus was located in Fars Province (Counties of Shiraz and Kazeroon) in southwestern Iran. These two counties are two of the largest counties in Fars Province and are located near each other in the northwestern area of this province. Most remaining foci were centrally located in the Provinces of Tehran, Alborz, Khorasan Razavi, Yazd, Hormozgan, and Khuzestan. In Iran, larger cities tend to be located centrally in provinces and human case-patients seeking treatment go to the larger cities for medical care. Therefore, more records might be available at these centers.

Domestic livestock such as sheep, cattle, and goats do not show any signs after infection with CCHF; IgG levels starts to increase approximately 12 days after infection and can be present in the blood for 5–6 years. The presence of IgG against the virus in blood confirms a prior infection in livestock. In this study, serologic measurement of IgG in 4,525 livestock from 26 provinces showed that IgG was present > 40% of all livestock under study. Thus, CCHF is probably endemic in the livestock population in most parts of Iran. In addition, in this study, most CCHF serum antibody conversions were detected in sheep, which are main host among all domestic livestock in this study, as was the case in similar studies. Sheep have been known to be one of the main hosts acting as a reservoir for the virus and also a main and primary host for vector ticks in areas to which CCHF is endemic.[25] Because approximately 60% of 90 million domestic livestock in Iran are sheep, the infection among them is considerable.

As for livestock foci, the smoothed map of CCHF serum antibody conversion in livestock in Iran showed two probable foci, one in the northeastern Iran and one in northwestern Iran. The northwestern focus is also located next to Turkey, where there are many reports of the disease.[26] Thus, infection from this neighboring country is likely. The livestock CCHF serum antibody conversion rate in southern, northern, northwestern, and certain central areas of Iran was lower than in other regions. This finding might be due to the fact that samples were not sent from these areas. Thus, CCHF serum antibody conversion values for these areas have likely been substantially affected by neighboring regions.

In this study, livestock blood samples sent from each area were assumed to be a livestock index of that particular region. However, the sampling method and number of samples sent did not follow any specific sampling design. If one considers the low number of samples sent for various livestock, the known CCHF serum antibody conversion rate of all species was applied in the analysis of livestock foci. This factor was one of the limitations of this study on livestock samples. Thus, results of livestock samples were solely presented as field observations around which hypotheses were developed. If one takes into consideration the fact that livestock have a shorter life span than humans, their spatial serum antibody conversion distribution could be used as an index for new transmission of the infection and also human risk of acquiring the disease.[27]

A comparison of the human hot spot map and the smoothed map of livestock CCHF serum antibody conversion showed that there was no significant correlation between human and livestock foci. This finding is an unresolved question that awaits further testing and analysis.

The northeastern livestock focus of CCHF covers the main human foci, Counties of Zabol and Zahedan, and > 60% of all human cases were reported from this region. This human and livestock focus borders Afghanistan and would support the hypothesis of infected livestock imported from this country.

The northwestern CCHF serum antibody conversion focus in Iran showed no overlap with the human foci of CCHF because a limited number of human cases have been reported from these areas during the study period. Such information necessitates more attention being given to this area to better clarify the actual infection status of this region. This focus borders Iraq, in addition to Turkey, and infection caused by livestock being moved from Iraq to Iran is also feasible. One of the explanations for the low number of human cases reported for certain livestock foci is lack of surveillance by the health care systems of these areas regarding CCHF. Thus, it is essential that awareness of the health system for CCHF is enhanced in these regions.

Although evaluation of human foci showed that some are located in certain counties in the provinces of Isfahan, Tehran, Hormozgan, and Khuzestan, these counties are designated as areas with low infection rates in their livestock. However, it should also be noted that although domestic livestock are regarded as the main hosts of the disease and can transfer the disease during their viremic stage to humans,[28] high-risk behaviors such as slaughtering or examining livestock without wearing masks or gloves, unauthorized slaughtering of animals (outside slaughterhouses) facilitate transmission of the disease. Thus, high-risk behaviors in these counties could account for transmission to humans from the low percentage of infected livestock. It is also probable that the actual livestock infection rate is higher than that determined from submitted livestock samples.

During this period, human samples were not obtained from the provinces of Ardebil, Ghazvin, and Kohkiluyeh and Boyer-Ahmad. However, livestock seroconversion rates were > 20% in all of these regions. Thus, absence of any report of human cases in a province does not necessarily imply that the virus circulation is not present there.

In this study, it is also possible that the city of treatment was erroneously registered as the city of residence. As a result, misclassification bias was inevitable. If one considers the problems in validation of these data, this factor could also be another limitation of this study.

Hyalomma spp. ticks are considered to be the most important vector and reservoir of CCHV. Although the virus has been reported from *Hyalomma* spp. and other genera of ticks in some local studies,[14,29] a national study should be conducted to assess the geographic distribution of tick vectors relative to CCHF infections in humans and livestock. It is recommended that future studies use predictive models to map the habitat suitability for the vector tick from satellite-based climate data and features of the vegetation covering the whole country.

Another limitation of this study was use of data from laboratory submissions obtained through passive surveillance. For spatial analysis and modeling, it would be better to have data based on comprehensive surveillance through systematic sampling methods. As for this study, spatial analysis processes relied on data collected by less than optimal methods and sampling bias was probable. This finding could originate from the fact that more samples have been sent from counties with previous reports of the disease. It is strongly suggested that molecular genetic studies also be conducted for livestock foci in northeastern and northwestern Iran to determine relationships among various geographic strains.

Available evidence suggests that a systematic connection between human and livestock information in different parts of the country is challenging because this connection requires a much higher level of livestock samplings from different parts of the country. This challenge necessitates high costs for serologic laboratory tests that are not available at the present time. In this regard, it is recommended that priority of sampling be given to those counties with no reported human cases or those known to be human foci of the disease.

Although the Getis-Ord General G statistic was useful in identifying spatial clusters, use of this method was most effective when we were able to establish the distribution of the entities being measured, which might be influenced by other factors. When these measures are taken over a large area, such as the boundaries of a country, it becomes more of a problem. Therefore, it is advisable to estimate the zones or distances of spatial influence of the observations by using tests such as multi-distance spatial cluster analysis involving Ripley's K function.[30] When spatial clusters are detected, especially on a country-wide scale, it is best to confirm these clusters with other tests based on different assumptions and different statistical models. Thus, in our study it was better to conduct further analysis, but complex analysis was not used to simplify results, and it was assumed that more advanced analysis would not change the final results and conclusions.

On the basis of the findings of this study, it is strongly recommended that more attention be given to evaluation and assessment of surveillance programs in high-risk areas without any decrease in the awareness of surveillance system in other regions. If these recommendations are implemented, awareness of CCHF by health systems in these counties should be enhanced. Authorities responsible for disease surveillance in Iran are also advised to annually update this model with new data to gain a better perspective of the epidemiology of the disease and increase the validity of the model.

This study has shown that CCHF virus is highly focal with evidence of virus activity in most regions of Iran. Disease outbreaks in humans are likely to continue to be a threat because livestock hosts, tick vectors, and the virus are found nationwide. Because of common borders of eastern and northwestern provinces with disease-endemic countries and the high frequency of travel and livestock transport, control of the disease in border areas should be more thorough and border quarantines should be improved and better supervised.

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REFERENCES

1. Whitehouse CA, 2004. Crimean-Congo hemorrhagic fever. *Antiviral Res 64:* 145–160.
2. Ergonul O, 2006. Crimean-Congo haemorrhagic fever. *Lancet Infect Dis 6:* 203–214.
3. Alavi-Naini R, Moghtaderi A, Koohpayeh HR, Sharifi-Mood B, Naderi M, Metanat M, Izadi M, 2006. Crimean-Congo hemorrhagic fever in southeast of Iran. *J Infect 52:* 378–382.
4. Chinikar S, Ghiasi SM, Hewson R, Moradi M, Haeri A, 2010. Crimean-Congo hemorrhagic fever in Iran and neighboring countries. *J Clin Virol 47:* 110–114.
5. Mostafavi E, Chinikar S, Esmaeili S, Amiri FB, Tabrizi AM, KhakiFirouz S, 2012. Seroepidemiological survey of Crimean-Congo hemorrhagic fever among sheep in Mazandaran Province, northern Iran. *Vector Borne Zoonotic Dis 12:* 739–742.
6. Randolph SE, 2004. Evidence that climate change has caused 'emergence' of tick-borne diseases in Europe? *Int J Med Microbiol 293 (Suppl 37):* 5–15.
7. Kelly-Hope LA, Alonso WJ, Thiem VD, Canh do G, Anh DD, Lee H, Miller MA, 2008. Temporal trends and climatic factors associated with bacterial enteric diseases in Vietnam, 1991–2001. *Environ Health Perspect 116:* 7–12.
8. Haghdoost A, Alexander N, Cox J, 2008. Modelling of malaria temporal variations in Iran. *Trop Med Int Health 13:* 1501–1508.
9. Pfeiffer DU, Hugh-Jones M, 2002. Geographical information systems as a tool in epidemiological assessment and wildlife disease management. *Rev Sci Tech 21:* 91–102.
10. Chumakov MP, Smirnova SE, 1972. *Detection of Antibodies to CCHF Virus in Wild and Domestic Animal Blood Sera from Iran and Africa*. Moscow: Institute of Polio and Viral Encephalitis.
11. Saidi S, Casals J, Faghih MA, 1975. Crimean hemorrhagic fever-Congo (CHF-C) virus antibodies in man, and in domestic and small mammals, in Iran. *Am J Trop Med Hyg 24:* 353–357.

12. Bokaie S, Mostafavi E, Haghdoost AA, Keyvanfar H, Gooya MM, Meshkat M, Davari S, Chinikar S, 2008. Crimean Congo hemorrhagic fever in northeast of Iran. *J Animal Vet Adv 7:* 354–361.

13. Chinikar S, Shayesteh M, Khakifirouz S, Jalali T, Rasi Varaie FS, Rafigh M, Mostafevi E, Shah-Hosseini N, 2012. Nosocomial infection of Crimean–Congo haemorrhagic fever in eastern Iran: case report. *Travel Med Infect Dis*.

14. Mehravaran A, Moradi M, Telmadarraiy Z, Mostafavi E, Moradi AR, Khakifirouz S, Shah-Hossein N, Varaie FS, Jalali T, Hekmat S, Ghiasi SM, Chinikar S, 2013. Molecular detection of Crimean-Congo haemorrhagic fever (CCHF) virus in ticks from southeastern Iran. *Ticks Tick Borne Dis 4:* 35–38.

15. Rezaeian M, 2004. Large scale clustering and its application to the health and epidemiological studies. *Journal of School of Public Health and Institute of Public Health Research 3:* 61–70.

16. Anselin L, 1995. Local indicators of spatial association—LISA. *Geogr Anal 27:* 93–115.

17. Getis A, Ord JK, 2010. The analysis of spatial association by use of distance statistics. *Perspectives on Spatial Data Analysis*. New York: Springer, 127–145.

18. Štěpánek P, Zahradníček P, Huth R, 2011. Interpolation techniques used for data quality control and calculation of technical series: an example of central European daily time series. *Q J Hungarian Meteorological Service 115:* 87–98.

19. Ormsby T, Napoleon E, Burke R, 2004. *Getting to Know ArcGIS Desktop: The Basics of ArcView, ArcEditor, and ArcInfo Updated for ArcGIS* 9. Redlands, CA: ESRI Press.

20. Fabi A, Varvaro L, 2009. Application of geostatistics in studying epidemiology of hazelnut diseases: a case study. *Acta Hortic 845:* 507–514.

21. Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, McGillivray GM, Erasmus MJ, Searle LA, Gill DE, 1987. Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. *Am J Trop Med Hyg 36:* 120–132.

22. Drosten C, Minnak D, Emmerich P, Schmitz H, Reinicke T, 2002. Crimean-Congo hemorrhagic fever in Kosovo. *J Clin Microbiol 40:* 1122–1123.

23. Cromley EK, 2003. GIS and disease. *Annu Rev Public Health 24:* 7–24.

24. *Animal Trafficking Trade and Iranian Officials Concerns*, 2008. Interview with Dr. A. Mokhtari, Reporter of the Assembly Health Committee of Iranian Parliament. Report of Government Suspended Organization.

25. Gonzalez JP, Camicas JL, Cornet JP, Wilson ML, 1998. Biological and clinical responses of west African sheep to Crimean-Congo haemorrhagic fever virus experimental infection. *Res Virol 149:* 445–455.

26. Chinikar S, Ghiasi S, Hewson R, Moradi M, Haeri A, 2010. Crimean-Congo hemorrhagic fever in Iran and neighboring countries. *J Clin Virol 47:* 110–114.

27. Wilson ML, LeGuenno B, Guillaud M, Desoutter D, Gonzalez JP, Camicas JL, 1990. Distribution of Crimean-Congo hemorrhagic fever viral antibody in Senegal: environmental and vectorial correlates. *Am J Trop Med Hyg 43:* 557–566.

28. Shepherd AJ, Leman PA, Swanepoel R, 1989. Viremia and antibody response of small African and laboratory animals to Crimean-Congo hemorrhagic fever virus infection. *Am J Trop Med Hyg 40:* 541–547.

29. Tahmasebi F, Ghiasi SM, Mostafavi E, Moradi M, Piazak N, Mozafari A, Haeri A, Fooks AR, Chinikar S, 2010. Molecular epidemiology of Crimean- Congo hemorrhagic fever virus genome isolated from ticks of Hamadan Province of Iran. *J Vector Borne Dis 47:* 211–216.

30. Schröter M, Härdtle W, von Oheimb G, 2012. Crown plasticity and neighborhood interactions of European beech (*Fagus sylvatica* L.) in an old-growth forest. *Eur J For Res 131:* 787–798.

FIGURE 1. Centroids and provinces of Iran.

FIGURE 2. Number of laboratory-confirmed human cases of Crimean-Congo hemorrhagic fever (CCHF), Iran, 1999–2011.

FIGURE 3. **A**, Hot spot map of human Crimean-Congo hemorrhagic fever (CCHF), Iran, 1999–2011. The counties of Zabol and Zahedan (shown in red) had significantly more reports of CCHF during these years ($P < 0.01$). **B**, Hot spot map of human CCHF cases, Iran, 1999–2011. To show the second foci of the disease, Zabol and Zahedan information was omitted and not entered into analysis. **C**, Choropleth map of CCHF serum antibody conversion in referred livestock samples, i.e. cattle, goats and sheep, during 1999–2011. The infection rate is based on the percentage of submitted samples that were seropositive for CCHF from that geographic location. **D**, Smoothed map of CCHF serum antibody conversion in livestock, Iran, 1999–2011. There are estimations in areas with no sampling. This figure appears in color at www.ajtmh.org.

Figure 1

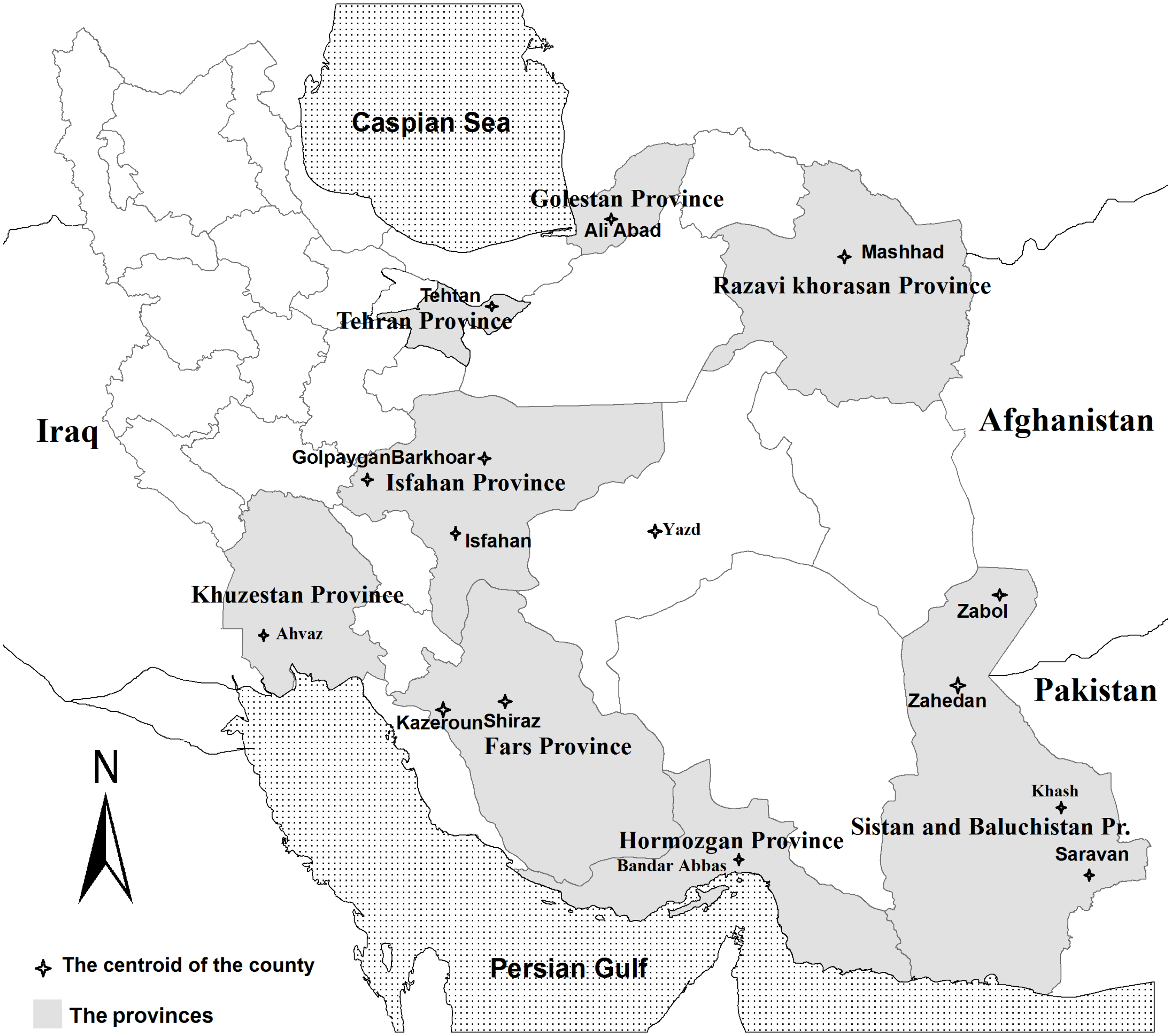

Caspian Sea
Golestan Province
Ali Abad
Mashhad
Razavi khorasan Province
Tehtan
Tehran Province
Iraq
Afghanistan
GolpayganBarkhoar
Isfahan Province
Isfahan
Yazd
Khuzestan Province
Ahvaz
Zabol
Zahedan
Pakistan
KazerounShiraz
Fars Province
N
Khash
Sistan and Baluchistan Pr.
Hormozgan Province
Bandar Abbas
Saravan
Persian Gulf
✧ The centroid of the county
▨ The provinces

Figure 2

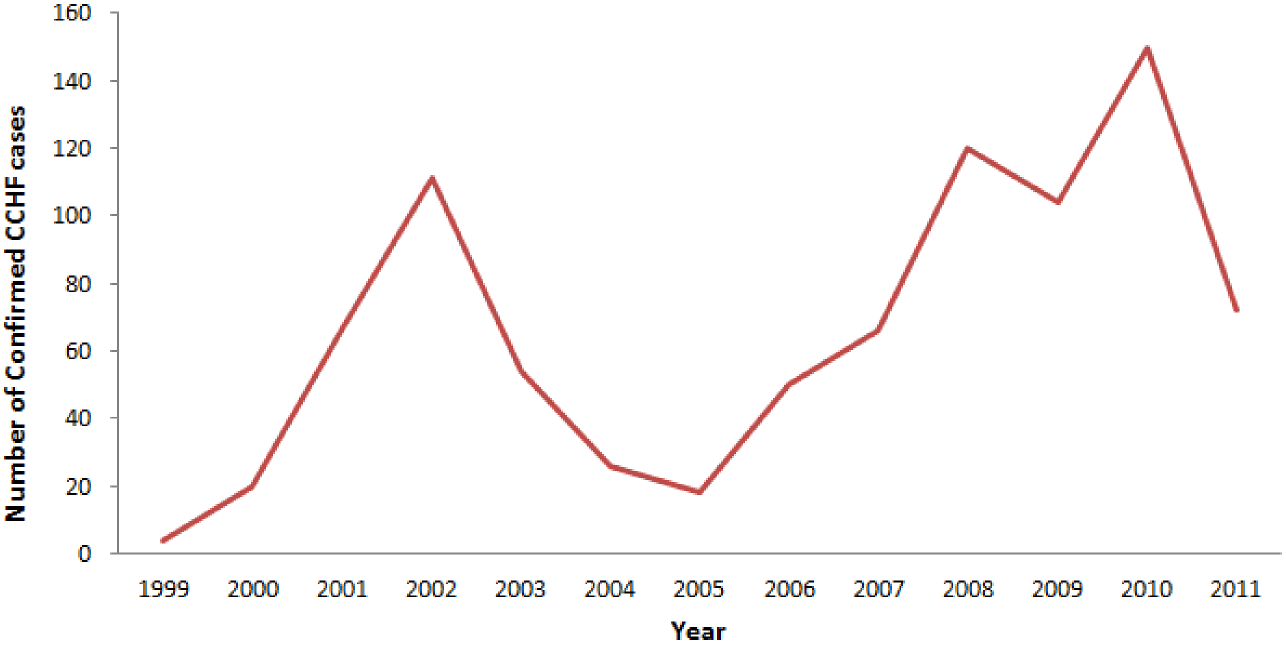
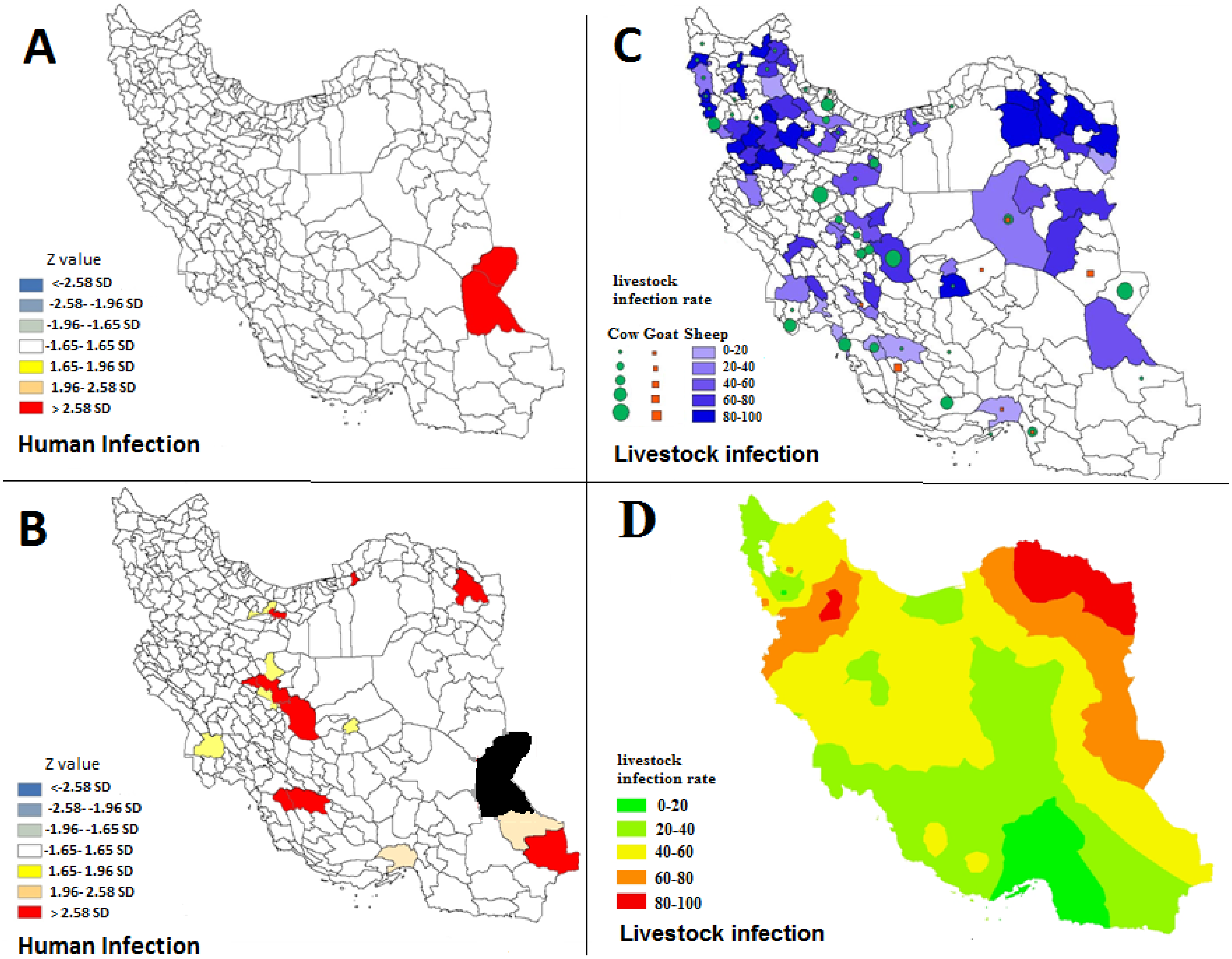

160
140
120
100
80
60
40
20
0
Number of Confirmed CCHF cases
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
Year

Figure 3


A
Z value
<-2.58 SD
-2.58- -1.96 SD
-1.96- -1.65 SD
-1.65- 1.65 SD
1.65- 1.96 SD
1.96- 2.58 SD
> 2.58 SD
Human Infection
B
Z value
<-2.58 SD
-2.58- -1.96 SD
-1.96- -1.65 SD
-1.65- 1.65 SD
1.65- 1.96 SD
1.96- 2.58 SD
> 2.58 SD
Human Infection
C
livestock infection rate
Cow Goat Sheep
0-20
20-40
40-60
60-80
80-100
Livestock infection
D
livestock infection rate
0-20
20-40
40-60
60-80
80-100
Livestock infection