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Crimean-Congo hemorrhagic fever in Sistan and Baluchestan Province of Iran, a case-control study on epidemiological characteristics

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Summary *Objectives:* Several cases of Crimean-Congo hemorrhagic fever (CCHF), an arboviral disease, have been reported since summer 1999 in different areas of Iran. The main objectives of this research were to determine the most important means and patterns of transmission and the epidemiologic characteristics of this disease.

Design: In this population-based case-control study, 24 patients from Zabol and Zahedan Districts in the Sistan and Baluchestan province, reported to the Center for Disease Control of Iran, were compared with 300 controls. The controls were sampled through the 'probability proportional to size cluster sampling' method from the general population of the same districts. The following variables were checked: age, sex, living environment (rural versus urban), education years, job, past history of tick bite, contact history with livestock, history of livestock slaughtering, presence of a designated place for animals at home, history of keeping livestock in the house.

Results: Variables which increased the chance of disease include: history of slaughtering (OR = 7.57, CI: 2.21—25.91), high-risk occupations (OR = 4.97, CI: 0.97—25.43), history of tick bite (OR = 105.89, CI: 9.32—1202.44), age above 40 years (OR = 7.32, CI: 1.06—50.26).

Conclusion: The results of this study confirm that the scheme of risk factors and risk groups for Crimean-Congo hemorrhagic fever (CCHF) in Iran do not differ substantially from the other parts of the world. Even though tick bite is one of the most important risk factors for CCHF, it cannot explain all cases and there are other important risk factors such as high-risk occupations and having contact with livestock. Even taking care of livestock for a short period at home can increase the chance of contracting CCHF.

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Introduction

Since 1999 there have been several reports of Crimean-Congo hemorrhagic fever (CCHF) in the form of local outbreaks that have been confirmed using special ELISA methods (data from Center for Diseases Control, Ministry of Health). This disease has been recognized in some of Iran's neighboring countries for many years[1–7] and within the past few years there have been several reports from the countries around the Persian Gulf.[6,8,9] There is also some evidence of this disease about 30 years ago in the north-west parts of Iran (M. Sadeghi Tehrani, 1969, unpublished data).

A widespread serologic study on anti-CCHF virus antibodies was conducted in the northern parts of Iran in 1975. Using agar gel diffusion precipitation (AGDP), widespread distribution of the disease in the study area was uncovered. In that survey 13% of 351 studied human samples were seropositive. Seropositive rates of sheep and cattle were 38% and 18% respectively.[10] In 1978, during an arbovirological survey conducted in the north-eastern region of Iran, Crimean-Congo hemorrhagic fever virus was isolated, for the first time, from the engorged larvae of *Alveonasus lahorensis* ticks.[11]

Although the most important ways of transmission are known in other parts of the world, patterns of transmission and epidemiological characteristics of this disease are unknown in Iran. In spite of the fact that CCHF is an occupational disease, in some reports up to 82% of suspected female cases have been housewives (data from Province Health Center of Sistan and Baluchestan Province). On the other hand, even though the most important vector of this disease is the *Hyalomma* tick, which according to some studies is highly distributed in different parts of Iran,[12] some experts believe that the proportion of confirmed cases in Iran that are due to tick bites is lower than expected.

The Sistan and Baluchestan province currently has the highest number of reported confirmed and suspected cases of CCHF in Iran (data from Center for Diseases Control, Ministry of Health). This study investigates the most important means of transmission and risk groups in two northern districts of this province, containing almost half the people of the province.

Material and methods

The source population, which is about 800,000, is the population of Zahedan and Zabol Districts in the northern part of Sistan and Baluchestan Province. The population of Zahedan is about 450,000 and Zabol 350,000. Zahedan is the center of the province and most of the population of the district has gathered in Zahedan city. Zahedan city has a non-homogenous pattern. The newly-developed parts of this city are fully urbanized while some outlying areas are rural. In the rural areas of Zahedan district, the population is highly scattered and villages are usually located far apart. The primary health care (PHC) system is well developed and almost all the population has registered. There are also some nomadic populations that frequently move settlements; their usual occupation being sheep and goat breeding and trading.

Zabol is one of the largest districts of the province and is located about 205 kilometers to the north of Zahedan. The population of Zabol is about 350,000. Around half the population lives in Zabol city and the rest in the rural areas. Most of the rural population is scattered in a plain around the city of Zabol. Villages are located near each other and most of them are not further than 30 kilometers from the city of Zabol.

This area is located near to the Afghanistan and Pakistan borders to the east, and for many years Afghan refugees have constituted about 10% of the population of both Zahedan and Zabol districts. Afghan refugees have mostly settled in the urban regions; some of them reside transiently while others are long-term settlers.

The primary health care coverage of Zabol district is over 95% (102 rural health houses and nine urban health centers) and in Zahedan it is about 84% (48 rural health houses and 34 urban health centers). The health network in Iran follows a step-wise referral system. The patients are referred from health houses to urban health centers and if necessary the physician in charge of the rural health center will refer the patients to hospital. All rural health centers have necessary transport facilities (such as cars and sometimes ambulances).

In this population-based case-control study, 24 serologically confirmed cases were compared with 300 controls sampled from the population. The only inclusion criterion for cases was having a clinical history of CCHF, confirmed using IgM and IgG capture ELISA. All the tests were carried out in the national reference laboratory of arboviral diseases, Pasteur Institute of Iran, Tehran, Iran. There were no restrictions on the inclusion of controls, only the absence of history of a clinical CCHF.

All cases occurred between 6 July 2000 and 13 May 2002. During this period 32 ELISA-confirmed cases occurred in Sistan and Baluchestan province

of Iran. One of these cases was from Nimrooz province of Afghanistan and two others were from Khash and Saravan districts. Of the remaining 29 cases, only 24 were included in the retrospective study, as the addresses of five of the cases were incomplete. Two of these 24 cases and two of the lost cases (four cases in total) died of CCHF. We know that this infection has sub-clinical cases and in addition not all clinical cases of the infection become hemorrhagic.[17] However, all 24 cases in this study were hemorrhagic cases which, according to their surveillance forms, were identified and reported as suspected cases of CCHF by hospitals.

The controls were selected and sampled within the period of 10 January 2002 to 20 March 2002. During interview, after a short explanation about the most important signs and symptoms of CCHF, the interviewees were asked about their previous experiences of the disease in the past 12 months. The first confirmed reports of CCHF in this province began in July 2000 and the documented history of controls covered most of this period. With regard to the few reported cases up to 20 March 2002 (even considering sub-clinical infections), some misclassification of sub-clinical infections in the control group is presumed.

There were no age or area restrictions made on the sampling of the controls and the sampling method was according to a modification of classical probability-proportional-to-size (PPS) cluster

Table 1 Questions asked about some key variables.

Contact of the subject with livestock (such as cow, sheep, goat, donkey, horse): a) ☐ The subject has no contact with livestock. b) ☐ The subject has occasional contact with livestock. c) ☐ There is no routine contact with livestock; however, he/she comes in close contact with them at least fortnightly. d) ☐ Job or the residential place of the subject requires him/her to have close contact with livestock almost routinely. e) ☐ One of the duties of the subject (at home or as a job) is taking care of livestock. Please define the animal: __________________
History of livestock slaughter by the subject: a) ☐ The subject has not had any role in slaughtering of livestock yet. b) ☐The subject takes part in slaughter of livestock only occasionally in religious ceremonies. c) ☐The subject occasionally takes part in slaughtering of livestock (as a job or as a home duty). d) ☐One of the duties of the subject in his/her place of work is slaughtering of livestock routinely. Please define the animal: __________________
Is there any allocated place at home for keeping livestock? ☐Yes ☐No
Have they kept any livestock at home within the past 12 months (even temporarily, and for a short period)? ☐Yes ☐No
Do they occasionally take care of livestock for a short time period until its slaughter? ☐Yes ☐No

sampling.[13] A cumulative list of the study population was produced and a systematic sample was selected from a random start. By dividing the total population of the communities by the number of communities to be selected (30 communities in this study) the sampling interval was obtained. A random number between one and the result of the division was then chosen. This was fitted into position in the list to identify the first community in the sample. Then by adding the sampling interval to the initial random number, the remaining communities were selected. In both these districts there is almost a complete health register of all households and household members. We considered the dimension of each community to be 200 people. From each selected community we chose ten subjects at random. Usually no more than one member from every household was selected for the sample.[13]

All eligible individuals were cooperative and eager to answer our questions, however, some individuals who were selected had changed their address and emigrated. We replaced these with other subjects from the same community using more random numbers.

A questionnaire was completed for each control. All adults responded for themselves but children who were not cooperative or were not able to answer were assisted by one of the parents (mostly the mother). For the two cases where the individual died due to CCHF, a proxy respondent completed the questionnaire (in one instance the daughter and in another the wife responded to our questions). The variables which were considered within the questionnaire were: age, sex, living environment, education years, occupation, history of tick bite, history of contact with livestock, history of slaughtering of livestock, and having a special place for taking care of livestock at home. All the exposure histories were considered for the previous 12 months.

A multiple-choice question with five options asked every subject about their present type of contact with livestock (Table 1). In the analysis, respondents who chose 'b' and 'c' were combined and those who chose 'd' and 'e' were also combined. In another question we asked about history of animal slaughter by the subject. In the analysis of this question those who chose 'a' and 'b' were again combined, as were those who chose 'c' and 'd'. The presence of a designated place for taking care of livestock at home was confirmed by a yes/no question and the history of taking care of livestock at home was ascertained by two yes/no questions. A positive response to either of these last two questions was considered as a 'positive' history of taking care of livestock at home and negative response to both questions was considered as a 'negative' history of taking care of livestock at home.

Concealing the case/control status of the interviewees was impossible in most instances and even though the interviewers were not aware of the specific objectives of the study, they knew that CCHF was involved. Interviewer bias was minimized by training and teaching the interviewers. In addition, a nine-page pamphlet on the questionnaire had been prepared and every interviewer had one copy with him in the field.

Table 2 Personal characteristics of cases and controls.

Levels of variable	Cases No. (%)	Controls No. (%)
Districts		
Zahedan	12 (50)	190 (63.3)
Zabol	12 (50)	110 (36.6)
Nationality		
Iranian	19 (79.2)	226 (78.7)
Afghan	5 (20.8)	61 (21.3)
Sex		
Male	17 (70.8)	143 (47.7)
Female	7 (29.2)	157 (52.3)
Environment		
Urban	8 (33.3)	158 (54.3)
Urban with rural culture	6 (25.0)	42 (14.4)
Rural	10 (41.7)	91 (31.3)
Age groups		
1 to 10	0 (0.0)	78 (26.0)
11 to 20	7 (29.2)	92 (30.7)
21 to 40	9 (37.5)	92 (30.7)
41 to 60	8 (33.3)	27 (9.0)
61 and over	0 (0.0)	11 (3.7)
Education years		
Age $<$6 yrs	0 (0.0)	49 (16.3)
Illiterate	9 (37.5)	93 (31.0)
1 to 5 yrs education	4 (16.7)	66 (22.0)
6 to 12 yrs education	10 (41.7)	87 (29.0)
$>$12 yrs education	1 (4.2)	5 (1.7)
Occupation		
1) Shepherd, farmer, farm worker	3 (12.5)	14 (4.8)
2) Butcher, slaughterhouse worker	5 (20.8)	1 (0.3)
3) Physician, nurse	0 (0.0)	1 (0.3)
4) Soldier, worker, others	8 (33.3)	66 (22.5)
5) Housewives and offspring aged 10 to 15 yrs	8 (33.3)	137 (46.8)
6) Age group $\leq$10 yrs	0 (0.0)	74 (25.3)

A computerized data bank was produced, based on the completed questionnaires. These data were analyzed using SPSS (ver. 9) and Stata (ver. 6). For this analysis the odds ratio statistic was used and for the multivariate analysis the logistic regression method was performed. To select a model the backward elimination procedure was used, starting with a complex model and successively taking out terms.

Table 3 Frequency of study variables in case and control groups and estimation of crude and adjusted odds ratio.

Variables	Cases No (%)	Control No (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	*P*-value
History of tick bite*					
Negative	14 (63.64)	296 (99.00)	1.00	1.00	
Positive	8 (36.36)	3 (1.00)	56.38 (13.48—235.86)	105.89 (9.32—1202.44)	0.000
History of contact with livestock (past 12 months)**					
No contact at all	3 (12.5)	134 (45.12)	1.00	—	
Temporary contact	9 (37.50)	95 (31.99)	4.23 (1.11—16.04)	—	
Constant contact	12 (50.00)	68 (22.90)	7.88 (2.15—28.88)	—	
Slaughter history					
No history or slaughtering; only in religious ceremony	6 (25.00)	237 (82.29)	1.00	1.00	
Slaughtering as a constant or temporary job	18 (75.00)	51 (17.71)	13.94 (5.27—36.86)	7.57 (2.21—25.91)	0.000
Presence of designated place for livestock at home					
Negative	9 (37.50)	208 (71.97)	1.00	1.00	
Positive	15 (62.50)	81 (28.03)	4.28 (1.80—10.17)	2.91 (0.81—10.44)	0.081
Taking care of livestock at home**					
Negative	4 (16.67)	130 (43.62)	1.00	—	
Positive	20 (83.33)	168 (56.38)	3.87 (1.29—11.59)	—	
Occupation***					
High risk occupations (groups 4, 5, 6)	16 (66.67)	203 (93.12)	1.00	1.00	
Low risk occupations (groups 1, 2, 3)	8 (33.33)	15 (6.88)	6.76 (2.49—18.35)	4.97 (0.97—25.43)	0.040
Age					
$\leq$15 yrs	3 (12.50)	127 (42.33)	1.00	1.00	
16—40 yrs	13 (54.17)	135 (45.00)	4.08 (1.14—14.64)	1.91 (0.37—9.89)	0.439
>40 yrs	8 (33.33)	38 (12.67)	8.91 (2.25—35.27)	7.32 (1.06—50.26)	0.043
Education years****					
$\leq$5 yrs	13 (54.17)	159 (63.35)	1.00	1.00	
$\geq$6 yrs	11 (45.83)	92 (36.65)	1.46 (0.62—3.39)	10.60 (1.89—59.33)	0.002
Sex**					
Female	7 (29.17)	157 (52.33)	1.00	—	
Male	17 (70.83)	143 (47.67)	2.66 (1.07—6.62)	—	
Nationality					
Iranian	19 (79.17)	226 (78.75)	1.00	1.00	
Afghan	5 (20.83)	61 (21.25)	0.97 (0.35—2.72)	4.66 (0.66—33.00)	0.023

* One case had only a history of crushing a tick on her body and the other seven cases had a history of tick bite.
** These variables were eliminated from the model in logistic regression analysis.
*** Job groups are according to those mentioned in Table 2. Crude odds ratio does not include age groups below ten years.
**** Crude odds ratio does not include age groups below six years.

Table 4 Epidemiologic characteristics of female cases.

No.	Special place for livestock in home	Nationality	Living environment	Occupation	History of tick bite	Slaughter history
1	Positive	Iranian	Rural	Housewife	Negative	Negative
2	Positive	Iranian	Rural	Housewife	Negative	Positive
3	Positive	Iranian	Rural	Housewife	Positive	Negative
4	Positive	Iranian	Rural	Housewife	Positive	Negative
5	Positive	Afghan	Rural	Housewife	Negative	Positive
6	Negative	Iranian	Urban	Housewife	Positive	Positive
7	Negative	Iranian	Urban	Ex-teacher	Negative	Positive

At each stage the term in the model that had the largest *P*-value was eliminated and it was checked that its parameters equaled zero. Maximum likelihood (ML) estimation was calculated by using the likelihood ratio test.[14] Asymptotic standard errors (ASE) were used to find confidence intervals for parameters in the model.

Results

Table 2 compares demographic data for cases and controls. In the univariate analysis (Table 3) a significant relationship was found between those in the case group and the following variables: history of tick bite, history of contact with livestock within the past 12 months, slaughter history, having a designated place for livestock at home, history of taking care of livestock at home, occupation, age and sex.

With the sampling methods, only one person was selected from each family. However since random numbers were used for the selection of controls from the communities of 200 people, there may have been more than one person selected from one family. But the design effect would be too small to be considered.

In multivariate analysis (logistic regression) some of the variables (such as nationality), which in univariate analysis showed no relationship with being in the case group, clearly showed a significant relationship. Some of the variables (such as sex), which in univariate analysis had a significant relationship, were eliminated from the model.

In total, five cases and 61 controls were from Afghanistan, which consisted of almost 20% of both cases and controls. This proportion was equal in cases and controls, but in adjusted analysis (Table 3) 'nationality' clearly became a risk factor (OR $= 4.66$, 0.66—33.00, [$P = 0.023$]).

If housewives as a separate occupation group are compared with other groups, both in crude analysis (OR $= 0.56$, CI: 0.19—1.59) and adjusted analysis (OR $= 0.45$, CI: 0.11—1.87), no significant relationship can be found. In this study, seven out of 24 cases were female and Table 4 shows some of the most important epidemiologic characteristics of the female cases.

For the variable 'living environment' the territorial partitioning of areas (rural and urban) was not followed. Instead it was considered as an ordinal variable (urban area, urban area with rural culture, rural area) and it was left to our interviewers to judge according to their instructions. No significant relationship was found in either univariate or multivariate analysis of the living environment.

Discussion

In this study the most important risk factors for being in the case group were conditions of close contact with livestock (such animal husbandry and slaughtering livestock), having an age above 40, and a history of tick bite.

In 1991 in a study in the northern part of Senegal (rural areas), the most important risk factors were sleeping outside during seasonal migration, tick bite and contact with sick animals. Seropositivity rates increased significantly with age of nomads.[15] In another case-control study in 1992 in a South African rural community, antibody prevalence among farmers increased with age. Other risk factors were physical contact with ticks or tick bite, contact with a recognized CCHF case, and handling of livestock.[16]

In this study, controls were selected from the general population of Zabol and Zahedan districts and were generally representative of the study population. The cases were IgM and/or IgG ELISA positive patients, who were diagnosed and reported to the Center for Diseases Control (CDC) of Iran. According to the surveillance forms of these cases, all were identified and reported as having suspected CCHF

by hospitals. As previously mentioned, this infection has sub-clinical cases and in addition not all clinical cases become hemorrhagic.[17] It is therefore thought that these cases are representative of the severe cases within the study population.

In the univariate analysis (Table 3) of the variable 'education years', the age group '6 years and younger' was omitted. Although they are illiterate, they are not in the school-age range, so regarding them as illiterate is not appropriate. The situation for occupation was similar. In univariate analysis of occupation groups, the age group '10 years and younger' was omitted as this age group cannot usually have an occupation. However, for both these variables, since the elimination of the above age groups in logistic regression had no important effect, all age groups were included in the modeling process.

In the analysis of the variable 'education years', the chance of falling in the case group is unexpectedly higher for subjects with five years education or more. This may be one of the consequences of selection bias.

It is not surprising to see shepherds, farmers, butchers, and slaughterhouse workers as being at risk. These results are consistent with reference books[18] but more important were the results concerning housewives. As stated in the introduction, in some reports up to 81% of suspected cases have been in the housewives' group. When interpreting the relationship of housekeeping with this disease we must consider several parameters. Duties of housewives differ in different cultures. In this study seven out of 24 cases were female, and of these six were housewives and each had at least one of the known risk factors of the disease (Table 4).

In the univariate analysis, no significant relationship is seen between nationality and being in the case group. But in the multivariate analysis, nationality clearly shows a meaningful relationship (see Table 3). This relationship has to be related to more Afghan refugees being in contact with more risk factors. Of the five Afghan cases in this study, all were residents of rural areas (three in urban areas with rural culture, two in rural areas), all had a positive history of livestock slaughtering, four had a special place for livestock in the home and two had a history of tick bites.

The highest odds ratio belonged to the 'history of tick bite'. Of the 300 controls, only three could remember a tick bite within the previous 12 months, while of 24 cases, eight could remember it — one had crushed a tick on her body and the other seven cases had history of tick bite (see Table 3). This sharp difference, without any doubt, relates at least partly to 'recall bias'.

In a study in South Africa, five out of 31 infected CCHF cases had a history of tick bite.[19] In a study in Senegal (OR = 3.52, $P = 0.026$) and in another case-control study in South Africa (OR = 6.36, CI: 1.68—35.49), a history of tick bite or tick contact were among the most important risk factors[15,16]

As mentioned before, no significant relationship was found between the living environment and this disease. This probably reflects similar conditions for the transmission of the infection in urban and rural communities. This also may be due to the equal presence of risk factors in these two environments or because the urban population is originally from rural areas and therefore travels frequently, for various reasons, to rural areas.

The chance of contracting the disease increases with age (chi-square for linear trend = 11.993, $P = 0.002$) (Table 3) both in multivariate and univariate analysis; odds ratios show the same trend. Table 2 shows that there are no cases in the age groups 1—10 years and >60 years. However, exclusion of these age groups from control groups in logistic regression changes the results very little from those in Table 3. In no other studies carried out in other countries is age referred to as a risk factor. However, in serologic studies seroprevalence frequently increases with age. In a study on a nomadic population of northern Senegal, seroprevalence increased significantly with age to a maximum of 31.6% among those 60—79 years old.[15] In another study in South Africa, antibody prevalence among farmers increased with age ($P < 0.001$) and was correlated with handling lambs.[16]

This study shows that even though tick bite is one of the most important risk factors for CCHF, it cannot explain all cases and there are other important risk factors such as high-risk occupations and having contact with livestock. Even taking care of livestock for a short period at home can increase the chance of acquiring CCHF. There was no increased risk of infection for housewives and in fact it is high-risk activities such as taking care of livestock and taking part in slaughtering that determines the risk of infection.

These results can be used in health promotion activities and in defining the high risk groups. Determination of prevalence and incidence of this disease in future studies can further improve our understanding of the epidemiology of this infection.

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