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Nosocomial Outbreak of Crimean-Congo Hemorrhagic Fever (CCHF) among health workers in Kandahar Province, Afghanistan, 2023: A Case-Control Study

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ABSTRACT

Background: Since 2008, more than 1600 cases of Crimean and Congo Hemorrhagic Fever (CCHF) have been reported in Afghanistan. We aimed to investigate the nosocomial outbreak of CCFH and its associated factors among health workers in Kandahar Province.
Methods: This case-control study was conducted during CCHF outbreak in a private hospital during April 2023 in Kandahar Province with 1:3 ratio of cases to controls. Cases were confirmed for CCHF infection using PCR and ELISA tests. Controls were selected from health workers of the general population. Data were managed and were analyzed using Epi Info v7.2.5 and STATA MP17 with an alpha level of 0.05 as well as 95% confidence. Penalized Logistic Regression (PLR) with firth correction was used.
Results: Fourteen cases and 43 controls were enrolled with mean age of 24±6.25 and 29±11.26 yr respectively. All the cases and two-third of controls were health workers while nine (64%) of cases and 39 (88%) of controls were male. Prominently, fever 64% and agitation/mood swings (64%) were recorded among cases. Multivariate analysis of the exposures showed that contact with CCHF suspected individual without considering Personal Protection Equipment (PPE) (OR 95%: 59.6, 6.02 – 589. 62P=0.001) was significantly associated with CCHF infection risk leading to emergence of this outbreak ($P<0.05$).
Conclusion: CCHF outbreak in this setting was associated with negligence of preventive measures by health workers. It is recommended for healthcare facilities to ensure the availability and utilization of PPE and enforcement of infection control practices while undertaking health education programs on transmission routes and preventives measures of CCHF.

Keywords: Crimean-Congo Hemorrhagic Fever, Nosocomial, Risk Factors, Case-Control, Penalized Logistic Regression, Afghanistan

Introduction

Crimean-Congo Hemorrhagic Fever (CCHF) is a tick-borne viral disease caused by Nairovirus, which belongs to the Bunyaviridae family. With a case fatality rate ranging between 5% and 50%, this highly pathogenic virus is commonly endemic in the Middle East, Asia, the Balkans, and Africa (1). This virus is mainly transmitted through the *Hyalomma* genus of *Ixodid* ticks, which act as both reservoir and vector for the virus. The virus primarily infects cattle, goats, sheep, and hares, which act as reservoirs. Although animals do not exhibit symptoms, their blood and tick bites serve as significant sources of human infection. Contact with infected blood and bodily fluids are human-to-human transmission routes, while improper sterilization of medical equipment (e.g., contamination of medical supplies) in healthcare settings has also been reported (2).

The incubation period for Crimean-Congo Hemorrhagic Fever (CCHF) varies depending on the mode of acquisition. This period usually ranges between 1 and 3 days, with a maximum of 9 days reported after tick bite infection. However, this period extends to 5-6 days after encountering infected blood or bodily fluids, with a maximum reported of 13 days (1). In the early stages of the disease, symptoms include fever, headache, and muscle pain. These are often followed by gastrointestinal symptoms such as nausea, vomiting, and diarrhea, as well as respiratory symptoms such as cough and sore throat. Patients may also experience abdominal pain, joint pain, and dizziness. As the disease progresses, more severe symptoms may occur, including bruising, petechiae (small, red, and purple spots on the skin), and bleeding from the mouth, nose, or other sites. Some patients may also develop neurological symptoms, such as confusion, agitation, and seizures (3).

The very first outbreak of CCHF was recorded in Takhar Province of Afghanistan in 1998, with 19 cases and 12 deaths (4). Neighboring countries of Afghanistan, such as Pakistan (5) and Iran (6), however, experienced recorded epidemics of this virus during that time. With the establishment of active CCHF surveillance under the roof of the National Diseases Surveillance and Response (NDSR) department in 2007 by the Ministry of Public Health (MoPH), CCHF outbreaks in Afghanistan became more likely to be reported and investigated. During 2007-2018, Afghanistan recorded 1,284 CCHF cases, with a case fatality rate of 43.4% during 2006-2018. The majority of cases were recorded from Herat and Kabul provinces, while some provinces, such as Kandahar, recorded a lower number of cases. More than two-thirds of cases were male, while housewives (15%) and health staff (13%) were the most frequent occupational groups (7).

Infectious diseases could potentially be transmitted in healthcare facility settings among health workers (8). The very first case of nosocomial CCHF among health workers was reported from Pakistan in 1980 (9), followed by such outbreaks emerged in countries with a context similar to that of Afghanistan. Tajikistan reported health workers as one of the predominant risk groups for CCHF, and the extremely high case-fatality rate of CCHF cases was associated with nosocomial/direct blood contact (10). Similarly, the emergence of CCHF infection among health workers after attending to infected patients has been reported from Gujrat state in India (11). Furthermore, an anti-CCHF IgG seroprevalence study of health workers in two endemic regions of Iran found a higher seropositivity rate among those health workers with skin contact with bodily fluids of the patients (12). A multi-center study of healthcare-associated CCHF cases among health workers in Turkey over a 12-year span reported 51 nosocomial exposures, with 25 confirmed cases of CCHF and 4 deaths (13).

In late April 2023, a cluster of CCHF-suspected cases among healthcare workers at a private hospital in Kandahar Province of Afghanistan was reported. The cluster was reported days after the admission of a confirmed CCHF case from the neighboring province of Helmand to this health facility.

We aimed to investigate this outbreak and explore the associated risk factors. Furthermore, the findings of this study could provide a foundation for evidence-based recommendations to prevent similar events in the future.

Materials and Methods

This case-control study was conducted to investigate the suspected outbreak of CCHF among health workers at a private health facility in Kandahar Province from April 27th to May 1st, 2023. This hospital is in the city of Kandahar and offers various specialties, including an infectious disease ward that admits patients from Kandahar Province as well as neighboring provinces. The index case of this outbreak was a 40-year-old housewife admitted from Helmand Province to this health facility, where she received the required management and investigations. Three days after admission, the patient eventually died due to CCHF. However, five days after the admission of the index case, a cluster of suspected CCHF cases among health workers at this health facility was reported.

Operational Definition

Case

The investigation team adapted the case definition of the WHO and the National Diseases Surveillance and Response (NDSR) of Afghanistan to identify suspected cases and proceed with confirmation. According to this case definition, a suspected CCHF case is defined as a patient with the sudden onset of high-grade fever (>38.5 °C) and exposure to at least one of the following risk factors in the last 15 days:

- Experiencing a tick bite or crushing a tick with bare hands.
- Coming into direct contact with animal blood or other tissues during or immediately after slaughter.
- Having direct contact with the blood, secretions, or excretions of a CCHF case.
- Residing in or visiting an area that is endemic or affected by an outbreak where exposure to livestock or ticks was possible.

In addition, laboratory confirmation using ELISA for IgG and IgM antibodies, along with Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) for the virus, was required for the enrollment of individuals in the case group.

Control

The control group for this study comprised health workers employed in wards other than the infectious diseases ward at the hospital, health workers from other neighboring health facilities in Kandahar City, and members of the general population who exhibited no clinical symptoms consistent with CCHF and/or were not confirmed by laboratory tests. Controls were selected at a ratio of 1:3 (three controls for each case), with two-thirds of the controls being health workers. On the other hand, selection of controls from general population paved the way for exploring risk factors and better causal inference based on available literature (14).

Preventive measures

Preventive measures were defined as the use of Personal Protective Equipment (PPE) for infection control, as outlined by the Centers for Disease Control and Prevention (CDC) of the United States of America (15). The absence of any component of PPE during the treatment and management of the CCHF index case was classified as "not considering preventive measures" in the study's exposure assessment.

The cases were line-listed, and clinical specimens were collected and delivered to the Kandahar Regional Reference Laboratory (KRRL) for confirmation of the presence of the CCHF virus. ELISA for IgG and IgM antibodies, along with RT-PCR for the virus, were used for confirmation among suspected patients.

For data collection, a structured questionnaire was designed to include socio-demographic factors, clinical features (e.g., signs, symptoms, and platelet levels of cases), and exposure history. The questionnaire was piloted on a smaller scale (15 individuals) and analyzed for internal consistency, with Cronbach's alpha determined to be 0.7 in IBM SPSS 26 (IBM Corp., Armonk, NY, USA). The reliability analysis indicated good internal consistency, with a Cronbach's alpha of 0.81, which exceeds the acceptable threshold of 0.7. Based on the reliability analysis results, the finalized questionnaire was administered during the data collection process.

The data collection team was oriented regarding the study tool's aspects and procedures. Consent forms were completed and signed by the cases and controls participating in the study after the data collection team provided a full explanation and ensured participants understood their rights. Additionally, a publication consent form was obtained from the patients, and data were subsequently collected.

The collected data were entered into Epi Info v7.2.5 analyzed using both Epi Info and STATA MP17. Descriptive findings were represented using frequencies and percentages. To identify associated exposures and risk factors related to the outbreak, a two-stage analysis was conducted.

In the first stage, 12 exposures reported by the cases and controls were analyzed using bivariate methods to calculate the odds ratios (OR) individually. Exposures that were not significantly associated with the study's outcome during bivariate analysis were excluded in the second stage. Due to the presence of sparse data and the ultra-low prevalence of risk factors in some exposure variables, Penalized Logistic Regression (PLR) with Firth correction and boosting was used for multivariate analysis. A 95% confidence interval and an alpha level of 0.05 were applied, as recommended in similar settings. The goodness of model fit and the explanation of model variance were assessed using Cox-Snell/ML and Cragg-Uhler/Nagelkerke R-squared values, which were presented as percentages (16, 17).

Ethical Considerations

This case-control study was conducted in full adherence to the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from study participants prior to data collection, following an explanation of the study's purpose, procedure, potential risks, benefits, and their right to withdraw from the study at any time. Furthermore, participants were assured of the confidentiality and anonymity of their data.

Results

The suspected outbreak of CCHF among health workers in a private hospital in Kandahar Province began on April 27th and lasted for 4 days (Fig. 1). Blood specimens from suspected health worker cases were collected, and RT-PCR and ELISA antibody tests were performed to confirm the suspected cases of CCHF. Of 28 health workers working in the infectious diseases ward of the hospital, 14 were confirmed by the tests and enrolled as cases in this study. Consequently, three controls were enrolled for each case from different populations. Among the controls, one-third were from the general population, while the rest were health workers from infectious diseases wards of other health facilities.

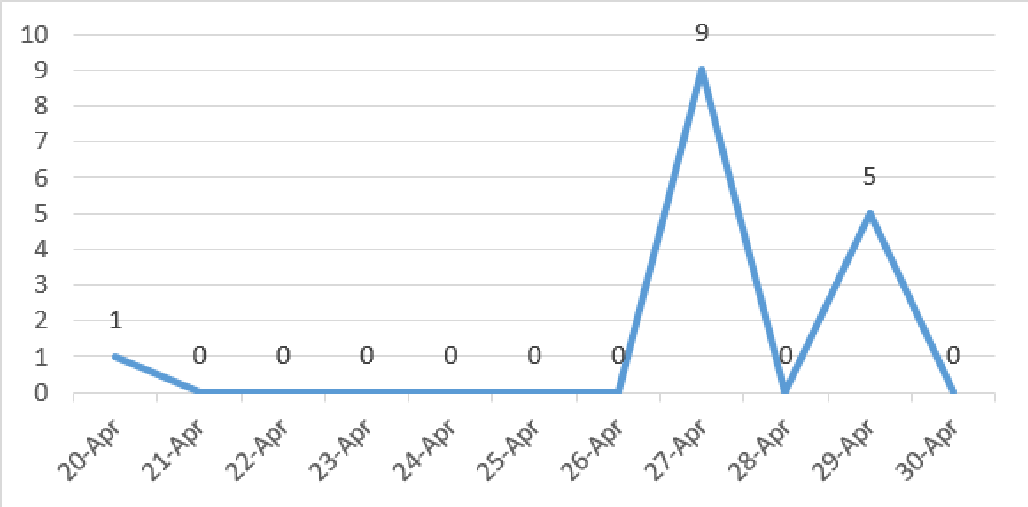

Figure 1: Epidemic curve of CCHF nosocomial outbreak in Kandahar province, 2023.

The cases were assessed for clinical manifestations of the infection. Most cases reported high fever (9, 64%), agitation and/or mood swings (9, 64%), headache (7, 50%), and myalgia (5, 43%) as the main signs and symptoms during the infection period (Fig. 2). However, only 1 (7%) case reported petechiae, mouth and/or gum bleeding, and severe nose bleeding. Additionally, there were no reports of thrombocytopenia, and the median platelet level was 200,000, with an interquartile range of 104,000. The cases were treated with ribavirin as well as other symptomatic treatments, and no deaths were reported in this cluster of cases.

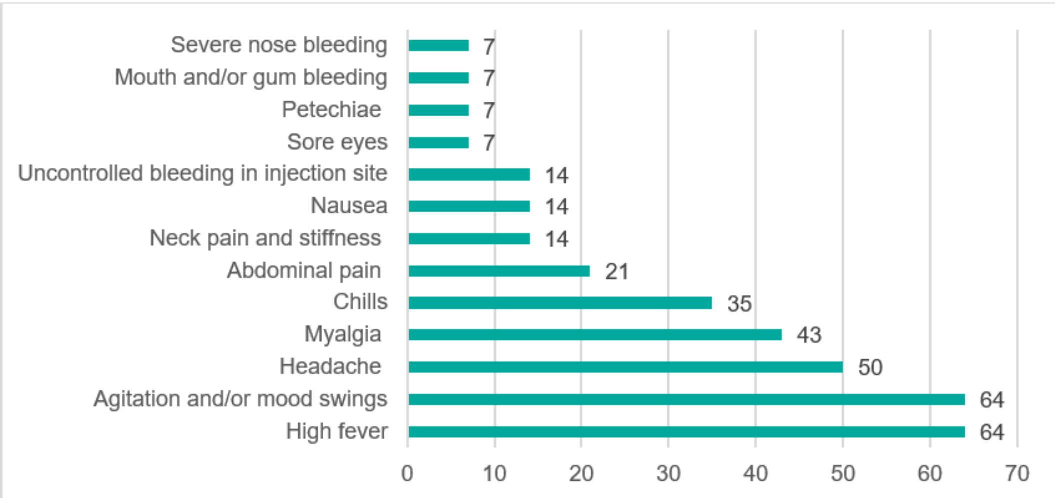

Figure 2: Clinical sign and symptoms of cases (N=14)

A total of 14 cases and 43 controls were enrolled. The average age of the cases was 24 (SD = 6.25) years, while for the control group it was 29 (SD = 11.26) years. Among the cases, more than four-fifths (12, 85%) were in the 20-35 age category, and this age category was prominent in the controls, with 33 (77%) in this group (Table 1). In terms of sex distribution, nearly two-thirds of the cases (9, 64%) and more than four-fifths of the controls (39, 88%) were male. All of the cases and controls were from Kandahar Province, residing in both urban and rural areas. All the cases were from urban settings, while only 9 (20%) of the controls were from rural areas.

Table 1: Sociodemographic characteristics of case and control groups.

Variable	*Case (N=14) n (%)*	*Control (N=43) n (%)*	*P-Value*
Age (yr)			
20-<35	12(85)	33(77)	0.58
35-<50	2(15)	5(11)	
>50	--	5(11)	
Sex			
Male	9 (64)	39 (88)	0.036
Female	5 (36)	5 (12)	
Marital Status			
Single	8 (57)	14 (31)	0.089
Married	6 (43)	30 (69)	
Living environment			
Rural	--	9 (20)	0.066
Urban	14(100)	35 (80)	
Occupation			
Healthcare worker	14 (100)	28 (64)	0.008
Other	--	16 (36)	

Bivariate analysis of the exposures among cases and controls showed that of the 12 potential exposures for CCHF infection, four were significantly associated with the CCHF outbreak cases (Table 2).

Table 1: Bivariate Analysis of the exposures.

Exposure	*Case (N=14) n (%)*		*Control (N=43) n (%)*		*OR (95 CI)*	*P-Value*
	Yes	No	Yes	No		
Having contact with livestock	0 (0)	14 (100)	7 (16)	37 (84)	0 (0.0 – 1.6)	0.11
Slaughtering livestock	0 (0)	14 (100)	4 (9)	40 (91)	0 (0.0 – 3.5)	0.31
Transporting livestock	0 (0)	14 (100)	3 (7)	41 (93)	0 (0.0 – 5.7)	0.32
Consuming raw milk	0 (0)	14 (100)	5 (11)	39 (89)	0 (0.0 – 2.5)	0.18
Touching raw meat	0 (0)	14 (100)	1 (2)	43 (98)	0 (0.0 – 59.7)	0.56
Allocated space for livestock in home	0 (0)	14 (100)	5 (11)	39 (89)	0 (0.0 – 2.5)	0.18
Contact with a person who is bleeding without considering preventive measures	13 (92)	1 (8)	6 (14)	38 (86)	82 (9.04 – 849)	0.01
Accidental skin-wounding stab from needle containing another person’s bodily fluid or blood	4 (29)	10 (71)	2 (4)	42 (96)	7.98 (1.25 – 69.81)	0.01
Having a contact with needles, syringes, gauze pads during discarding it	7 (50)	7 (50)	4 (9)	40 (91)	9.44 (2.18 – 46.19)	0.01
Experience splash of an infected patient bodily fluid and/or blood on to you	5 (36)	9 (64)	0 (0)	44 (100)	Undefined (4.85 – Undefined)	0.01
Diagnosed with CCHF during last six months	0 (0)	14 (100)	1 (2)	43 (98)	0 (0.0 – 59.71)	0.56
Receive a blood transfusion recently (last one month)	0 (0)	14 (100)	6 (14)	38 (86)	0 (0.0 – 1.98)	0.14

Among the cases, 13 (92%) had contact with the infected patient without considering protective measures (OR, 95% CI = 82, 9.04–849, *P* = 0.0001). Additionally, 4 (29%) experienced accidental skin-wounding from a needle containing the infected patient's bodily fluids (OR, 95% CI = 7.98, 1.25–69.18, *P* = 0.01), 7 (50%) had contact with needles, syringes, and/or gauze pads used for the infected patient during the discarding procedure (OR, 95% CI = 9.44, 2.18–46.19, *P* = 0.001), and 5 (36%) had experienced blood splash from the infected patient during treatment and management (OR, 95% CI = Undefined, 4.85–Undefined, *P* = 0.001). None of the cases had previous contact with livestock handling, slaughtering, or raw meat, and these exposures were not significantly associated with the outbreak.

Significant associated risk factors from the bivariate analysis were introduced to the multivariate analysis model using Penalized Logistic Regression (PLR) with Firth correction (Table 3). Based on the Cox-Snell/ML and Cragg-Uhler/Nagelkerke R-squared values, the regression model explained between 44.1% and 67.2% of the variance in the variables. Additionally, the Wald chi-square results for the model indicated significance (Wald Chi-Square (4) = 17.23, *P* = 0.001). The multivariate analysis revealed that only one exposure, contact with the infected patient without considering protective measures, was significantly associated with CCHF infection among the study cases (OR, 95% CI = 59.62, 6.02–589.62, coefficient = 4.08, *P* = 0.0001). The remaining three exposures were not found to be significantly associated with the study outcome in this model.

Table 3: Multivariate analysis of the exposures.

Exposure	***Odds Ratio (95% CI)***	***Coefficient***	***Std. error***	***P-value***
Contact with a person who is bleeding without considering preventive measures	59.6 (6.02 – 589.62)	4.08	1.17	0.01
Accidental skin-wounding stab from needle containing another person's bodily fluid or blood	0.7 (0.08 – 5.72)	- 0.34	1.06	0.75
Having a contact with needles, syringes, gauze pads during discarding it	0.38 (0.05 – 2.81)	- 0.24	1.01	0.34
Experience splash of an infected patient bodily fluid and/or blood on to you	11.2 (0.46 – 271.92)	2.41	1.62	0.14

Discussion

The confirmed CCHF outbreak among health workers of a private hospital in Kandahar during late April 2023 lasted for four days and 14 health workers were eventually infected. We aimed at exploring nosocomial outbreak of CCHF elucidates that lack of preventive measures consideration led to this emergence of this outbreak. Lack of preventive measures consideration was reported during attendance of healthcare workers during index case admission.

Viral hemorrhagic fever diseases in healthcare settings have been mainly associated with gaps in infection control practices and lower compliances to preventive measures reported in available literature (18). On the other hand, susceptivity of healthcare workers to CCHF among hospital workers has been reported in Iran (12). Mainly, preventive measures being undertaken by health workers in Infection Control and Prevention (IP&C) includes using PPE kits by responsible health workers (19). Association of high compliance with PPE usage among health workers and lower chances of CCHF infection has been earlier explained in Türkiye (20) in contrast to findings of this study. Furthermore, secondary cases of a nosocomial outbreak of CCHF in Rajasthan state of India were avoided through barriers and preventive measures (21). Importance of PPE in control and prevention of infectious diseases has been elucidated in context of other infectious disease such as MERS as well (22).

Main clinical sign and symptoms among the infected health workers were fever and myalgia which is in accordance with the cluster of CCHF nosocomial cases in one of the hospitals in Türkiye (23) and Iran (24,25). Furthermore, the incubation period between admissions of the primary case to the hospital to emergence of the outbreak was exactly 5-7 days, which has been earlier, indicated in context of nosocomial infection of the CCHF in similar settings (23). Males were predominantly present among the cases, which has been elucidated in similar contexts as well (20). Age category of 20-35 were mostly infected by CCHF in this outbreak that could reflect the presence of the younger generation among the health workers of the facility and may suggest the need for constant capacity building and attending of much experienced health workers in management of these challenging conditions.

While this study contributes valuable insights into the CCHF outbreak dynamics within a specific hospital setting in Kandahar, the generalization of these findings to other settings or populations should be approached with caution and in broader and longer fashion. Further research, ideally encompassing a broader range of healthcare settings in a longer period of time and multicentral approach, is necessary to validate and extend these findings. Additionally, other diagnostic tests such as prothrombin time (PT), liver function tests (LFT) and activated partial prothrombin clotting time (aPTT) were not performed due to contextual limitations. The presence of the tests mentioned would have added further insights into the clinical picture of this outbreak. On the other hand, despite selection of controls from multiple sources to minimize the bias, sparsity in some of the exposures were visible. This challenge was then addressed by analytical methods; however, further investigations in similar settings are required to address this analytical method.

In the light of this study's findings, importance of considering preventive measures has been elucidated to control the dynamic of the virus transmission in hospitals setting. Additionally, utilization of preventive tools such as PPE is strongly recommended to be practiced among health workers particularly those in charge of infectious diseases. Along with practicing preventive measures, it is recommended to enhance the level of understanding of health workers regarding CCHF and other viral hemorrhagic fever diseases could be enhanced through workshops and training programs. Findings of this study suggest the presence of the younger generation among the cases, which can set the floor for capacity building opportunities.

Conclusion

This study underscores the importance of strict adherence to preventive measures, particularly PPE usage, in healthcare settings to prevent CCHF and other viral hemorrhagic fevers. It recommends enhancing the knowledge of health workers through workshops and training programs to improve their preparedness for managing such infectious diseases. Moreover, further research in diverse healthcare settings and over longer times is necessary to validate these findings and develop more strategies that are effective for preventing CCHF transmission in hospitals.

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Conflict of Interest

The authors declare no conflicts of interest related to this study.

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