DOI: https://doi.org/10.32345/2664-4738.4.2025.13
UDK 616.98:578.834.1-036.22:614.4

EPIDEMIOLOGICAL TRENDS OF CRIMEAN-CONGO HEMORRHAGIC FEVER IN NINEVEH (Literature Review)

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Aim: to examine the patterns of Crimean-Congo hemorrhagic fever (CCHF) in Nineveh Province in Iraq between the years 1997 and 2017.

Materials and methods. There were 18 known cases where the disease was confirmed with laboratory tests and a large outbreak took place in 2010. Cases were spread out differently over different years, with particularly high numbers in 2012, 2013, 2016 to 2017 and 2018.

Results. According to the findings, better surveillance and measures are needed to help stop future outbreaks. Even with its seasonality CCHF outbreaks, increased vector control programs, better diagnostic tools as well as improved public health surveillance are still vital towards managing its spread. Despite prevalently acting as an antiviral remedy, there is no certainty on the usefulness of ribavirin in achieving lowered levels of mortality, and there is no vaccination approved.

Conclusion. The findings find an urgent need for the implementation of broad-based preventive measures, such as awareness campaigns on the training of healthcare workers and livestock handlers to minimize transmission risks. The future studies should be aimed at developing vaccines and perfecting rapid diagnostic methods to enhance the strategy of responding to the outbreaks.

Key words: Crimean-Congo Hemorrhagic Fever; Nairovirus; Epidemiology; Disease Outbreaks; Incidence; Prevalence; Zoonoses; Public Health Surveillance; Iraq.

Introduction. A fever usually comes on quickly when an infection spreads rapidly among humans and animals. But infected animals are healthy and do not show any signs which increases the chance of unnoticed transfer and makes this disease more dangerous. Crimean-Congo hemorrhagic fever (CCHF) is a severe contagious zoonosis disease caused by Crimean-Congo hemorrhagic Virus (CCHFV). Most cases of Crimean-Congo hemorrhagic fever virus (CCHFV) in Europe, North Africa and parts of Asia are spread through contact with Hyalomma marginatum ticks. Although other kinds of ticks may sometimes carry the virus, they usually do not cause the virus to be passed on. The affected animals though having the virus do not show clinical signs thus making the detection and prevention efforts more difficult [1]. The secondary transmission occurs by direct contact with body fluids like blood and secretions from infected patients which is of great risk especially health workers during treatment and funeral arrangements. The virus circulates in nature through a cycle of ticks, wild and domestic animals and sporadic human infections, where outbreaks are maximized during tick activity in the summer seasons [2]. The virus has seasonal pattern with a peak in tick activities during summers. The locations of the surrounding countries, especially Turkey and Iran have reported steady increases in the reported cases of CCHF since 2000, where more extensive surveillance has been required [3].

CCHF history

Between 1944 and 1945, soldiers in the Crimean Peninsula developed a disease, later known as Crimean-Congo hemorrhagic fever (CCHF). In 1956, the Belgian Congo released a statement saying the virus had been identified there, changing its name at that time. It is not completely clear when hemorrhagic fever was identified because historical stories from the 12th century do not have scientific support [1]. CCHF was initially recognized in Soviet soldiers in the Crimea in the year 1944 and was given the name 'Crimean hemorrhagic fever'. The first time when the virus was isolated was from a child in Congo during 1956, the virus was known as Congo virus [4, 5]. The first casualties were registered in 1979 in Iraq. The incident was identified to have led to the deaths of a number of doctors at this Yarmouk hospital- Baghdad because of the injury of a citizen in Baghdad city. The neighbor countries of Iraq including specifically Turkey and Iran had become an epidemic in in addition Uganda, Russia and Pakistan. [5].

CCHFV structure

CCHFV is grouped as the genus Orthonairovirus of the Nairoviridae family. The virus is formed in a spherical shape (~90–100 nm in diameter) with surface spike-like projections for the possible purpose of host cell attachment. With a single-stranded, negative-sense RNA (-ssRNA), genome, it has three ambisense segments (S, M, L). S segment encodes Nucleoprotein (NP), essential for viral RNA encapsidation to establish the Ribonucleoprotein(RNP) complex. The M segment encodes glycoproteins Gn and Gc that play a paramount role in viral entry and evading the immune system while the L segment encodes RNA-dependent RNA polymerase (RdRp) for genome replications and transcriptions. The ability of the virus to escape host immune responses is associated with the processing of Gn / Gc in the Golgi complex providing effective virion assembly procedures [6, 7]. RNA genome is encapsidated by protein N to provide the ribonucleoprotein (RNP) complexes. The encapsidation of the CCHFV is critical to replicative cycle and encasing of the genome in the virions. The replication and evasion of the immune system by Crimean-Congo hemorrhagic fever virus (CCHFV) is possible because viral RNA is packaged within the nucleocapsid during encapsidation. To develop treatments, it's important to understand this mechanism, because NP is vital for viral assembly, supporting RNA and managing immune response. NP is also important in the formation of spherical particles that look like in bunyaviruses which imply a possible role in the viral budding [2]. There is limited opportunity to compare the nucleoprotein of CCHFV with that of the Lassa virus. The structure of the NP of the Lassa virus has been solved, showing different ways the virus is able to bind to caps and avoid detection by the immune system. Researchers still need to investigate whether CCHFV has the same features found in other viruses.(Lassa virus LASV) [3]. The NP protein of the CCHFV is shaped in three dimensions, showing different places responsible for holding RNA and wrapping it. The structure enables the virus to protect its genes as it interacts with host elements, so it is an important target for antiviral efforts, Figure [1]. When RNA viral is not present, the NP seems to occur in the form of a monomer because RNP binds RNA weakly [8;9].

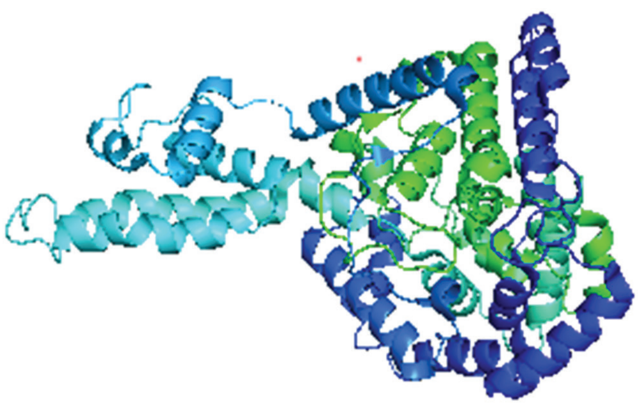

Fig. 1. Crystal structure of CCHFV NP (https://swissmodel.expasy.org/repository/uniprot/C7F6X7)

CCHFV glycoproteins (Gn and Gc) play roles in entry/fusion, virion formation and evasion from immune system. It is thought that both Gn and Gc mediate entry, fusion. The Pre-Gn and Pre-Gc are commonly localize at Golgi complex of the host cell. The Figure [2] gives the entire layout of the CCHFV, showing the outer protein layer protecting the genome. Thanks to its complicated architecture, HIV can more easily get into cells and interact with the immune system. Apart from that, an M segment encodes nonstructural protein (NSM) [1]. Nairoviruse large L protein has an unusually (~4000 amino acids). The L protein is used for transcription of RNA of the virus and the replication of viral genome [9].

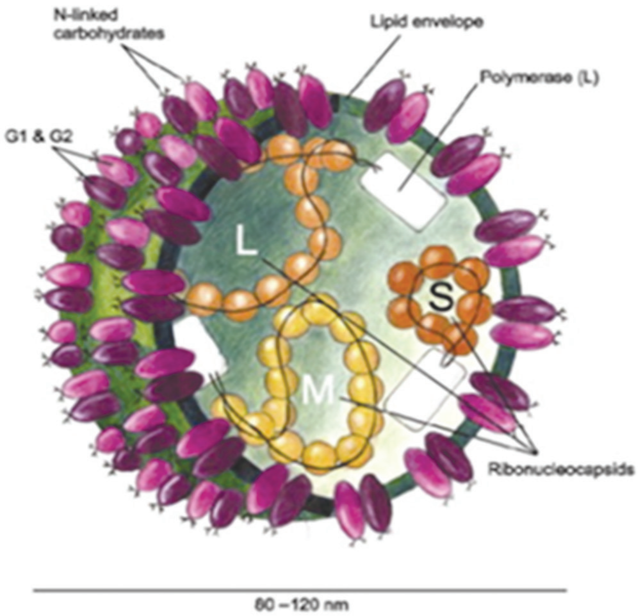

Fig. 2. CCHFV structure (https://www.sciencedirect.com/topics/neuroscience/crimean-congo-hemorrhagic-fever)

Clinical presentation

Either asymptomatic or mildly symptomatic, CCHF infections can occur. The disease takes four definite stages to develop. incubation, prehemorrhagic, hemorrhagic, and convalescence. The incubation period is usually 2-7days, it is dependent on the route of infection and the viral load. Early symptoms are like other common febrile diseases such as fever, aches in the muscles, nausea, headache, and sore-throat. In a severe form, there is rapid conversion to hemorrhagic manifestations with profuse bleeding, thrombocytopenia and various multi-organ involvement. [1, 9 10]. Seriousness of CCHF correlates with high viremia, low titers of CCHFV antibodies, degree of thrombocytopenia, prolonged clotting times, haemorrhage and high prevalence of pro-inflammatory cytokines. Convalescent phase starts from 10-20 days following the commencement of illness. The patient in this stage experiences feeble pulse, tachycardia and also loss of hearing, memory and hair. But, the last consequences have been reported in a few outbreaks [11].

In figure (3), immunoglobulin antibodies IgG against CCHFV could be detect using ELISA in patient serum from the 7th day of the onset of infection. A cross-sectional survey of this study is carried out to identify the number of human cases of Crimean-Congo hemorrhagic fever (CCHF) in Nineveh Province. The researchers looked at laboratory-confirmed cases to spot trends in the disease and to identify factors that cause transmission. [3, 12]. Many reports record IgG and IgM antibody responses by days 7-9 of illness in all survivors of the infection initiation. IgM persists for up to 4 months in convalescence period, while IgG remains detectable for at least 5 years. Epidemiological research shows that cases of CCHF are rising in Iraq, especially in the south, where there are more ticks. Data from WHO for 2021 to 2023 found 986 reported cases and 16.8% of them were fatal. Although most species of birds seem to be resistant to infection, CCHFV can be found in blood for one to four days and in visceral organs for up to five days after experimental infection [13].

Therapy and Vaccination

Because it has a high epidemic potential, causes death in many cases and has no effective treatment, the WHO has classified Crimean-Congo hemorrhagic fever (CCHF) as a priority pathogen. The WHO highlights how necessary is to strengthen R&D on vaccines and therapies for CCHF. Such improvements should increase CCHF prevention and management by the end of 2030.

Even so, many doubt its effectiveness in curing CCHF. Early use of ribavirin saved lives, but its results differed between various studies. Preliminary results indicate that treating severe hemorrhagic cases with both corticosteroids and ribavirin

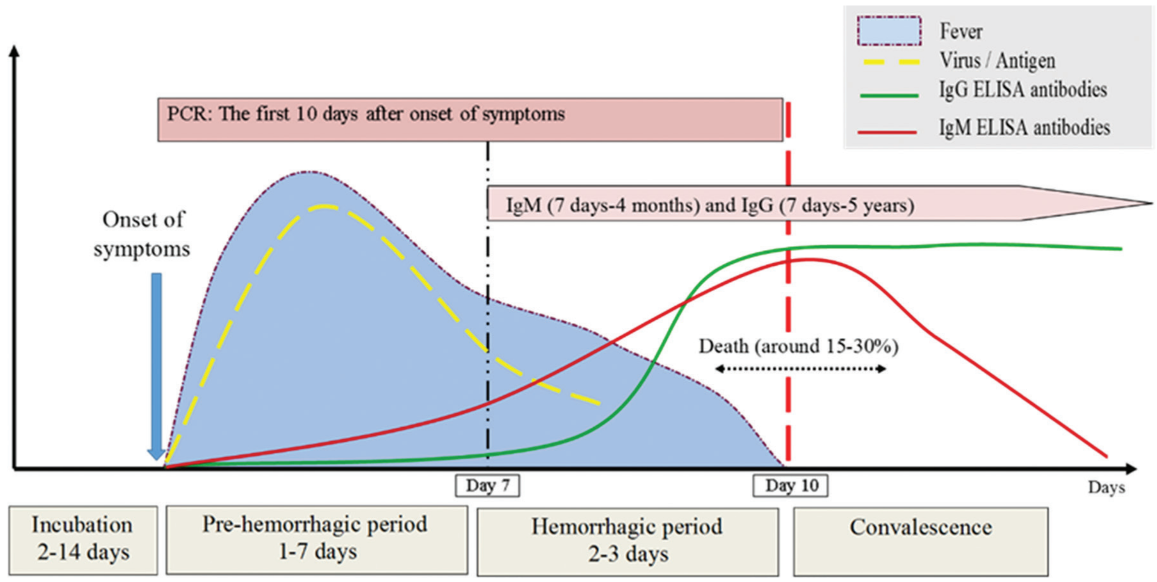

Fig. 3. Progression clinical phases of CCHFV infection with the typical serological course

might improve patient prognosis. But the effectiveness of ribavirin in preventing mortality is still inconclusive. As no vaccine has been approved, preventive measures include effective isolation of patients, better biosafety for healthcare workers, and regular vector control programs for tick constraints [8].

Nowadays, there is no safe and effective vaccine available for human against CCHFV. Since 1970, a vaccine was developed based on CCHFV cultivated in suckling mouse brain [10]. Next attempt, anti- CCHFV antibodies were developed in vaccinated individuals with low activity. The vaccine is licensed in Bulgaria and used on a small scale in Eastern Europe. Newly developed mouse models that mimic human CCHFV are useful to promote vaccine.

The Immune System of People After SARS

Research in Uganda discovered that survivors of CCHF had antibodies and memory T-cells that could fight the infection for up to 9 years after they became ill. This makes us think that such vaccines may give lasting protection and be helpful for future vaccine design.

Issues Faced by the Vaccine Development Process

So far, no vaccines for CCHF have received approval. The findings suggest that NP and Gn/Gc make good targets for a vaccine, although immune escape by the virus can affect its effectiveness.

Therapeutic Efficacy

WHO research points out that antiviral drugs are urgently needed, since ribavirin is questionable in its effectiveness. Latest findings suggest that blood pressure control early on can reduce the risk of death, yet it does not cure the disease [14].

Prevention

CCHF is best prevented by separating patients, providing PPE for caregivers and managing insects. All healthcare facilities need to follow standard steps to lower the spread of germs inside the hospital and public health strategies must focus on finding and reporting ticks as well as signs of disease in the community..To prevent nosocomial transmission, precautions face shields, surgical masks, double gloves, surgical gowns, and aprons should be used [10]. Health-care workers should be educated about the modes of getting infected with CCHF virus and for strict implementation of infection control measures within health-care facilities [15]. CCHF is still a matter of concern to the Nineveh public health in the regard of frequent outbreaks reported through the livestock contact with ticks. Boosting surveillance programs and tick controlling efforts are critical to prevention of human cases. Going forward, attention should be placed on strengthening healthcare procedures and creating effective vaccines to alleviate the effect of disease in the region.

Laboratory Diagnosis

There are different laboratory techniques which are used for the diagnosis of CCHF, some of which have higher sensitivity and specificity than the others. The common procedures are immunofluorescence (IFA), enzyme-linked immunosorbent assay (ELISA) and reverse transcription polymerase chain reaction, (RT-PCR). ELISA and IFA find a broad application for serological detection of IgG and IgM antibodies but may not provide early-stage confirmation as it is associated with a delayed immune response. The molecular detection based on RT-PCR and quantitative real-time PCR (qRT-PCR) provides greater specificity, allowing for detection of viral RNA in the samples from the blood at the acute phase. WHO warns that the commercial tests can be expensive and difficult to undertake in developing areas, thus requiring other low cost rapid diagnostic assays to be used [15-18]. WHO (2024) found that money problems in low-income areas can keep certain diagnostic tests, treatments and preventive action for CCHF away from people who need them. Quantitative real-time PCR (qRT-PCR) has better performance over conventional RT-PCR or nested RT-PCR with higher sensitivity and specificity, and less time-consuming. Rapid diagnostic tests can influence with the same antibody/antigen capture agents as an assay of ELISA with minimal specimen processing (blood, plasma, swabs). This enables a faster time to get the result through10–30 min, however with a lower detection sensitivity [19-20].

Recent cases out world

Recent outbreaks of CCHF emphasize its persistent transmission cycle across multiple regions. The Ministry of Health and Social Services of Namibia declared an outbreak in several districts [21], reinforcing the need for vector control programs and heightened surveillance. Similarly, Spain's 2017 CCHF cases serve as a reminder of the virus's silent circulation in nature, with sporadic human infections linked to tick exposure and imported animal hosts. These incidents highlight the importance of cross-border epidemiological collaboration to detect and mitigate emerging cases [21-23]. There were three CCHF cases in Spain since 2016, the latest taking place in 2022. Spain is still a major concern because Hyalomma ticks in the region carry the virus. CCHF has been reported in Namibia from time to time, but data on outbreaks in recent years (2022–2025) is minimal in public sources. Even so, areas near South Africa have recorded tick exposure in people and animals dealing with livestock [19-21].

CCHF in Nineveh province

CCHF has been reported in Iraq since 1979 and the initial outbreak caused casualties among medical staffs at Yarmouk hospital. In the last two decades, there were 18 confirmed cases that were reported in Nineveh province with a major outbreak being recorded in 2010, associated with the selling of infected meat from the unauthorized butcher shops. In 2012 and 2013, sporadic cases occurred, and even deaths were reported, but breath surveillance measures limited the widespread spread of it. From 2016 and 2017 cases reduced but cases were confirmed in 2018 five hence showing the risk of viral circulation even with reduced cases [17, 19]

In Nineveh governorate, 18 laboratory confirmed cases were registered during the past two decades, including two in 2007. In 2010, an epidemiological outbreak of the CCHF occurred in a specific geographical area, namely Al-Quds, on the left side of Mosul city. The reason for the outbreak is that several families bought the flesh of an infected animal from unlicensed butcher who is not authorized to slaughter and sell. The epidemic affected eight people with the disease, all of them in the average age (15-45 years), of which three died. Unlicensed meat shops were closed to prevent the spread of the disease. People suspected of contracting the virus and methods of burying the dead have been followed according to WHO rules because of serious transitional diseases. CCHF was controlled within two weeks and no infection was reported outside the geographical area. The most numbers recorded in 1992- 1995 and 2010 figure (4).

Two infections were recorded during 2012, which is the annual rate of recorded injuries for previous years. There was no epidemiological correlation between the two cases (a male with age 40 and a female aged 51).

In 2013, only one injury was recorded and 6 suspected cases (with 4 casualties recorded in all of Iraq). A 26-year-old male was enrolled in the right-side of Mosul city and the patient's condition was become healthy. Through 2016 - 2017 did not record any satisfactory cases of CCHF.

The Center for Transitional Diseases in the Ministry of Health announced the registration of 5 cases of CCHF since the beginning of 2018. One case in Erbil, other case in Nineveh province, and 3cases in Diwaniyah city. Four of them were died.

A bar graph [4] represents the number of confirmed CCHF cases in Nineveh Province between 1992 and 2018. The x-axis is marked by years and the y-axis has the number of cases. Numbers of cases have changed over time, with a sharp rise to 8 in 2010 and a reduction the following years. From 1996 to 2006, there were few reported cases, as the graph shows between 0 and 2 during those years. It seems that environmental conditions, increase in vectors like mosquitoes and observing efforts affect how severe these outbreaks become.

The suspected injuries are immediately reported and documented by sending a patient-specific form sent from the health institution to the Public Health Department and to the Centers for Disease Control CDC in Baghdad. Laboratory testing is carried out at the Baghdad Public Health Laboratory using conventional PCR technique to confirm the condition [24, 25]. The Iraqi ministry of health has provided key control measures to reduce the rate of CCHF, which include; Daily immersion of livestock in pesticides to contain tick infestations. Health awareness campaigns aimed at the livestock owners and butchers to minimize the risk transmission. Extreme isolation procedures for infected patients to avoid human-human transmissions. Monitoring and regulation of slaughterhouses to adhere to the biosecurity standards. Closure of illegal meat shops dealing with unregulated products related in past outbreaks [26, 27].

To prevent spread of the disease, the Ministry of Health is recommended to: CCHF prevention is based on health education as well as preemptive preventive actions. It targets the livestock owners, healthcare workers as well as the general public on safe animals handling practices; tick control and personal protective measures. In high risk areas, improved biosecurity measures like appropriate burial, infection control in slaughterhouses and organized system of disinfection for the environment assist in restraining viral spread. CCHF has continued to be a threat to public health, especially in endemic areas. Although the use of the existing treatment strategies like early application of ribavirin can help reduce serious outcomes, the lack of an approved vaccine is still a serious issue. Fortification of epidemiological surveillance, tick control programs as well as healthcare protocols is vital to-

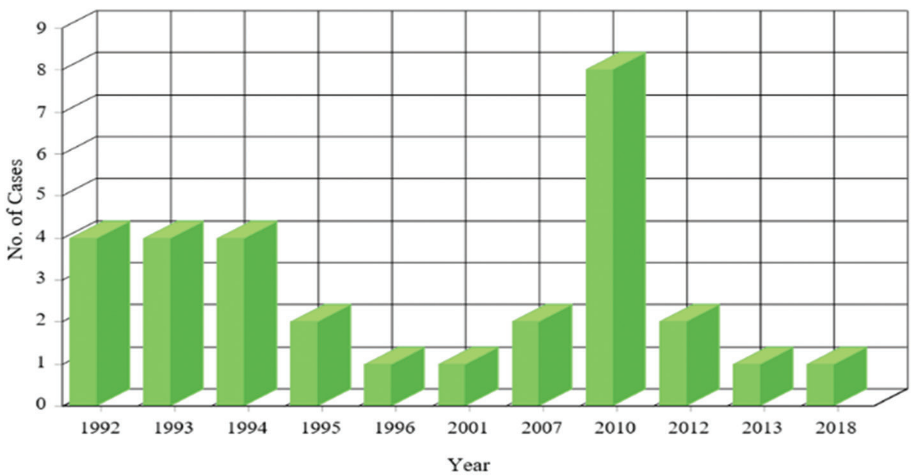

Fig. 4. Confirmed CCHF cases in Nineveh province from 1992-2018

wards containing human infections and mortality rates. In the future, studies should focus on vaccine development, improvement of diagnostics, and international cooperation in outbreak response to reduce the CCHF risks efficiently [28-30].

Fig. 5. CCHF case reported in Nineveh province in 2010

CONCLUSIONS

1. Following an epidemiological study of CCHF in Nineveh Province, the 2010 outbreak, with eight confirmed cases, is seen as the highest number of infections. The biggest reason for tick transmission is exposed livestock, so focused methods are needed to control the threat.
2. Due to the growing number of CCHF cases in Iraq (from 33 in 2021 to 511 in the first half of 2023), improving efforts to control carriers, using personal safety equipment for health workers and making early diagnostics available is essential. Improvements in stepped up tick surveillance, education for farmers and biosafety training in each region will allow for better management of risk and faster response to outbreaks.

Data Availability. The data supporting the findings of this study are available upon request from the corresponding author.

Funding. No external funding was received for this research.

AI Disclosure. No AI tools were used in the analysis or writing of this manuscript.

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

Ethical Approval. Not applicable.

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