Watching brief	
Title	An Outbreak of Crimean-Congo Hemorrhagic Fever (CCHF) in South Africa in 2022
Authors	Dr Utkarsh Betodkar, Dr Zonunsangi Khiangte and Dr Vanlalrengpuia
Date of first report of the outbreak	The exact date of first case is not publicly known. The second Crimean-Congo Hemorrhagic Fever (CCHF) case in South Africa in 2022, a 32-year-old man from Burgersfort, was confirmed on 10 September 2022 (1).
Disease or outbreak	Crimean-Congo Hemorrhagic Fever (CCHF)
Origin (*country, city, region*)	Western Cape and Burgersfort, South Africa
Suspected source (specify food source, zoonotic or human origin or other)	Zoonotic in origin, CCHF is a vector borne disease caused by a tick-borne virus (*Nairovirus*) of the Bunyaviridae family (2).
Date of outbreak beginning	Laboratory confirmation on 10 September 2022 (1).
Date outbreak declared over	Ongoing
Location of the outbreak	The first was a fatal case of CCHF reported from the Western Cape Province in early September. On 10 September, a confirmed second case was reported in a 32-year-old man from Burgersdorp of South Africa, who was hospitalized in Free State province (1).

Number of cases (specify at what date if ongoing)	There were two reported cases in September 2022.
Clinical features	The onset of CCHF is sudden, with initial signs and symptoms including headache, high fever, back pain, joint pain, stomach pain, and vomiting. Red eyes, a flushed face, a red throat, and petechiae (red spots) on the palate are common. Symptoms may also include jaundice, and in severe cases, changes in mood and sensory perception (2). As the illness progresses, severe bruising, nosebleeds, and uncontrolled bleeding at injection sites can occur, which can be life-threatening (2). These symptoms may begin on about the fourth day of illness and can last for about two weeks (2). The high fatality rates of up to 50% in hospitalized patients emphasize the severity of the illness and the importance of early diagnosis and treatment.
Mode of transmission (dominant mode and other documented modes)	Transmission to humans occurs through contact with infected ticks or animal blood. CCHF can be transmitted from one infected human to another by contact with infectious blood or body fluids (2). Documented spread of CCHF has also occurred in hospitals due to improper sterilization of medical equipment, reuse of injection needles, and contamination of medical supplies (2).
Demographics of cases	There were 2 reported cases of CCHF in South Africa, in September 2022. The second case was involved with culling operations on farms and reserves, and a tick bite was identified as the source of infection (1). Although CCHF is primarily seen in individuals in animal related occupational or recreational activities, outbreaks are also seen in hospital settings too through close contact with the blood, secretions,

	organs or other bodily fluids of infected persons (3).
Case fatality rate	Out of the two reported cases in the current outbreak, one of them has resulted in a fatality, resulting in a case fatality rate (CFR) of 50%. In documented outbreaks of CCHF, fatality rates in hospitalized patients have ranged from 9% to as high as 50% (2).
Complications	Usual complications are due to thrombocytopenia and subsequent hemorrhagic manifestations which was also observed in current outbreak (1). In a previous hospital outbreak in Cape Town, the first patient experienced hematemesis and subsequently suffered from a severe gastrointestinal hemorrhage, leading to death from multiple organ failure. Another patient, who was the seventh to be affected and a surgeon at the hospital, died due to severe thrombocytopenia and bleeding (3).
Available prevention	Agricultural workers and others working with animals should use insect repellent on exposed skin and clothing. Insect repellents containing DEET (N, N-diethyl-m- toluamide) are the most effective in warding off ticks (2). Wearing gloves and other protective clothing is also recommended (2). Individuals must avoid contact with the blood and body fluids of livestock or humans who show symptoms of infection (2). It is important for healthcare workers to use proper infection control precautions to prevent occupational exposure (2). An inactivated, mouse-brain derived vaccine against CCHF has been developed and is used on a small scale in animals in Eastern Europe (4). However, there is no safe and effective vaccine currently

	available for human use (2). Recently Immunoinformatics pipeline and reverse vaccinology were used in one of the studies to design a multi-epitope vaccine that may elicit a protective humoral and cellular immune response against CCHF virus infection (5). These robust computational analyses demonstrated that the proposed multi-epitope vaccine is effective in preventing CCHFV infections. However, it is still necessary to conduct both in vitro and in vivo experiments to validate the potential of the vaccine (5).
Available treatment	Treatment for CCHF is primarily supportive. Care should include careful attention to fluid balance and correction of electrolyte abnormalities, oxygenation, and hemodynamic support, and appropriate treatment of secondary infections (2). The virus is sensitive *in vitro* to the antiviral drug Ribavirin (6). It has been used in the treatment of CCHF patients reportedly with promising results (2).
Comparison with past outbreaks	CCHF is a tick-borne viral infection, the virus belonging to *Nairovirus* of Bunyaviridae family. “CCHF” was first detected in the Crimean Peninsula in 1944, and the virus was subsequently found to be identical to Congo virus isolated in the Belgian Congo (now Democratic Republic of Congo) in 1956 (7-10). **<u>CCHF globally</u>** Studies on animals have suggested that the virus is widespread in all countries within the global distribution of Hyalomma ticks, which includes many countries in Africa and Eurasia (11). CCHF is predominantly found in Eastern Europe, particularly in the former Soviet Union, throughout the Mediterranean, in north-western China, central Asia, southern Europe, Africa, the Middle East, and the Indian subcontinent. From 1 January 1956 to 25 July 2020, 494

	CCHF cases, with 115 deaths have been reported in Africa. Since 2000, nine countries (Kenya, Mali, Mozambique, Nigeria, Senegal, Sierra Leone, South Sudan, Sudan and Tunisia) have reported their first CCHF cases (1). In Iraq, between 1 January to 26 June 2022, 219 confirmed cases of CCHF were reported, with case fatality ratio (CFR) of 16.4% (12). Among confirmed cases, most had direct contact with animals, and were livestock breeders or butchers (13). In one of the major outbreaks in Iraq in 2022 the median age of the cases was 34.5 years, the majority of cases were male, and cases had exposure with livestock and came in close contact with animals (12). **CCHF in South Africa** CCHF is a viral disease that is endemic in many African countries, including South Africa. The first reported case of CCHF in South Africa was in 1981 (11). One of the earliest documented outbreaks occurred in September 1984, near Cape Town, where seven medical personnel were infected after treating an index patient (3). The first patient who had contact with farm animals initially had symptoms of sore throat, muscle pains, and fever, which eventually progressed to severe gastrointestinal bleeding and multiple organ failure, leading to death (3). Three nurses who cared for him and two who came into contact with contaminated materials also developed similar symptoms and were confirmed to have CCHF through virus isolation and increasing antibody titers (3). The seventh patient, a young surgeon who had visited the intensive-care unit before isolation, experienced headache and fever 5 days after exposure, followed by severe thrombocytopenia and bleeding 5 days later, resulting in death 8 days after the onset of symptoms (3). The eighth patient, who had contact with all other CCHF patients, likely acquired the infection from a needle prick while nursing one of them. She had a

	milder illness and did not develop thrombocytopenia (3). A 2018 study conducted in South Africa on 387 adults at risk due to their occupational or recreational activities found a low seroprevalence of CCHF virus (14). In 1987, the significance of regular animal surveillance reported the detection of antibodies in a considerable proportion of cattle and herds in South Africa (28% of cattle and 78% of herds) and Zimbabwe (45% of cattle sera and 94% of herds) (11). However the high prevalence in wild and domestic animals suggests that the virus is endemic in the country and highlights the potential for further outbreaks (15). In November 2021, South Africa reported the first case of CCHF since February 2020, in a 70-year-old woman, who suffered a tick bite while on a guided trip in the Namaqualand Flower Route, Northern Cape Province. The patient presented with malaise, fever, chills, headache, muscle and back pain, ecchymosis, maculopapular rash and a tick was detected on the patient's neck (16). The case of CCHF is unusual in that the patient has no known area source and no related close contact with animals and livestock (16).
Unusual features	Some unusual features have been present in reported global cases: 1. CCHF with subdural hematoma was reported from Nouakchott, on 2 July 2012. Brain hemorrhage in persons with CCHF is rare but possible. This case of acute subdural hematoma secondary to CCHF, where thrombocytopenia was the main cause of cerebral hemorrhage and management of such case is challenging due to the underlying bleeding tendency of the patient and risk for nosocomial infection (17). 2. A 51-year-old man from the Northeast Anatolia region of Turkey, working in animal husbandry for 20 years, presented

	with CCHF and the right scrotal area showed mild edema, sensitivity to touch, and a mild rash. Such a presentation is possible and need to rule out other causes of epididymo-orchitis (18). 3. A 70-year-old patient with CCHF exhibited complications by acute pancreatitis, including pleural and intra-abdominal effusions. This is possible due to the diffuse endothelial injury involved in the pathogenesis of CCHF (19).
Critical analysis	CCHF not only forms an important public health threat but has a significant effect on the healthcare personnel, especially in resource-poor countries (20). Although there were only two CCHF cases reported in South Africa in 2022, the unknown source is of concern and should be considered a warning signal for increased numbers in the future. These two cases can be a source of more cases in community or can lead to a hospital outbreak in health care workers. Similarly, other areas in the African continent, like Uganda and Mauritania, have detected more case numbers than usual (21,22). Mauritania reported an outbreak with 7 confirmed cases with a CFR of 29% (21). All past outbreaks have shown a high CFR, ranging from 10 to 40%. In the first reported outbreak in Gujarat, India, among the 13 suspected cases, 30.76% CFR was reported. Of these 13 suspected CCHF cases, 9 were positive for CCHF virus, 2 were negative for CCHF virus and in 2 instances, samples could not be taken because of early deaths of the cases. Cases were reported in the middle age group only (23). To determine the prevalence and impending outbreak, surveillance among livestock and animals is important. In 2016, the first case of

	CCHF was reported in humans in Spain. A multidisciplinary study to describe the nationwide distribution of ticks with CCHF virus was conducted. Ticks collected from animals and vegetation and molecular methods were used to look for the virus. Total samples pooled were 12,584 ticks; 4,556 pools were collected, out of which virus was detected in 135 pools. CCHF virus genotypes I, III and IV were found in the tick species, and the most common was *Hyalommalusitanicum.* The red deer (*Cervus elaphus*) was the host that most frequently yielded positive ticks (13). Two studies among farm workers conducted in the 1980s in South Africa found a seroprevalence of 1.3%–1.5% (15,24). It is therefore recommended to have a very strong CCHF surveillance system in place for humans as well as in animal husbandry in South Africa, especially in high risk occupations or people involved in recreational activities, along with routine surveillance in animals.
Key questions	1. What is the cause of the current cases in South Africa? 2. What needs to be done in order to contain the spread? 3. Does Mauritania and South Africa CCHF have a common origin/relationship as increase in cases occurred during the same period in the same continent? 4. Can we incorporate a dedicated surveillance and response team among the high-risk groups-farmers, livestock workers and butchers in South Africa? 5. What is the cause of the current large outbreak of CCHF in Iraq, and what containment are being used?

Acknowledgements	This Watching Brief is an output of an epidemiology workshop between The National Institute of Epidemiology and EPIWATCH.
References	1. South Africa reports 2nd Crimean-Congo hemorrhagic fever case of 2022 [Internet]. Outbreak News Today. 2022 [cited 2022 Nov 22]. Available from: http://outbreaknewstoday.com/south-africa-reports-2nd-crimean-congo-hemorrhagic-fever-case-of-2022-2022/ 2. Crimean-Congo Hemorrhagic Fever (CCHF) | CDC [Internet]. 2019 [cited 2022 Nov 22]. Available from: https://www.cdc.gov/vhf/crimean-congo/index.html 3. Centers for Disease Control and Prevention. International Notes Crimean-Congo Hemorrhagic Fever -- Republic of South Africa [Internet]. MMWR Morb Mortal Wkly Rep. 1990 Mar 30 [cited 2023 May 22];39(12):194-5. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00000489.htm 4. Dowall S, Buttigieg K, Findlay-Wilson S, Rayner E, Pearson G, Miloszewska A, et al. A Crimean-Congo hemorrhagic fever (CCHF) viral vaccine expressing nucleoprotein is immunogenic but fails to confer protection against lethal disease. Hum Vaccines Immunother. 2015 Aug 26;12(2):519–27. 5. Omoniyi AA, Adebisi SS, Musa SA, Nzalak JO, Bauchi ZM, Bako KW, Olatomide OD, Zachariah R, Nyengaard JR. In silico design and analyses of a multi-epitope vaccine against Crimean-Congo hemorrhagic fever virus through reverse vaccinology and immunoinformatics approaches. Sci Rep. 2022 May 24;12(1):8736. doi: 10.1038/s41598-022-12651-1. PMID: 35610299; PMCID: PMC9127496.

6. Treatment | Crimean-Congo Hemorrhagic Fever (CCHF) | CDC [Internet]. 2019 [cited 2022 Nov 22]. Available from: https://www.cdc.gov/vhf/crimean-congo/treatment/index.html

7. Casals J (1969) Antigenic similarity between the virus causing Crimean hemorrhagic fever and Congo virus. Proc Soc Exp Biol Med 131:233–236.

8. Chumakov MP (1974) Contribution to 30 years of investigation of Crimean-Congo haemorrhagic fever. In: Chumakov MP (ed.) Medical virology. Trudy Inst Polio Virus EnstefAkad Med Nauk SSSR (In Russian). English translation: NAMRU3–T950.

9. Chumakov MP, Smirnova SE, Tkachenko EA (1970) Relationship between strains of Crimean haemorrhagic fever and Congo viruses. Acta Virol 14:82–85.

10. Simpson DKH, Knight EM, Courtois MCG, Weinbren MP, Kibukamusoke JW (1967) Congo virus: a hitherto undescribed virus occurring in Africa. Part 1. Human isolations-clinical notes. E Afr Med J 44:87–92.

11. Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, McGillivray GM, Erasmus MJ, Searle LA, Gill DE. Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am J Trop Med Hyg. 1987 Jan;36(1):120-32. doi: 10.4269/ajtmh.1987.36.120. PMID: 3101525.

12. Alhilfi RA, Khaleel HA, Raheem BM, Mahdi SG, Tabche C, Rawaf S. Large outbreak of Crimean-Congo haemorrhagic fever in Iraq, 2022. IJID Reg. 2023 Jan 18;6:76-79. doi: 10.1016/j.ijregi.2023.01.007. PMID: 36818019; PMCID: PMC9931897.

13. Crimean-Congo Hemorrhagic Fever in Iraq [Internet]. [cited 2022 Nov 22]. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON386

14. Vawda S, Goedhals D, Bester PA, Burt F. Seroepidemiologic Survey of Crimean-Congo Hemorrhagic Fever Virus in Selected Risk Groups, South Africa. Emerg Infect Dis. 2018 Jul;24(7):1360-1363. doi: 10.3201/eid2407.172096. PMID: 29912704; PMCID: PMC6038756.

15. Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP. Investigations following initial recognition of Crimean-Congo haemorrhagic fever in South Africa and the diagnosis of 2 further cases. *S Afr Med J*. 1985;68:638–41.

16. South Africa reports 1st Crimean-Congo hemorrhagic fever case of 2021 [Internet]. Outbreak News Today. 2021 [cited 2022 Nov 22]. Available from: http://outbreaknewstoday.com/south-africa-reports-1st-crimean-congo-hemorrhagic-fever-case-of-2021/

17. Kleib AS, Salihy SM, Ghaber SM, Sidiel BW, Sidiya KC, Bettar ES. Crimean-Congo Hemorrhagic Fever with Acute Subdural Hematoma, Mauritania, 2012. Emerg Infect Dis. 2016 Jul;22(7):1305–6.

18. Kerget F, Demirdöğen ŞO, Kerget B. Case Report: A Rare Case of Crimean–Congo Hemorrhagic Fever Associated with Epididymo-Orchitis. Am J Trop Med Hyg. 2021 Mar;104(3):1055–7.

19. Bastug A, Kayaaslan B, But A, Aslaner H, Sertcelik A, Akinci E, et al. A case of Crimean-Congo hemorrhagic fever complicated with acute pancreatitis. Vector Borne Zoonotic Dis Larchmt N.

2014 Nov;14(11):827–9.

20. Appannanavar SB, Mishra B. An update on crimean congo hemorrhagic Fever. J Glob Infect Dis. 2011 Jul;3(3):285-92. doi: 10.4103/0974-777X.83537. PMID: 21887063; PMCID: PMC3162818.

21. Boushab BM, Yanogo PK, Barry D, Benane HA, El Bara A, Abdellah M, Basco LK, Meda N. Investigation Around Cases of Crimean-Congo Hemorrhagic Fever-Mauritania, 2022. Open Forum Infect Dis. 2022 Oct 12;9(10):ofac534. doi: 10.1093/ofid/ofac534. PMID: 36320199; PMCID: PMC9605700.

22. UNICEF. Uganda Response Report (Karamoja) - October 2022.pdf. 2022.

23. Gandhi S, Dave P, Patel GC, Khatri HJ, Shah N, Mishra U. An epidemiological investigation of a multisource outbreak of Crimean-Congo hemorrhagic fever in Gujarat. J Commun Dis. 2011 Sep;43(3):161–7.

24. Fisher-Hoch SP, McCormick JB, Swanepoel R, Van Middlekoop A, Harvey S, Kustner HGV. Risk of human infections with Crimean-Congo hemorrhagic fever virus in a South African rural community. *Am J Trop Med Hyg*. 1992;47:337–45. 10.4269/ajtmh.1992.47.337