Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, ***Watching Briefs*** *are intended as a rapid resource for public health or other first responders in the field on topical, serious or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.*

Watching brief

Title	Brucellosis Outbreak in China, 2019
Authors	Shah Marzia Mahjabin Lina, Mohana Priya Kunasekaran, Aye Moa
Date of first report of the outbreak	November 2019
Disease or outbreak	Brucellosis affects both animals and humans all over the world and is caused by gram-negative bacteria of genus Brucella (1). Twelve species of Brucella have been identified, of which four (B. melitensis, B. abortus, B. suis and B. canis) are pathogenic to human (2). Brucellosis is more common in countries that lack effective animal health programs. The Mediterranean basin, Asia, Africa, South and central America, Mexico, the Caribbean, the Middle East and Eastern Europe are listed as high-risk regions for Brucellosis (3). Brucella is also a category B bioterrorism threat.
Origin (*country, city, region*)	China
Suspected Source (specify food source, zoonotic or human origin or other)	During late July to August 2019, Zhongmu Lanzhou Bio-pharmaceutical plant of Gansu province was producing brucella vaccine for animals and reportedly used an expired disinfectant for cleaning, which failed to kill all the bacteria. At the same time a leak occurred in the plant, which allowed the contaminated waste in the form of aerosol to be leaked in the air. The direction of the wind was south-east in the downwind trajectory of the Lanzhou Veterinary Research Institute. This caused the first outbreak in the Lanzhou Veterinary Research Institute as the contaminated aerosols were carried and spread there. Community transmission took place after this event (4-5).
Date of outbreak beginning	July, 2019 and reported November, 2019 (4)
Date outbreak declared over	Ongoing.

Affected countries & regions	Lanzhou, Northwest China's Gansu Province, Shaanxi Province and Inner Mongolia
Number of cases (specify at what date if ongoing)	The infection has so far been confirmed in 10,528 people after testing - 68571 people up to November 30, 2020.
Clinical features	The clinical manifestation of human brucellosis starts with numerous non-specific symptoms including fever, headache, sweating, weight loss, general aches, and chills (6-8). Residual disability and musculoskeletal symptoms are also observed in brucellosis (arthralgia, arthritis, myalgia, backpain, spondylitis and sacroiliitis) (9). The symptoms can be acute and usually take 2 to 4 weeks to manifest after a person gets infected (10). In high-risk regions, additional haematological complications such as anaemia, leukopenia, pancytopenia and immune thrombocytopenic purpura have been reported in paediatric patients (11,12). Intra uterine foetal death (IUFD), spontaneous abortion, pre-term labour and congenital malformations were reported in pregnant women (13,14). Less common features of brucellosis are meningitis, pancytopenia and endocarditis. Though endocarditis happened rarely, but it is the main cause of death associated with brucella infection (15).
Mode of transmission (dominant mode and other documented modes)	Zoonotic transmission: Infected animals act as the main reservoir of the pathogen and it transmits to humans not only from direct contact but also several other indirect means. Human can be affected by brucellosis either by ingestion of dietary products produced from infected animals, such as raw milk or other dairy products, from inhalation from a contaminated environment, through conjunctiva, or through cuts or abrasions on the skin (16-18). The main sources of Brucellosis in China are infected cattle, sheep, and swine (19). The infected animals often excrete the pathogens through their urine, feces, placenta or even miscarriages. It is reported that in Saudi Arabia and other Arabic countries ingestion of raw milk is the main cause of Brucellosis, whereas intake of various kinds of cheese is also very common means of transmission since the pathogen can live for an average of 20 days (20, 21). On the other hand, intake of meat is rarely a cause of transmission of the pathogen since most of the time meat is well cooked before eating. Since animals are the main source of this pathogen it is evident that the people who are responsible for the handling of the animals are at high risk of being affected by this pathogen. The people who work in the laboratories are also very much susceptible for getting infected (22, 23). Typically, aerosol transmission is thought to only occur as a result of a deliberate biological attack. Human to Human transmission: Most Transmission is zoonotic, and human to human spread is rare, but there are several documented cases where human to human transmission occurred (24). The most commonly reported means of human to human transmission is breastfeeding and also vertical transmission from mother to child through placenta (25). Cases may be both symptomatic or asymptomatic in nature (26-29). In 2019, mother-children transmission of brucellosis was reported in China (30). Sexual transmission has also been reported (16, 31). However, there are very few cases where the presence of

	bacteria was detected in semen (32). Bone marrow transplantation (33, 34) and secondary blood transfusion (35, 36) are also identified as means of transmission of Brucellosis in human. A case was reported in Turkey where a liver transplant patient got brucellosis two months after the operation (37). In this current outbreak, there seems to be aerosol transmission with some evidence of zoonotic transmission. According to sources from the institute, in mid-November 2019, some laboratory mice were found infected with Brucella bacterium, and two students involved in the research and had contact with mice had tested positive for the pathogen as well (38)
Demographics of cases	The first four cases found with positive serology were the students at Lanzhou Veterinary Research Institute of the Chinese Academy of Agricultural Sciences. Then upon further investigation and testing of personnel in the laboratories and others, total of 65 cases were reported on 6th December 2019 (39,40). On 10th December 2019, the second cluster of cases were then reported from another veterinary institute, the Graduate School of Veterinary Medicine of the Chinese Academy of Agricultural Sciences (Harbin Institute), around 2600 km to the northeast of Lanzhou. 13 students who tested positive had short-term research work at the Lanzhou Veterinary Institute and had animal contact history (41,42). As of 6 November 2019, 6,620 cases were confirmed according to report of Lanzhou Veterinary Research Institute (43). It was also reported that the outbreak was spreading to farms from Gansu province to Shaanxi province and Inner Mongolia. The means of spreading was reported as improper screening of farm animals to diagnose brucellosis and continuation of trade of infected animals (44,45).
Case fatality rate	There were no deaths reported related to this outbreak (46). The outcome of brucellosis is more severe in people with underlying health issues (47). Historically, the case fatality rate as recorded in the British Army and Navy stationed in Malta in 1909 was 2% and endocarditis was the predominant cause of mortality (47). In 2019, China reported 44,036 cases with one death due to brucella, up from 37,947 cases and zero deaths a year earlier (48). The attack rate based on the 55, 725 people tested in Lanzhou city is about 12.9% (6,620 people tested positive (48).
Complications	Endocarditis, arthritis, inflammation of the testicles, inflammation of spleen and liver, and infection of the central nervous system (CNS) are the known complications.
Available prevention	Brucella can survive in the environment for months but is killed by high heat and some disinfectants (49). Since the main reservoir for the pathogen is animals it is very important to control Brucellosis in animals and prevent spread between animals to control it in humans. One of the most important preventive measures is the use of vaccines for the animals since there is no established vaccines for human. Isolation, quarantine, or culling of infected animal are also effective measures to control disease spread.

	Raw milk or unpasteurized milk should be strictly prohibited as well as other milk products like ice-cream or cheese. People should avoid uncooked or under cooked meat or meat products. Moreover, the people who handle the animals should use proper personal protective equipment which includes gloves, gowns, shoes and also goggles. Also, the people who work at the laboratory and handle samples should use proper precautionary measures. Upon confirmation of initial cases, the Lanzhou Veterinary Research institute implemented closures of facilities and halted research operations while investigating the cause of the outbreak and to prevent more cases (50) Finally, people should be provided education about food hygiene and occupational hygiene, so they become aware about preventive measures (51,52). In this case, however, the outbreak spread by aerosolization, which is highly unusual. Aerosol transmission can result in accumulated aerosols in indoor settings, and in outdoor settings, wind currents can carry aerosolized material long distances. During an accidental release of anthrax in the Soviet Union, infection occurred up to 4km down wind of the release (53).
Available treatment	The primary goal of the treatment is to control acute illness and antimicrobial therapy should be selected based on the presence of focal disease (54). Single therapy is not an effective option for the treatment of brucellosis due to relapse of the disease and also the possibility of drug resistance (55,56). For the treatment of human brucellosis, the World Health Organization (WHO) recommends two combination therapies (57), Doxycycline and Rifampicin combination for six weeks or Doxycycline for six weeks in combination with Streptomycin for 2 or 3 weeks (58). However, the relapse rate is about 14.4% (59). Optimal regimes may vary according to endemic regions (60). The combination of doxycycline and gentamicin is also accepted, and some countries may use parenteral streptomycin (61). Some other combination therapies including quinolones are also used but their efficacy and safety need to be confirmed (62). Triple therapy containing sulphamethoxazol and trimethoprim or rifampicin and streptomycin with tetracycline may also be used to treat brucellosis (63,64).
Comparison with past outbreaks	In China the first human brucellosis case was reported in 1905 (65) and incidence has been divided into three stages. From the 1990s to present is a re-emergence period, whereas up to the1960s it was high incidence and 1970s-1980s saw a declined in incidence (66). In 2019, the incidence reported was 3.2513 per 100, 000 population (67). The previous outbreaks were zoonotic, due to transportation of animal food products, animals, and movement of humans from brucellosis risk regions to another provinces (68). This outbreak is different; it was caused by an industrial accident and spread through aerosolization, with case numbers increasing exponentially and continuing for a whole year from November 2019 to November 2020 and not yet declared over.

Unusual features	In this case, a large-scale aerosolised outbreak is highly unusual, as the usual transmission is zoonotic. However, even in zoonotic outbreaks, such as in abattoirs, airborne transmission can occur. In another outbreaks, spread has been shown to people with no direct contact with infected animals in areas distal to the animals (69).
Critical analysis	Aerosolized infected particles from Lanzhou Bio-pharmaceutical company was identified as the source for the first cluster of human cases of recent Brucellosis outbreak in China. Students from Harbin Institute who were positive in the second cluster had contact history, as they went to work in Lanzhou where they came in contact with the infected animals. Though contaminated pharmaceutical waste was identified as the main source of this outbreak, the transmission mechanism nor the reason for ongoing transmission for 12 months is not clear. Between November 2019 to November 2020, a high number (6,620) of human cases occurred in the local area. According to news reports after the report of this outbreak, the number of infected animals in farms from Gansu province to Shaanxi province and Inner Mongolia is increasing. Local farmworkers think that inability to identify infected animals, unwillingness to cull or isolate rather than selling the identified animals in local market due to fear of financial loss, and not giving leave of those workers who are infected with Brucellosis are mainly responsible for the rise of Brucellosis outbreak in farm houses and in humans. Investigation is required to identify how many people and animals were affected by the initial leakage and the total area the infected aerosolized particles travelled, which may be responsible for the increase of number of infected animals afterwards. There could have been an initial period of aerosol spread, followed by human and animal infections, and then zoonotic transmission resulting from the infected animals. This is possible, given that Brucella can survive for months in the environment. The initial aerosolization may have resulted in a very high concentration of Brucella being disseminated, which may have remained viable for months even if the initial factory leak was stopped and continued to cause infection of animals and humans in the area. It is very important to identify whether transmission from the pharmaceutical company has stopped. Moreover, it needs to be investigated urgently how long bacteria can live in aerosolized form and if any other local farmhouse was affected other

	than the research institute by this event. Since the infected number is still increasing after authority took several initiatives to resist spreading and the outbreak is yet to be announced over, there may be some epidemiological connection between the increase number of human cases and animals in the farm house.
Key questions	1) How long did aerosol transmission from the pharmaceutical factory occur? 2) How long does aerosolized Brucella persist in the air? 3) What is the viability of bacteria in aerosolized form? 4) Can bacteria be re-aerosolised after airborne particles settle in the environment? 5) How has the outbreak spread from Gansu to Shenyang province? Was the outbreak initially aerosol spread, followed by widespread human and animal infection, and then zoonotic and some human to human spread?
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