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Glanders: re-emergence of an ancient zoonosis

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Glanders, although known to be endemic in certain regions/countries of the Old and New Worlds for centuries, had been largely overlooked as a threat to equine and human health until the disease re-emerged in the Middle East in 2004. The exponential growth in international horse movements, both legal and illegal, mainly for performance purposes, has enhanced the risk of global spread of glanders in the Middle East and elsewhere. Ever since the First World War, the glanders bacillus has been recognised as a potential biological warfare agent.

The organism

Glanders is an OIE (World Organisation for Animal Health) listed notifiable disease caused by *Burkholderia mallei*, a Gram-negative, non-motile and non-spore-forming bacterium. Previously known as *Pseudomonas mallei,* it is genetically closely related to the agent of melioidosis, *Burkholderia pseudomallei*. It is an obligate pathogen of domestic equids. Glanders is one of the oldest recorded diseases of horses dating back to Aristotle (350 BC), and long recognised as a very important zoonotic disease of humans.

The incubation period of glanders varies from a few days to many months according to the route and level of exposure and

intrinsic host factors[1]. For the purposes of the OIE Terrestrial Animal Health Code, the infective period of *B. mallei* in equids is lifelong and incubation period for glanders is up to 6 months[2].

The disease

The signs of glanders are relatively non-specific. Three clinical forms are described (nasal, pulmonary and cutaneous forms) but more than one form of the disease may occur in the same animal concurrently. Fever, mucopurulent nasal discharge, coughing, difficulty breathing, and enlarged sub-mandibular lymph nodes are characteristic of the nasal and pulmonary forms of the disease (hence glanders). The cutaneous form of glanders or farcy is also associated with the development of subcutaneous nodules along the course of the lymphatics of the face, eyes, costal region, legs or ventral abdomen. Diseases that can be confused with glanders include strangles (*Streptococcus equi equi*), a common disease of horses, melioidosis (*B. pseudomallei*), epizootic lymphangitis (*Histoplasma capsulatum var farciminosum*), ulcerative lymphangitis (*Corynebacterium pseudotuberculosis*) and sporotrichosis (*Sporotrichum schenckii*)[1,3,4].

Acute disease occurs mainly in donkeys; glanders in horses can be acute, but more often chronic or latent[1,3]. Humans are susceptible and if untreated, infection in man is frequently fatal[5]. Small ruminants and dromedary camels kept in close contact with infected horses can contract the disease[6], as can carnivores by eating infected or contaminated meat[1,3].

Diagnosis

Glanders presents diagnostic challenges and diagnosis cannot be based on clinical signs alone. Isolation of *B. mallei* from lesions and exudates is the 'gold' standard; difficulties arise however when infections are sub-clinical or latent. Other tests resorted to can include the Mallein test (preferably the intradermo-palpebral test). This is a hypersensitivity skin test which does not distinguish infection with *B. mallei* from *B.pseudomallei*[3,7,8].

The complement fixation test (CFT), the OIE recommended serological test for international trade[9], is complex to perform, difficult to standardise and can result in anti-complementary reactions with some sera. Its sensitivity and specificity can vary depending on the antigen and methodology used[7,8]. Newer more sensitive and specific diagnostic tests e.g. the polymerase chain reaction test, competitive enzyme-linked immunosorbent assay (C-ELISA) and the Western immunoblot test have been developed to overcome the limitations of traditional diagnostic tests. However, none of these tests have yet been validated by the OIE for use in international trade[7,10].

Transmission

Glanders is usually introduced to a free area by an asymptomatic carrier animal[7,8]. Spread can occur by direct or indirect contact with an infected animal. The disease is frequently contracted by the ingestion of food or water from communal troughs contaminated by nasal discharges or pus from skin lesions. Spread by inhalation can also occur. The cutaneous form of glanders is spread by contaminated saddlery, harness or grooming equipment. Latent infection can be reactivated by stress, for example, travel, poor husbandry or over-crowding[1,3,4].

Disease in humans

Naturally occurring disease occurs infrequently in humans and usually results from occupational exposure involving close and prolonged contact with an infected equid(s). People most at risk include veterinarians, grooms and abattoir workers[5]. It is now generally accepted that glanders caused the death in 1793 of Charles Vial de St Bel, inaugural Professor of the recently established London Veterinary College, although the zoonotic potential of glanders was not actually recognised until the beginning of the 19th century[11]. Deaths in laboratory workers have also been reported, including European scientists studying glanders after the initial isolation of the aetiologic agent in 1882[11], and military research microbiologists in the USA[11,12].

B. mallei was used as a biological warfare agent against animals in Europe, Russia and the USA during the First World War. In the USA, cultures were grown by a German agent in a basement laboratory in Washington, DC. The microbes were suspended in liquid in test tubes, and dockworkers recruited by the Germans went among mules and horses assembled for shipment to the Allied forces in Europe and jabbed animals with needles that had been dipped into the microbial cultures[13].

Glanders is classified as a Category B biothreat agent by the Centres for Disease Control and Prevention in the USA[14] and all potentially infected or contaminated material must be handled in a laboratory with appropriate biosafety and biosecurity controls[9].

Geographic distribution and re-emergence

Glanders was once widespread globally primarily due to the movement of horses for war, transportation and agriculture. Throughout history, when horse-mounted troops invaded new territories, glanders almost invariably accompanied them[8,11]. Mandatory national test and slaughter control programs in the early to mid-20th century eradicated the disease from many countries, including the USA, Canada and Western Europe. Since then, these countries have

maintained their glanders-free status by strict import policies and border controls[1,7,8].

Glanders still persists in parts of Eastern Europe, the Middle East, Asia, Africa, the Indian subcontinent,and Brazil in South America[1,3]. Over the past 15 years glanders has been reported with increasing frequency from the Middle East (United Arab Emirates, 2004; Iran, 2007; Kuwait, 2009 and 2019; Bahrain, 2010; Lebanon, 2011) and is considered a re-emerging disease in that region[1,15,16]. Cases have been reported from Kuwait as recently as July 2019[17] and most recently in Turkey in late 2019. Movement of horses from Syria appears to have played a prominent role in the disease's re-emergence[16,18,19].

Glanders has also made an unwelcome reappearance in Western Europe. A 2009 report described a horse imported into Germany from Brazil in 2006 with certification of no known exposure to the disease and of negative CFT status. It became ill after arrival and the animal was subsequently diagnosed as having glanders[15,20]. In 2015, another case, and this time of latent or occult glanders, was reported in a German horse where the source of infection was not identified[21].

Confirmation of a case of glanders has a substantial economic impact in non-endemic areas. There is no effective long-term treatment or any vaccine against the disease. Horses eventually die. A test and slaughter program must be introduced if a country wishes to regain its free status[2]. Diseased animals and animals that test positive must be killed, severe restrictions on horse movement imposed within the country and the international trade in equids and their products suspended for an extended period.

What factors are contributing to the renaissance of this ancient disease?

- Foremost is the exponential growth in international movement of horses for equestrian sports or racing purposes, particularly legal and illegal movements between Middle Eastern countries[8,15,16].
- Inadequate regulation, biosecurity and supervision of international horse movements including failure of countries to harmonise their national regulations for importation with OIE disease specific recommendations[15].
- Regional conflicts can disrupt national government control programs[7].
- *B. mallei* can evade the host's immune response and result in latent infections and the potential for the introduction of infection into glanders-free countries[8].
- Absence of an OIE validated diagnostic serological test for glanders. The current OIE approved CF test for international trade can give rise to false positive and false negative results. Unreliable diagnostic tests compromise the efficacy of disease control programs[1].
- Lack of awareness of the clinical signs of glanders may result in an incorrect or delayed diagnosis and failure to detect or report an outbreak. Reduced commercial use of horses has led to diminished veterinary awareness of glanders, its clinical signs, epidemiology and diagnostic methods[7,8].
- Disease investigations carried out by private veterinarians have hampered government authorities and prevented timely and appropriate action[16].
- Failure to report the disease – economic and cultural circumstances may hinder the culling of asymptomatically infected animals; fear of restrictions and the absence of adequate compensation may also deter official reporting[1,4,7,19].

An Australian perspective

Glanders has never gained a foothold in Australia. Australia was remote from Europe (and its major wars and disturbances) and had no land borders. It was not an attractive target for European invaders until the British came by sea to establish the first penal colony in 1788 accompanied by a few horses sourced from South Africa[22]. Luckily these and other horses imported in the early wild colonial days did not introduce glanders. Freedom from significant equine diseases such glanders provided an important trade advantage for the export of Australian horses to the Indian market as army remounts[23].

Nevertheless, in November 1891, swift and efficient action by New South Wales (NSW) quarantine authorities prevented disaster. Glanders was detected by a government veterinarian in circus horses imported from the USA. Fortunately, they were still held in quarantine. Their only Australian contacts were horses recently recruited to the circus. The two imported clinical cases and their Australian contacts were destroyed. The imported horses were then transferred to Shark Island in Port Jackson where four more animals developed the disease. The remaining circus horses were shipped back to San Francisco in February 1892. Their export occurred despite considerable opposition from certain NSW veterinary practitioners who thought the rest of the American circus horses could be safely admitted to Australia because the diseased animals had been killed. Unlike the recent experience in the Middle East[16], the strong stand taken by the government authorities prevailed[24].

Subsequently, Australia has maintained strict border controls and maintained its glanders free status. An import risk analysis covering *inter alia* the biosecurity risk posed by glanders in imported horses was conducted in 2010 and reviewed in 2013[25,26]. Australia only imports horses directly from countries in which glanders does not occur. To be eligible for import, horses must have been resident for at least 6 months prior to shipment or since birth in an approved country free of glanders.

In the unlikely event that glanders did ever manage to penetrate our borders again, Australia is well prepared for its eradication with a response plan and a government/industry disease control cost sharing formula agreed in advance of any outbreak[27].

Future research

To improve global control of glanders while facilitating future international horse movements, the International Horse Sports Confederation and the OIE have supported projects to identify and validate improved diagnostic tests[7,10].

More sensitive tests will allow more accurate certification of the disease freedom of individual animals and reduce the risk of introduction of glanders to new areas by the international movement of infected carriers. More specific tests will also reduce false positive results that lead to unnecessary and expensive obstacles to trade[7,10].

Conflicts of interest

The author declares no conflicts of interest.

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Biography

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