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Editorial Review

Ebola virus transmission

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The recent outbreak of Ebola virus infection in the rural Zairean town of Kikwit has generated considerable discussion in both the medical and lay press. Over 200 confirmed cases have been identified, with a mortality rate of over 70%. The World Health Organization, in reporting this health crisis, has been at pains to damp speculation, or indeed panic, that we are on the verge of an Armageddon induced by rapid world-wide spread of a horrific, uncontrollable flesh-eating infection. This re-emergence of Ebola virus activity in humans, which has been dormant for the past 15 years, adds topicality to the report in this issue by Johnson and colleagues from the Army Medical Research Institute in Frederick, USA, of aerosol spread of Ebola virus infection in an experimental animal model (Johnson *et al.* 1995).

Ebola virus belongs taxonomically in the Filovirus family (Kiley *et al.* 1982). Filoviruses possess a negative strand RNA genome, and a characteristic long filamentous morphology when visualized in the electron microscope. Two antigenically and genomically distinct types of filovirus have been identified thus far. Marburg virus (named in 1967 after the German town where it was first characterized) was responsible for simultaneous outbreaks of a haemorrhagic fever syndrome occurring in laboratory workers in Germany and Yugoslavia who handled a batch of African green monkeys imported from Uganda. There were 7 deaths among a total of 31 confirmed cases (Kissling *et al.* 1978). Small numbers of cases have since been described in South Africa and Kenya (Gear *et al.* 1975; Smith *et al.* 1982). Ebola virus (named after a small river in north-west Zaire) was first identified in 1976, in association with two concurrent outbreaks of haemorrhagic fever in Zaire and Sudan, involving 500 individuals, with case fatality rates of 88% in Zaire and 53% in Sudan (Johnson *et al.* 1977). A smaller outbreak (34 cases, 22 deaths) occurred at the same site in Sudan in 1979 (Baron *et al.* 1983). The viruses isolated from the original Zairean and Sudanese outbreaks are not identical, and are classed as subtypes of Ebola. They possess both common and unique epitopes, and clearly display differing degrees of pathogenicity both in animal models and in humans, with Ebola (Zaire) being one of the most lethal known human pathogens (McCormick *et al.* 1983). A third subtype, Ebola (Reston), is of Asian origin and was identified in monkeys imported into the USA from the Philippines (Jahrling *et al.* 1990).

The pathogenesis of the fulminating disease induced by these viruses is not clear. The viruses appear to be pantropic, inducing necrosis of many internal organs, most notably the liver. It has been suggested that the haemorrhagic and shock manifestations may be a consequence of endothelial cell infection, with consequent loss of endothelial integrity leading to rapid hypovolaemic shock, multiple effusions, and multiple bleeding sites (Fisher-Hock *et al.* 1985).

In the African outbreaks of Ebola virus infection, case-to-case spread occurred via direct contact with contaminated body fluids, and also through re-use of contaminated needles. Secondary transmission did occur among family members looking after sick relatives, but such secondary attack rates rarely exceeded 10%, indicating inefficient transmission (Baron *et al.* 1983). Although there is epidemiological evidence of airborne spread (e.g. seroconversion amongst animal-care workers in the absence of a history of parenteral exposure), such spread is not considered important. Simple infection control measures to prevent direct contact with body fluids, and appropriate quarantining of ill patients, have been sufficient to contain past outbreaks (Bennett & Brown 1995).

How can these observations be reconciled with the data of Johnson *et al.* (1995) which clearly demonstrate fatal Ebola (Zaire) infection of rhesus monkeys acquired via the respiratory tract? The authors offer a number of possible explanations. Perhaps the titres of virus within the respiratory tract of infected humans are not high enough to establish effective aerosol transmission. In support of this, the lungs have not been reported as a major site of virus-induced damage at post-mortem. Alternatively, the virus may not be able to survive in the conditions of high temperature and humidity

pertaining in sub-Saharan Africa. If the latter is the true explanation, then it is indeed cause for concern. The 1989 outbreak of Ebola (Reston) infection in a monkey colony in Reston, Virginia, was not associated with serious disease in humans, although several monkey-handlers demonstrated serological evidence of infection (CDC 1990). The implication of the 'virus survival' hypothesis is that this lack of morbidity and mortality was fortuitously due to the lower pathogenicity of the Reston strain compared to the African strains of virus. One further alarming thought arises from the observation of Johnson and colleagues that their monkeys exposed to aerosolized virus had large amounts of virus demonstrable in their respiratory epithelium and secretions. This suggests that once established, aerosol transmission will become a truly vicious circle, as the respiratory tract in individuals infected in this manner becomes a site of active virus replication, leading to respiratory shedding of virus in high titre.

There are a number of unresolved enigmas in relation to filoviruses. Despite extensive efforts, the natural host and reservoir of these viruses has not been identified. The mechanisms underlying the severe manifestations of disease have not been elucidated, begging the question as to whether pharmacological intervention may reduce the morbidity and mortality associated with infection of humans. The molecular basis for the marked differences in pathogenicity exhibited by the African and Asian strains of Ebola virus is unknown. In comparison with certain other virus infections, there is an abundance of potential animal models of infection – monkeys, mice, guinea-pigs and hamsters have all been successfully infected experimentally with filoviruses (McCormick *et al.* 1983; Bowen *et al.* 1977; Kissling *et al.* 1970). Presumably it is the classification of these viruses as 'Biosafety Level 4' pathogens, and the difficulties in working in the consequent maximum containment facilities, which have hindered experimental exploration of these issues. The data reported in this issue suggest that we would be ill-advised to become complacent about the threat to the public health posed by these exotic viruses, lest the stuff of Hollywood thrillers, such as the recently released film *Outbreak*, becomes reality.

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