Tropical Medicine and International Health

VOLUME 7 NO 10 PP 902–906 OCTOBER 2002

Short communication: **A cluster of Marburg virus disease involving an infant***

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Summary A noteworthy cluster of six cases of Marburg haemorrhagic fever (MHF) was identified in the Democratic Republic of Congo. One of the cases is the first infant Marburg fever patient ever documented. Three of six cases presented surprisingly mild symptoms. The results of epidemiological and virological investigations are compatible with person-to-person transmission through body fluids and with mother-to-child transmission while nurturing. The findings show that mild cases of MHF have to be expected during an outbreak and point out the difficulty to base patient management decisions on clinical case definitions alone.

keywords Marburg haemorrhagic fever, filoviridae, active surveillance, outbreak control, Democratic Republic of Congo

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Introduction

Between October 1998 and May 1999, an outbreak of Marburg haemorrhagic fever (MHF) occurred in Durba and Watsa in the north-east corner of the Democratic Republic of Congo, a region marked by economic decline and the ongoing armed conflict. The outbreak caused 73 cases and 61 deaths (own data) and was the first MHF epidemic ever observed in a community setting; gold diggers appeared to be particularly affected (WHO 1999). In the past, Marburg virus had only been implicated in laboratory outbreaks in Germany and Yugoslavia (1967) among individuals who had handled monkeys imported from Uganda (Martini 1971; Stille & Böhle 1971; Todorovitch *et al*. 1971; Slenczka 1999), and in isolated cases in East, Central and Southern Africa (Gear *et al*. 1975; Smith *et al*. 1982; Johnson *et al*. 1996). During the Durba outbreak, we identified a particularly noteworthy family cluster of suspected and confirmed cases, which we were able to document in detail.

*On behalf of the International Scientific and Technical Committee for Marburg Haemorrhagic Fever Control in the Democratic Republic of Congo.

Methods

Upon arrival of a team of national and international experts for the investigation and control of the epidemic in early May 1999 – several months after the beginning of the outbreak – an active surveillance system was set up in Durba and Watsa, with health workers and trained volunteers making house-to-house visits to look for incident cases suspected to be MHF.

The following case definitions were used by the surveillance teams: a *clinical case* was any severely ill person with acute fever and at least one of the following signs of haemorrhage: haematemesis, bloody diarrhoea or melaena, gingival bleeding. Clinical cases were taken to the isolation unit for assessment by a physician, who would decide on diagnosis and isolation on epidemiological and clinical grounds. *Suspect cases* were (a) ill persons with a risk profile (being gold diggers or having had contact with another suspect case in the past 3 weeks) with acute fever

not responding to treatment with antibiotics and antimalarial drugs, or (b) ill persons with a risk profile presenting at least three of the following symptoms: headache, vomiting, nausea, anorexia, diarrhoea, asthenia, abdominal pain, generalized pain, dysphagia, dyspnoea, cough, thoracic pain. Suspect cases were followed-up daily for 3 days, had a blood sample taken and were transported to the isolation unit if their health status became worse or if signs of haemorrhage developed.

Two serosurveys were conducted among the staff of the Watsa and Durba health facilities: the first on 10 May 1999 and the second on 21 July 2001.

Blood samples of clinical and suspect cases were shipped to the National Institute of Virology, Johannesburg, where a range of tests was undertaken: polymerase chain reaction (PCR) (Sanchez & Feldmann 1995), antigen capture enzyme linked immunosorbent assay (ELISA) (Ksiazek *et al.* 1992), IgG and IgM ELISA (Ksiazek *et al.* 1999) and virus isolation. Because of the remoteness of the area and infrequent transport opportunities for the samples, laboratory results often arrived in the field too late to be relevant for case management. Serosurvey samples were tested for anti-Marburg IgG and IgM by ELISA.

Results

Like most cases of the outbreak, the first two cases of the cluster were identified retrospectively after the arrival of the investigation team. A, a young gold digger, fell ill with fever, subsequently developed signs of haemorrhage and eventually died within days. His clothes, soiled with body fluids, were washed by B, approximately 25 years old and 4 months pregnant. On 22 April 1999, she became ill with high fever, headache, abdominal pain, nausea, vomiting and malaise. On 24 April, she was hospitalized, had a spontaneous abortion and died of vaginal haemorrhage. As A and B were retrospective cases, no biological samples could be taken; the case ascertainment was based on exposure factors and clinical symptoms reported by members of B's family (for A: working as a gold digger; for B: prior contact with another case; for both: acute fever and haemorrhagic symptoms).

On 15 May, the death of C, a 40-year-old female, was reported to the investigation team of the Marburg epidemic; she had died at home the day before. C turned out to be the mother of B whom she had been nursing during the 3 days of her illness. From 1 May onwards, C had developed high fever, haematemesis, diarrhoea, headache, abdominal pain, myalgia, arthralgia, dysphagia, dyspnoea and conjunctivitis. A post-mortem cardiac puncture was undertaken. This sample, processed at the National Institute of Virology, Johannesburg, South Africa (like all other samples reported here), was Marburg positive by PCR, antigen capture ELISA and virus isolation, but no Marburg antibodies were found by ELISA.

Furthermore, when C's case history and contacts were investigated, two more family members were found ill, although not severely: (1) D (age 22), B's sister, had been ill since 1 May, with unspecific signs and symptoms. She was not sure whether she had seen traces of blood in the stool; slight signs of purpura could be found. (2) E (age 8 months), D's daughter, who suffered from fever, diarrhoea and vomiting since 9 May. Splenomegaly, but no signs or haemorrhage were found in the child. Both D and E had reportedly not been seriously ill before the assessment by the investigation team. D had, like C, given nursing care to B. E received maternal care and was breastfed by D; E had not been in close contact with C. None of them had been in contact with another case of haemorrhagic fever outside the family. Venous blood was taken from D and E. While D fulfilled the field-case definition (prior contact with another case, acute fever and haemorrhagic symptoms), E initially did not; when re-interviewed two and a half years later, the family claimed to have seen traces of blood in E's stool. In the absence of laboratory results – which became available much later – E's initial clinical diagnosis was malaria, and considerable doubt surrounded the diagnoses of D because of the mildness of her disease. So neither were hospitalized in the isolation unit that had been installed upon arrival of the international team. Both recovered within one more week and survived.

Eventually, and somewhat surprisingly, Marburg genome was identified by PCR in the specimens of both D and E. Marburg virus could be isolated from D's blood only, possibly because of high storage temperatures of E's specimen. Antigen capture ELISA and serology were negative for both. The base pair sequences identified in specimens from D and E were identical with the one found in C. Two and a half years later, D and E were found healthy and positive for Marburg IgG.

F, a midwife at Watsa General Hospital, was negative for Marburg IgG on 10 May 1999, but had seroconverted in July 2001. The hospital register revealed that she had assisted B during her abortion on 24 April 1999. F told us that only one glove was available to her. She does not recall having been ill after her contact with B, but claims to suffer from 'malaria' (fever, arthralgia) frequently. F denies to have cared for Marburg cases after the 1998–1999 outbreak.

Discussion

The diagnosis of MHF in the two retrospective cases A and B is based on strong epidemiological evidence and reported

clinical symptoms, without laboratory confirmation; this is a limitation of the study. During an outbreak, the specificity of a case definition based on clinical and epidemiological evidence, as found in A and B, can be assumed to be reasonably high, particularly as no sample collected during the outbreak was found positive for another current viral haemorrhagic fever infection such as yellow fever, Crimean-Congo HF, etc. Diagnoses such as malaria for A or septic abortion for B, however, cannot be completely ruled out. For the incident cases C, D and E, there is no doubt about their diagnosis of Marburg HF. For F, epidemiological and serological evidence is also strong: her first, negative blood sample was taken only 16 days after presumed transmission, probably too early to detect an IgG antibody response; 2 years later she was seropositive, the exposure to Marburg virus during B's abortion being the only contact that could be identified.

The description of symptoms in the fatal cases A, B and C, and of symptoms in surviving cases D and E prior to assessment by the investigation team relies on reports by patient D and by other family members. As no obvious advantage could be expected from being classified as a Marburg case, we assume that reported symptoms were not exaggerated or biased towards MHF-specific ones. There is more reason to suspect that they may have been downplayed, fearing hospitalization in the isolation ward. However, the concerned family was perceived as being trustworthy and we do not have specific reasons to doubt their reports. The mildness of disease in D and E before and after the encounter with the investigation team is plausible given that they both have survived. F was interviewed in depth 2.5 years after her Marburg infection. She may have been asymptomatic, or may have suffered from mild disease without remembering, but we assume that severe disease would not have escaped her memory.

This cluster is interesting in several aspects: First, E is the first confirmed paediatric case of Marburg virus disease ever documented and also the only confirmed paediatric case in the Durba outbreak. The fact that children are underrepresented was found in other filovirus haemorrhagic fever epidemics too, e.g. the Ebola outbreaks in Kikwit (DRC) 1995 (Dowell 1996), but it remains speculative whether this suggests that children are rarely infected, or whether paediatric cases are underreported, possibly because they tend to be less severe, are more easily confused with other differential diagnoses, or simply get less attention.

Secondly, given an incubation period of 5–10 days (Centers of Disease Control and Prevention 2000), and including the two unconfirmed cases identified retrospectively, this cluster could correspond to four generations of Marburg cases (Figure 1), a number of generations that has not been documented before. It also constitutes the most important cluster of confirmed cases in this major outbreak in Watsa and Durba.

Thirdly, half of the cases had subjectively mild disease or may have been asymptomatic. These cases may easily be overlooked, even by active surveillance, if surveillance officers concentrate on impressive cases with frank haemorrhage. Mild cases may play a role in transmission, as was the case in this cluster from D to her child E. On the other hand, mild MHF is particularly difficult to distinguish from other, more frequent diagnoses on clinical grounds alone, without MHF-specific diagnostic tests in place. Lack of sensitivity of the case definition may lead to inappropriate control of human-to-human transmission, lack of specificity may overburden health services already stretched to their limit and may increase the incidence of transmission from true to false MHF patients in the isolation ward.

Fourthly, within this cluster, severity of disease and fatality appear to be decreasing with the number of passages through humans: the first, second and one of the third generation cases died, while the other third generation cases and the fourth generation case survived. For all earlier outbreaks together (referenced in the introduction), the case fatality proportion can be calculated to be 10 of 29 in primary cases, but 0 of 9 in secondary cases ($P = 0.08$, Fisher's exact test). These observations are consistent with the speculation that the virus might become attenuated during its passage through humans.

Fifthly, our epidemiological and virological data are compatible with the prevailing hypothesis, generated during the Durba outbreak, that gold diggers are – for unknown reasons – particularly at risk for primary infection (WHO 1999), and that they can be at the origin of subsequent person-to-person transmission within households (and, to a lesser extent, in health facilities). We suspect that the index case in our cluster, A, had been infected in the gold mine. It seems plausible that the adult women B, C and D were infected because of contact with body fluids while washing soiled cloths or providing nursing care. For the infant E, whose contacts were essentially limited to his mother, D, several routes of transmission via body fluids, including breastfeeding, could be hypothesized. While not probable, co-primary infection from a peridomestic reservoir like rodents, however, cannot be excluded for C, D and E, who all lived in the same household. Because of resource constraints, the collection of rodents, bats and other candidate reservoir hosts was limited to Gorumbwa gold mine and its surroundings, where the majority of primary transmission to man is hypothesized to have occurred; no trace of Marburg virus, however, could be found in the animals (Zeller 2000). F is one of the several cases of occupational Marburg infection during the outbreak in Watsa and Durba.

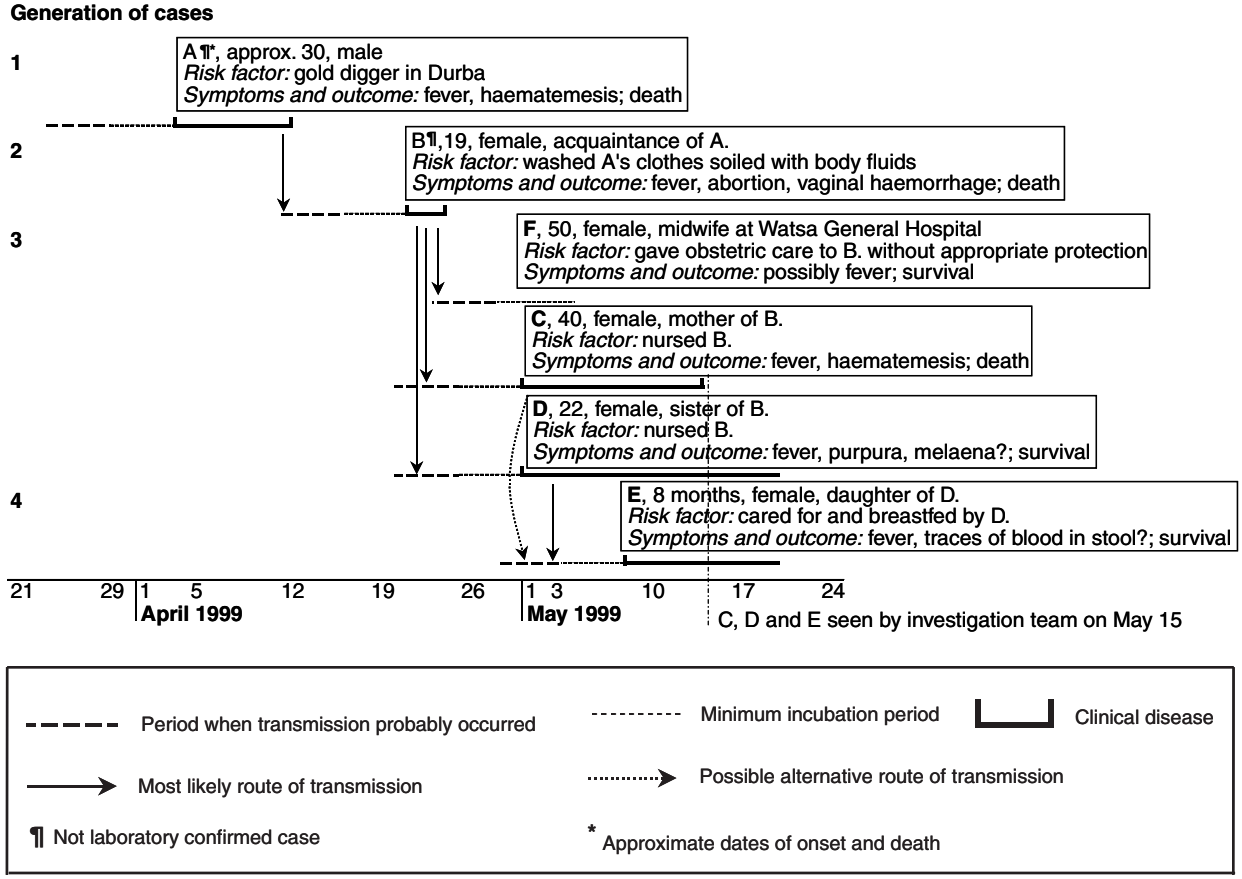

Figure 1 Cluster of Marburg haemorrhagic fever cases involving an infant, with possible ways of transmission.

In summary, our findings indicate that community outbreaks of MHF can affect infants, illustrate that during such outbreaks mild cases are likely to occur, as was the case in the non-community outbreaks in Europe. They also indicate that person-to-person transmission may be more common than ascertained by standard active surveillance. During an epidemic of MHF, one should also look out for mild cases fulfilling the case definition, whom one may have to isolate in order to avoid further secondary spread of the virus. The findings point out that it is difficult to base patient management decisions on a clinical case definition alone: patients may correspond to it but have such mild symptoms that clinicians fail to adhere to the definition and decline isolation (case D), patients may refuse isolation given the mildness of disease, the definition itself may lack sensitivity (cases E and F). This underlines the advantage of having specific VHF diagnostics in the field during an outbreak; that this is feasible, in principle, was demonstrated during the Ebola outbreak in Uganda 2000–2001 (WHO 2001).

Acknowledgements

MB and RC were part of the Médecins Sans Frontières team during the Marburg Haemorrhagic Fever outbreak in Durba; their mission was funded by MSF. We are grateful to Prof. Robert Swanepoel and his team for carrying out all laboratory investigations at the National Institute for Virology, Johannesburg, South Africa.

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