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Viewpoint: Filovirus haemorrhagic fever outbreaks: much ado about nothing?

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Summary The recent outbreak of Marburg haemorrhagic fever in the Democratic Republic of Congo has put the filovirus threat back on the international health agenda. This paper gives an overview of Marburg and Ebola outbreaks so far observed and puts them in a public health perpsective. Damage on the local level has been devastating at times, but was marginal on the international level despite the considerable media attention these outbreaks received. The potential hazard of outbreaks, however, after export of filovirus from its natural environment into metropolitan areas, is argued to be considerable. Some avenues for future research and intervention are explored. Beyond the obvious need to find the reservoir and study the natural history, public health strategies for a more timely and efficient response are urgently needed.

keywords emerging infectious diseases, filovirus haemorrhagic fever, public health

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Introduction

In May 1999, two dozen national and international experts and scientists spent three weeks and a hundred thousand dollars or more to investigate an outbreak of haemorrhagic fever (HF) in Durba, Democratic Republic of the Congo (DRC), an area suffering from war and economic collapse. Upon arrival of the team, 86 cases were suspected during the past 4–6 months causing 58 deaths, and one death had been confirmed to be Marburg HF. It was the first documented community outbreak of this disease, which partially explains the impressive expert/case ratio and the general excitement in the scientific community.

How should such activities be judged from a public health perspective? Given the overall precarious situation of DRC health services, are they a waste of scarce resources, spent on minor events of limited local importance? Are they a heroic struggle against 'Virus X', the 'Coming Plague', a paradigm for hazardous emerging diseases? Or are they just a job that has to be done?

The filovirus debut

In Marburg (Germany) 1967, 21 workers of a pharmaceutical company fell ill with a hitherto unknown disease over a period of three weeks. At the same time, 5 similar cases were observed in Frankfurt/Main and Belgrade (Yugoslavia). All 26 primary cases had been exposed to blood or tissues of vervet monkeys (*Cercopithecus aethiops*), imported via London from Uganda. Six secondary cases occurred among health workers (3 by needle puncture, 1 by cut with post mortem knife) and partners of the patients (1 by nursing care, 1 by sexual intercourse), resulting in a total of 32 cases.

The incubation period ranged from 3 to 8 days. The clinical picture consisted of fever, myalgia, vomiting and diarrhoea, a characteristic rash and enanthem; half of the patients developed a conjunctivitis and 22% severe haemorrhagic diathesis, with bleeding from the gums, nose, puncture lesions as well as haematemesis and melaena. Antibiotic therapy did not change the course of the disease, but reconvalescent serum made a 'favourable impression' on the clinicians. Under intensive symptomatic care of that time, the case fatality rate (CFR) was 23% (summarized from Martini & Siegert 1971; updated from Slenczka 1999).

It soon became clear that the disease was of viral origin. The virus could be demonstrated by electron microscopy in liver tissue, blood, throat washings, urine, etc. The Marburg virus had an unusual size and shape: very long with a median

length of 665 nm and maximum of 8000 nm, shaped like a string – hence the name for the new virus family, *filoviridae*, with a single genus, *filovirus*.

Exposure to monkey blood or tissue could explain the human cases, but the mortality among monkeys was so high that they were an unlikely natural reservoir. Between this initial outbreak and the Durba epidemic, only 8 further Marburg HF cases have been described on 4 occasions: 3 were primary cases occurring after travel in central and southern Africa, 3 were secondary cases among caregivers, and 2 cases occurred in a laboratory; half of the patients died (Slenczka 1999).

Ebola virus enters the stage

In August 1976, 318 cases of haemorrhagic fever, clinically similar to those in Marburg 1967 (Piot *et al*. 1978), occurred in 55 villages around the Catholic mission of Yambuku, north central DRC. 88% of the cases were fatal. Both sexes and all age groups were affected (Breman *et al*. 1978). The mission hospital, with 120 beds and 6000–12000 patients per month at the outpatient clinic, was the epicentre of the outbreak, from where it spread to neighbouring villages. The level of hospital hygiene can be appreciated by the following citation:

> 'Five syringes and needles were issued to the nursing staff each morning for use at the outpatient department, the prenatal clinic and the inpatient wards. These syringes and needles were sometimes rinsed between patients in a pan of warm water. At the end of the day they were sometimes boiled (Breman *et al*. 1978).'

An injection at the mission hospital was the only plausible risk factor in 26%, person-to-person transmission was likely in 47%, and both transmission modes were possible in 14%. The threat to health workers became apparent when 13 of 17 Yambuku hospital staff were infected and 11 died. One of the nursing sisters from Yambuku travelled by air to the capital Kinshasa, more than 1000 km away. She transmitted the virus to an accompanying sister and a hospital nurse in Kinshasa; all three died (Isaacson *et al*. 1978). No doubt this disease could be transported to distant places. The origin of the epidemic, however, remained unclear. The virus was morphologically similar to the Marburg virus: filamentous, with a remarkable maximum length of 14000 nm (Murphy *et al*. 1978); immunologically, however, the virus was different. It was named Ebola and became the second species of the *filovirus* genus.

A parallel outbreak in Southern Sudan started at the end of June 1976 in Nzara (Francis *et al*. 1978). For 14 cases, no plausible source of infection could be identified. As 9 of them worked in a cotton factory infested by rats and bats, an attempt was made to identify the virus reservoir in these animals, but nothing was found. The disease spread among family members, particularly among caregivers. It was transported to Maridi, 180 km away, where it was spread by an active teaching hospital. 76 of 230 hospital staff members became ill, 41 died (El Tahir 1978); about 20 patients and visitors were infected in hospital, with subsequent infection within households. In total, 284 cases were observed in Sudan, with a CFR of 53%.

Although there was road traffic between the areas affected by Ebola in Sudan and Zaire, no direct epidemiological link could be demonstrated (El Tahir 1978). In fact, the viruses proved to be two different strains, Ebola-Zaire and Ebola-Sudan, so that the two epidemics were independent events. A Sudanese specimen led to a nonfatal infection in a British high biological safety laboratory (Emond 1978).

Ebola virus becomes notorious

Filovirus outbreaks created considerable interest among virologists and experts in international health but remained largely unnoticed by the general public. This changed drastically after 1989, when the Ebola virus occurred in quarantine facilities for monkeys in Reston near Washington D.C. Cynomolgus monkeys (*Macaca fascicularis*) imported from the Philippines were found to be infected with a new Ebola strain (Jahrling *et al*. 1990). The Reston strain, while highly pathogenic for monkeys, fortunately was nonpathogenic for humans, even in serocoverted animal caretakers (Centers for Disease Control & Prevention 1990). Similar incidents occurred in 1990 (USA), 1992 (Italy) and 1996 (USA, Philippines). Although the transmission pattern could not be established reliably, there was circumstantial and evidence that transmission in monkeys could have occurred through the air (Peters *et al*. 1993; Rollin *et al*. 1999).

Combine the high fatality rate of Ebola-Zaire infections with possibly airborne transmission of Ebola-Reston and you get the kind of horror scenario that fuels the interest of media and public. The story took off in 1994 with 'The Hot Zone' (Preston 1995); meanwhile millions of copies of this thriller have been sold. Other books have followed, with a variable balance between science and fiction, 'Virus X' (Ryan 1998) being among the better ones, and Hollywood has had its share with the movie 'Outbreak'.

As a consequence, the next major Ebola outbreak 1995 in Kikwit, RDC (315 cases, CFR 81%)

> 'took place in an unprecedented atmosphere of legitimate news reporting and tabloid exploitation' (Peters & Leduc 1999b).

Heymann *et al*. (1999) describe the 'bittersweet lesson' of how the international press helped mobilize urgently needed

resources, but also hindered the containment of the epidemic and violated patients' rights. They conclude that it is a challenge for intervening public health specialists to make optimal use of international media while accommodating their needs without putting patient care, epidemic control and research at risk.

While media attention made a difference, the course of the epidemic was similar to that in Yambuku and Nzara/Maridi. As the index case was a charcoal worker (Khan *et al*. 1999), the source of the outbreak was thought to be in the forest. After secondary spread in the community, the epidemic was spread by health facilities, causing victims among patients and staff. Initially, cases were misdiagnosed as dysentery; thus it took several months to recognize the Ebola outbreak and initiate an appropriate response (Muyembe-Tamfum *et al*. 1999a). As in Yambuku, it was the death of European nuns that triggered the intervention. Unlike in former outbreaks, this epidemic had not yet peaked when the experts arrived. It was not only a challenge for outbreak containment, but also a unique opportunity for field research. Close contact to the patient and his body fluids, particularly during late stage of disease, was the most important risk factor for transmission, followed by contact during burial rites (Dowell *et al*. 1999). Caregivers, be they family members or professional health staff, were those most at risk for secondary infection. Airborne transmission between humans seemed nonexistent or rare (Khan *et al*. 1999). Despite considerable efforts, the reservoir host remained unknown. The development of an immunohistochemical diagnostic test (Zaki *et al*. 1999) based on formalin-fixed post mortem skin snips held some promise for surveillance, as specimen collection is simple, safe and cheap (Lloyd *et al*. 1999). A diagnostic test based on ELISA for anti-Ebola IgM became available; for seroprevalence studies, the ELISA for anti-Ebola IgG seemed to be more specific than the earlier indirect fluorescent antibody test (Ksiazek *et al*. 1999). The many lessons learnt in Kikwit have been recently published in a supplement of the *Journal of Infectious Diseases* (Peters & Leduc 1999a).

A price to pay for interfering with the biosphere?

There were three other Ebola outbreaks in Gabon between 1994 and 1997 (Georges *et al*. 1999) with 141 cases in total (CFR 67%), the first initially misdiagnosed as Yellow Fever (Amblard *et al*. 1997). Primary cases were among hunters or people who had butchered a chimpanzee found dead (WHO 1996), secondary transmission occurred to close contacts and caregivers (family members, health workers or traditional healers). There was considerable geographical spread within the country, including the capital Libreville, and even exportation to South Africa, leading to a fatal nosocomial transmission to a nurse (WHO 1997). By genome sequencing the virus was found to be very similar to the Zaire strain (Georges-Courbot *et al*. 1997). Anecdotes of fatal epidemics among great apes parallel to the Ebola outbreaks in *Homo sapiens* were reported. All three epidemics occurred in proximity to the tropical rain forest, partially in settings that involved significant disturbance of the forest integrity. A hypothesis explaining the increasing number of emerging infectious diseases by destruction of ecological niches gained popularity. Particularly interference with the tropical rain forest and its characteristic abundance of species would lead to encounters with pathogens formerly separated from man's habitat.

The relationship between filovirus disease in human and nonhuman primates was further clarified by a single Ebola case in Ivory Coast 1994. An ethologist studying chimpanzees in the Taï National Park fell ill after performing an autopsy on a chimpanzee found dead in the forest. The virus was of a hitherto unknown strain (Ebola-Ivory Coast). The role of apes and monkeys became clearer: the chimpanzees, observed since 1979, had suffered from episodes of high mortality in 1992 and 1994, and dead chimpanzees had been found with signs of haemorrhage. Consumption of Red Colobus monkey (*Colobus badius*) appeared to be a risk factor for the chimpanzees. Colobus monkeys, herbivores living in the tree canopy, could be intermediate hosts, infected by a possible reservoir such as arthropods, rodents or bats in the upper strata of the forest (Le Guenno *et al*. 1999). Bats are among the principal suspects (Monath 1999): firstly, they have been present in many settings where primary cases of Ebola and Marburg HF have occurred; secondly, after experimental infection they maintain a high viral load without dying from it (Swanepoel *et al*. 1996).

Come-back of Marburg

After Kikwit, Muyembe-Tamfum *et al*. (1999a) had expressed their optimism that 'any new Ebola outbreak hopefully will be diagnosed at a much earlier stage'. With respect to the Marburg outbreak in Durba 1998/99, there was indeed increased awareness at the periphery: the district medical officer in charge repeatedly informed the intermediate level about an outbreak suspicious of haemorrhagic fever. For reasons that are not clear, this did not lead to an immediate response. The total delay from the onset of the epidemic to an appropriate intervention was at least four months, and tragically, the district medical officer was among the fatalities. Moreover, there are indications that since 1994 or earlier, several small outbreaks have occurred in the region, which all remained undiagnosed; a survivor of a 1994 episode now proved IgG positive against Marburg virus. It appears that cases occurred predominantly among men involved in pit gold mining. Compared to the Ebola epidemics, secondary spread seems to

have played a relatively minor role (WHO 1999a,b). At the end of the epidemic, 75 cases had been identified (CFR 83%), most of them retrospectively based on a clinical case definition; laboratory confirmation was obtained in 9 cases (Muyembe-Tamfum *et al*. 1999b; updated). Media attention was limited as the area of the outbreak was difficult to access because of the ongoing armed conflict – circumstances which also hampered the investigation.

Assessing the actual damage …

To answer the question how much effort should be put into filovirus control and research, one should first consider the damage done by them. Since 1967, the year of their discovery, 1209 cases and 873 deaths due to Marburg and Ebola have been diagnosed – compared with 13.9 million deaths caused by HIV, another emerging virus, since the beginning of the AIDS epidemic in the 1980s (UNAIDS 1999). Based on serosurveys, it has been argued that outbreaks may have remained unrecognized (Johnson *et al*. 1993). But even if the reported number of cases and fatalities were underestimated by a factor of 100, filovirus outbreaks would contribute only marginally to the global burden of disease by infectious agents.

However, two aspects deserve further attention: first, the importance of an outbreak at the local level, second, the potential threat at national or international levels. The effects of a filovirus HF outbreak on the affected population as a whole have never been studied systematically, but there is little doubt that they have been dramatic sometimes. Fear and panic have ensued, occasionally leading to avoidable secondary transmission. The impact on health services, frequently the epicentre of the outbreak, has been particularly devastating. Health workers, often in a most tragic way victims and villains at the same time, have paid a heavy toll. Many have died, others have fled, some even have been imprisoned for suspected murder of their colleagues. At Maridi,

> 'at the height of the epidemic, the hospital was in chaos' (Francis *et al*. 1978);
> 'a few patients were left neglected, a large number or nursing staff, in panic, did not show up for work' (El Tahir 1978).

In Yambuku,

> 'the people in the community had already associated the mission hospital with the epidemic and had stopped coming to the outpatient department. The hospital staff … closed the hospital at the end of the month.'

In the absence of basic hospital hygiene and barrier nursing techniques, this turned out to be a good idea because it

> 'essentially stopped injection-transmitted disease and the epidemic shortly terminated' (Breman *et al*. 1978).

In Kikwit,

> 'news about the death of the health care workers … rapidly spread … among the population … This created great panic and mistrust in Kikwit General Hospital, and nearly all patients fled. … Health care workers also left their posts.' (Guimard *et al*. 1999).

Clearly, filovirus HF outbreaks have had most unfortunate consequences for the health facilities involved. However, it is important to keep in mind that the health system itself has contributed to the secondary spread of the infection. The most severe outbreaks have occurred where the health system had been weakened beforehand by economic crisis, breakdown of the public sector or armed conflict. The surveillance systems in place have failed to detect the epidemics in time: deficits have been observed on all levels. Either the outbreak was not recognized or not reported at the peripheral level, or the intermediate level did not respond appropriately. The central level has occasionally played down the seriousness of the situation or discouraged the disclosure of outbreak information to the international community. Several times, an appropriate response was initiated by the death of health staff, after months of neglecting the outbreak in the community. The channel by which information eventually spread was often not the official one maintained by the ministry of health, but a parallel one run by missions or NGOs. As a consequence of all these deficiencies, the chain of transmission was not interrupted as early as possible.

Another consequence of the degraded health system is the lack of hospital hygiene, which has lead to considerable iatrogenic amplification of the disease. Lack of resources, training, supervision and motivation have all contributed to the deplorably low standards of hygiene and medical care observed in some places.

… and the potential threat

Marburg and Ebola HF outbreaks are very rare events with a high case fatality rate, perceived as a severe health problem by the population, exacerbated by a weakened health system, and leading to further damage to this system. Nevertheless, the extreme rarity of the disease would prevent it from obtaining a prominent rank on the international public health agenda if there were not the potential threat of a large future epidemic.

We have learnt that Marburg and Ebola HF outbreaks are not confined to scarcely populated remote places, but may happen in medium-size cities (Kikwit has more than 200 000 inhabitants) and reach large centres (e.g. Kinshasa 1976, 1995, Libreville 1996, Johannesburg 1996). There is no doubt that within days or hours, the virus can reach any place in the world that is part of the international air travel web. Assuming unchanged transmission patterns, the extent to which the virus

will spread after arrival depends largely on the capacity of the health system to prevent and contain an outbreak.

One could argue that community outbreaks have tended to be self-limiting so far. Nosocomial amplification could be rapidly interrupted when standard rules of hospital hygiene plus barrier nursing methods were applied – and even the nosocomial route has been self-limiting when the hospital was abandoned. However, this could dramatically change if a virulent Ebola strain evolves which is able to spread by air, as was possibly the case in the Reston strain. It has been shown that the Zaire strain can be transmitted experimentally to monkeys by aerosol (Johnson *et al*. 1995; P'iankov *et al*. 1995) and it has been suggested that airborne transmission may have happened unintentionally to rhesus monkeys which served as controls in a therapeutic experiment (Jaax *et al*. 1995). It is not at all beyond possibility that some genetic mutation may improve the filoviruses' ability to spread by air. Airborne influenza in 1918–19 killed 20 million people (McNeill 1976) – what would be the toll of airborne Ebola? We are not joining those who suggest that our species is at risk of being wiped out by filoviruses – this is an exaggeration and does not correspond to the course epidemics usually take. However, we know that a virus may emerge and significantly change the global state of health: this is one of the lessons from the HIV pandemic.

Last not least, there is the possibility of filoviruses being used in biological warfare. Given *Homo sapiens*' amazing potential for auto-destruction, the unthinkable may become reality – some preparatory work has been done.

What is on the agenda?

Obviously, the health system in risk areas needs to be strengthened. It must be enabled to detect and report filovirus HF outbreaks early, offer care to patients without putting others at avoidable risk and interrupt the chain of transmission in the community. Nosocomial amplification must be avoided by all means. A strategy of early response to suspect cases, including confirmation of fatal cases by immunohistochemistry, has been proposed recently (Lloyd *et al*. 1999). Now it has to be assured that this approach – or another one – is known and applied by all parties intervening in the field, including NGOs. The challenge is to achieve these improvements in the context of economic crisis, breakdown of the public sector and armed conflict. As long as these fundamental problems prevail, only modest progress can be expected. However, failing to make any change at all will not only favour secondary transmission in the community and in health facilities, but also undermine people's trust in their health facilities, thus inflicting further damage on them.

CDC and WHO (1998) have published guidelines on how to control viral HF in African health care settings. A great effort has been made to adapt the recommendations to an environment where resources are scarce, and to facilitate comprehension by a large number of illustrations. This is without doubt a useful document from the district supervisor level upwards. However, it is a book of 198 pages – an amount of information not easily absorbed during an outbreak. Furthermore, the effort it takes to apply the complex rules of consequent barrier nursing as suggested by these guidelines should not be underestimated, particularly in settings where even the most basic rules have not been applied before. We suggest complementing this comprehensive manual by a concise protocol, aiming at first level health workers, concentrating on the essentials to start with. As an example, correct use of gloves as well as correct disposal or sterilization of needles, syringes, and surgical instruments appears to be particularly important. However, the particularities of viral HF control should not distract from the general rule: Universal principles of hospital hygiene should be applied everywhere, at any time. This would not only reduce the risk of hospital transmission of filoviruses, but of many other pathogens such as HIV and Hepatitis B which are probably more relevant for public health.

As part of the international preparedness for HF outbreaks, concise guidelines for emergency teams should also be set up, covering epidemiological, clinical and logistical aspects of the response, with activities ranked by priority. Once these guidelines are agreed upon, they should become part of the essential package to be taken to the field.

With respect to research, the reservoir and the transmission pattern to primary cases remain the most enigmatic aspects of filovirus diseases. Once we know where the viruses come from, and how they find their way from the reservoir to the human host, options for primary prevention may – or may not – be identifiable. This knowledge could also allow making predictions of future outbreaks should certain ecological events happen or activities continue – such as deforestation in the tropics.

There is no cure for filovirus HF beyond supportive therapy. Hyperimmune serum (Kudoyarova-Zubavichene *et al*. 1999), interferon (Jahrling *et al*. 1999), recombinant monoclonal antibodies (Maruyama *et al*. 1999) and antiviral drugs (Huggins *et al*. 1999) are experimental approaches to be pursued. Blood transfusions from convalescent donors have been tried in Kikwit, with encouraging yet statistically not significant results (Mupapa *et al*. 1999; Sadek *et al*. 1999). This therapeutic strategy should be tested in a randomized controlled trial if an opportunity presents itself; the protocol for such a trial should be prepared in advance.

Conclusion

Research in filoviruses is an investment into an uncertain future: nobody knows how useful it will be in the end. Until

AIDS, retrovirology was fundamental science with little prospect to be useful for human health. The same could become true for filovirology. Regarding intervention, the overall objective must be to enable the health system to cope with filovirus HF epidemics. This includes surveillance, care and outbreak investigation. Sustainability is a major challenge: after Kikwit, Peters and Leduc (1999b) have observed that

> 'despite intensive training, health care workers in Kikwit abandoned most of the improvements in medical hygiene within 3 months of the end of the epidemic'.

Training is essential – but what can we expect from health workers whose salaries are not paid and who face shortages of gloves and needles, while essential utilities like running water and electricity break down? Peters and LeDuc continue:

> 'It is unclear [how the necessary changes] might occur without marked economic and cultural changes'

– this looks like an understatement to us.

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