International Journal of Infectious Diseases 43 (2016) 58–61

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

Recurrence and reinfection—a new paradigm for the management of Ebola virus disease

C. Raina MacIntyre *, Abrar Ahmad Chughtai

School of Public Health and Community Medicine, Samuels Building, Room 325, Faculty of Medicine, University of New South Wales, Sydney, 2052, NSW, Australia

ARTICLE INFO

Article history:
Received 27 October 2015
Received in revised form 11 December 2015
Accepted 11 December 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Ebola
Healthcare workers
Recurrence
Reinfection
Body fluids
Infection control

SUMMARY

Ebola virus disease (EVD) is an understudied infection and many aspects of viral transmission and clinical course remain unclear. With over 17 000 EVD survivors in West Africa, the World Health Organization has focused its strategy on managing survivors and the risk of re-emergence of outbreaks posed by persistence of the virus during convalescence. Sexual transmission from survivors has also been documented following the 2014 epidemic and there are documented cases of survivors readmitted to hospital with 'recurrence' of EVD symptoms. In addition to persistence of virus in survivors, there is also some evidence for 'reinfection' with Ebola virus. In this paper, the evidence for recurrence and reinfection of EVD and implications for epidemic control are reviewed.

1. Introduction

Ebola virus disease (EVD) is an understudied infection, with uncertainty around many aspects of transmission and disease.[1,2] Acute infection is characterized by overwhelming viremia and immune evasion.[3] Direct contact with blood and body fluids is the dominant mode of transmission, but evidence is increasing that other modes, including blood-borne, vertical, sexual, and aerosol transmission, are possible. Ebola virus can cause symptoms in clinically recovered patients despite clearance of virus from the blood.[4,5] With over 17 000 EVD survivors in West Africa, the World Health Organization (WHO) has focused its strategy on managing survivors and the risk of re-emergence of outbreaks posed by chronic persistence of the virus.[6] In addition to chronic persistence of virus in survivors, there is also some evidence for reinfection.[7,8] 'Recurrence' or recrudescence refers to the reappearance of symptoms in survivors due to the persistence of virus at immunologically protected body sites, while 'reinfection' refers to survivors being susceptible to acquiring new infections after recovery. Both of these phenomena create a risk of emergence of Ebola virus outbreaks and are a challenge to disease control efforts. There is much we do not yet understand about Ebola virus, and it is timely to review the implications of recurrence and reinfection for epidemic control.

2. Recurrence of Ebola virus

Ebola virus may persist at immunologically protected sites in the body, including semen, vaginal fluids, sweat, aqueous humour, urine, and breast milk.[4,9–13] A study of 93 survivors showed that 100% had Ebola virus RNA in the semen at 2–3 months post onset of EVD, decreasing to 65% at 4–6 months and 26% at 7–9 months.[13] A positive PCR test may or may not indicate the presence of viable virus. Only a positive virus culture confirms infectious potential. During the outbreak in Kikwit, Democratic Republic of the Congo in 1995, in addition to positive PCR for urine, semen, conjunctiva, sweat, vaginal, and rectal samples from recovered patients, one patient had live virus isolated from seminal fluid up to 82 days after disease onset.[9] In another case, PCR was positive in sweat and urine up to day 40. The last urine culture was positive for Ebola at day 26 after onset, while sweat cultures were negative.[12]

The persistence of virus poses three risks: transmission to others while asymptomatic (e.g., sexual transmission), reactivation of illness (risk to the affected individual), and transmission to others from symptomatic individuals with recrudescent illness

* Corresponding author. Tel.: +61 2 9385 3811; fax: +61 2 9313 6185.
E-mail address: r.macintyre@unsw.edu.au (C.R. MacIntyre).

http://dx.doi.org/10.1016/j.ijid.2015.12.011

(which may go unrecognized as recurrent/recrudescent EVD). Animal studies support the persistence of Ebola virus at some sites and the subsequent re-emergence of symptoms.[14,15] However in most animal studies, especially non-human primate studies, the animals have tended to be sacrificed early; when this has not been the case, the animals have not always been followed up for long enough periods to be analogous to the time course of recrudescent illness described in humans.

During the 2014 outbreak, a 43-year-old US physician developed uveitis 9 weeks after clinical recovery and Ebola virus was isolated from the aqueous humour.[4] Whilst uveitis and ocular complications had been described previously, this was the first time viable virus had been demonstrated to persist in the eye. In past outbreaks, uveitis during convalescence was thought to be a delayed immunological phenomenon, but recent evidence has shown that reactivation of the virus can cause these symptoms. Uveitis in survivors may be due to one or both of these factors and needs further study.

More recently, neurological symptoms reappeared 9 months after recovery in a nurse who survived EVD.[5] She developed meningitis and Ebola virus was detected in blood and cerebrospinal fluid (CSF). She was treated with an experimental drug that had been used successfully to treat severe infection in primates.[16] Whilst similar syndromes had been described in past outbreaks, this was the first time viable virus had been isolated in the CSF. In a 30-year-old woman in Sierra Leone, Ebola virus was detected through RT-PCR at day 41 in CSF and at day 44 in sweat, while blood and urine tests were negative.[17] Studies of women who acquired the infection during pregnancy have indicated that while the woman may recover and clear the virus from blood, a high viral load persists in amniotic fluid, placenta, and foetus.[18] The delivery of recovered women, therefore, should be done with full infection control precautions.

There is a lack of data in relation to the transmission of Ebola through the body fluids of recovered Ebola patients. Rowe et al. examined the transmission of infection from convalescent patients (who had recovered from the acute phase) to household members and did not find direct evidence of transmission.[10] Five household members had serological evidence of Ebola infection and one was possibly due to sexual transmission after recovery.[10] To date, only one confirmed case of EVD has been documented due to transmission through the body fluid of clinically well Ebola survivors. During the 2014 West African outbreak, a 44-year-old Liberian woman acquired Ebola virus from a recovered Ebola survivor who was positive for Ebola virus by RT-PCR in semen at 199 days after recovery; the Ebola virus strain was genetically matched with that of the case patient.[19] The genetic sequencing of virus in this couple has provided strong evidence of sexual transmission of Ebola virus.[20]

3. Reinfection with Ebola virus

Anecdotal reports have raised questions around the possibility of reinfection with Ebola virus, however a confirmed case of reinfection has never been reported.[21,22] The first potential case of reinfection was reported by an aid worker, but was not confirmed.[7] In this instance, it was thought that lowered immunity in a recovered patient may have contributed to reinfection after exposure to a new Ebola patient.[7] In another report, virus was detected through PCR in two children aged <5 years in Monrovia who had recovered clinically and had negative PCR results at the time of discharge.[8] Whether this was recrudescence or reinfection is unclear.

Recovery from EVD requires both humoral and cell-mediated immunity, and variability in the immune response has been described between individuals and between outbreaks.[23] Animal studies also suggest that variability in host immunity can determine whether the host can become susceptible to reinfection. Conditions of partial immunity can lead to the reinfection of recovered mice, which have been shown to develop lethal infection after re-challenge with the virus.[15] In the trial of ZMAb in macaques, a second challenge with Ebola virus was done to test reinfection.[24] Viremia was demonstrated after re-challenge, and two of 12 monkeys that had lower immunity succumbed to a re-challenge. This shows that there is variability in individual host immune responses and that in some cases a first infection does not protect from a second. The converse of this is that some people, presumably with a more robust immune system, are thought to develop subclinical or asymptomatic infection.[25,26] According to a recent report, a group of women in Guinea were not infected despite repeated exposure to the virus, and only one of them had Ebola virus antibodies in the blood.[27] All of this points to great variability in individual host susceptibility to infection and reinfection based on innate immunity, as well as the viral load to which the individual is exposed during a challenge or re-challenge.

Reinfection is theoretically possible due to waning or partial immunity, a high viral load during a re-challenge, or a combination of both of these factors. Studies have shown that Ebola virus antibodies wane after a few years in some survivors.[28] The antibody level required for optimal protection or immune memory is not known, but cell-mediated immunity is also thought to play a role.[23] Figure 1 shows the possible outcomes for an EVD survivor and the pathways through which a new outbreak could occur.

4. Discussion

The 2014 West African epidemic is the largest in history, resulting in more than 28 000 cases and 11 000 deaths.[29] With over 17 000 survivors in West Africa, the magnitude and long-term implications of recurrence and reinfection are unknown. If more than one in four male EVD survivors has virus in the semen at 7–9 months,[13] further cases are likely through sexual transmission. In fact, at least two cases have been documented.[10,19]

Detailed studies of persistence in the vaginal fluid of female survivors have not been reported to date, but the available data suggest that this is an additional risk.[9] In terms of reinfection or recrudescence, variability in host immunity and waning immunity might be important. It is commonly said that healthcare worker EVD survivors are immune and can safely go back into the field to treat EVD patients again, and may not even need personal protective equipment.[30] Some have even claimed that survivors have 'super powers'.[30] This is clearly not the case, with increasing case reports of recrudescence of disease in survivors.[31] In addition, the possibility of reinfection exists and is a function of host immunity as well as the viral load to which an individual is exposed. It may be possible that individuals who clear the virus completely may be susceptible to reinfection under conditions of waning or lowered immunity and a high viral load on re-challenge. However, immunological conditions (e.g., arthralgia/arthritis) may not easily be differentiated from symptoms of virus reactivation – especially when it comes to treatment. Therefore, symptoms in survivors require thorough evaluation, where possible, to identify underlying infectious and non-infectious causes.

Whilst there remains uncertainty about the long-term sequelae of EVD, a range of precautions can be taken to minimize the risk of new cases and outbreaks in the context of a large number of survivors in West Africa. Firstly, the use of condoms for sexual contact should be promoted for survivors for at least 12 months, until further research is available to determine the possible duration of persistence in vaginal and seminal fluid. Past outbreaks indicate the presence of viral RNA in vaginal fluids,[9] and this needs