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Are we any closer to combating Ebola infections?

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In March, 2009, a scientist working in a high-containment laboratory in Germany pricked herself with a needle that had just been used to infect a mouse with the Ebola virus.¹ Although rare, similar laboratory accidents with Ebola virus have been reported in the UK (1976), USA (2004), and Russia (2004), of which the one in Russia was fatal.² Additionally, there have been at least three exposures to Marburg virus in laboratories, another member of the Filoviridae family, and again one of these exposures was fatal.²

The incident in Germany once again caught the high-containment research community off guard because of the lack of prophylactic and treatment options in circumstances of exposure to highly pathogenic agents. This and previous incidents coincide with increasing filovirus outbreaks in Central Africa since the mid-1990s, with at least three imported cases of filovirus infection (South Africa, Netherlands, USA), of which one was fatal and one resulted in the death of an assisting medical worker.^{2,3} Increases in the numbers of high-containment facilities and staff working in these facilities have increased the risk of potential exposures. The emergence and re-emergence of exotic and often highly virulent pathogens certainly justifies our attention, but also needs proper preparation to handle laboratory incidents and protect exposed populations in endemic areas, particularly family members, and medical and aid personnel.

Since the discovery of the Ebola virus in 1976, the research community has been active in developing treatments to counteract infections. Although there has been some success in vaccine development, development of effective treatments has been cumbersome.² Thomas Geisbert and colleagues' report in *The Lancet* today⁴ is long overdue and should be considered a milestone in what has been a difficult and frustrating specialty of filovirus research. The investigators improved their previously successful method of silencing the Zaire Ebola virus RNA polymerase L with small interfering RNAs (siRNAs) that protected guineapigs against lethal homologous challenge.⁵ Although rodents are valuable screening models for efficacy studies of filovirus drugs or vaccines, they often are not useful for prediction of the success in the gold-standard rhesus macaque model.^{6,7} Geisbert and colleagues used an siRNA targeting three genes of the Ebola virus (L, virion protein [VP] 24, and VP35) for postexposure treatment of macaques. Two groups of animals were intravenously injected 30 min after infection with a high challenge dose of Zaire Ebola virus followed by subsequent treatments on days 1, 3, and 5 (first group) or every day from days 1 to 6 (second group). The result was 66% and 100% protection, respectively—efficacies that had not been achieved previously.⁴

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RNA interference as an effective treatment strategy to combat infection with Ebola virus is not novel and has been successfully applied in rodent models and for prophylactic treatment of non-human primates.^{5,8,9} Reliable delivery of the nucleic acid, however, has been a longlasting obstacle that obviously has been overcome by Geisbert and colleagues' use of stable nucleic acid-lipid particles.⁴

Case management of Ebola virus is based solely on the principles of isolation and barrier-nursing procedures with mainly symptomatic and supportive treatment. Shock, cerebral oedema, renal failure, coagulation disorders, and secondary bacterial infection should be managed. There is no proof of any successful strategy for specific prophylaxis and postexposure treatment of Ebola-virus infections in human beings.^{10,11} The table summarises the most promising experimental approaches (postexposure). With the severe and rapid progression of this infection, combination therapy might be most beneficial, but proper efficacy studies are lacking.

On the basis of the success in non-human primate models, there were two promising experimental options for postexposure treatments that were offered to the German scientists: first, treatment with a nematode-derived anticoagulation protein,¹² or second, treatment with a recombinant vesicular stomatitis virus expressing the Zaire Ebola virus glycoprotein,¹⁴ both of which have shown 33% and 50% efficacy, respectively, in postexposure treatment of rhesus macaques that were lethally infected with the virus. The second option was chosen in Germany in 2009. Other than initial unspecific mild symptoms (fever, headache, and myalgia), no adverse effects of the vaccination were reported. However, efficacy was hard to prove because we do not know whether infection had actually occurred.

The specialty of haemorrhagic viruses is in desperate need of approved countermeasures against Ebola-virus infections. To wait for the next incident to happen in a high-containment laboratory before any progress takes place seems intolerable. We also urgently need to improve outbreak support and go beyond transmission control, and actually provide specific care for affected individuals, which should be an ethical obligation for all of us. This provision can only happen in a timely fashion if existing experimental approaches, such as the siRNA strategy presented by Geisbert and colleagues, are investigated in clinical trials and are given at least approval as investigational new drugs that are ready to use in emergencies. Funding is needed, and could come from governmental and nongovernmental agencies and industry.

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Table

Promising treatment options for Ebola haemorrhagic fever*

	Success in macaques	Issues or concerns	Reference
Antisense oligonucleotides			
Phosphorodiamidate morpholino oligonucleotides	Yes (only pre-exposure)	Genetic variation, delivery	Warfi eld et al ⁹
Small interfering RNAs	Yes	Genetic variation, delivery	Geisbert et al ⁴
Coagulation modulators			
Tissue-factor-pathway inhibitors	Yes	Manipulation of coagulation	Geisbert et al ¹²
Activated protein C	Yes	Manipulation of coagulation	Hensley et al ¹³
Postexposure vaccination			
Vesicular stomatitis virus vectors	Yes	Genetic variation, safety	Feldmann et al ¹⁴

* Only approaches that have shown in-vivo efficacy in macaque models are listed.