New rules needed to stop the Ebola epidemic

We are currently facing an Ebola epidemic that can assume huge proportions unless more effective counter-measures are implemented. Although vaccines and anti-virals exist, standard rules stipulate that none of them are ready for use on human beings. The World Health Organization (WHO) has now given approval for experimental interventions to be deployed. This is a wise move, but it may still be too cautious and too late.

I recently spent some time in Monrovia, Liberia on commission from Médecins Sans Frontières (MSF). During my stay I was able to see for myself how this disease can eradicate healthy families in the space of a few days. The ongoing Ebola epidemic is the most severe so far. It is too early to say how it will evolve since there is no overview of how widespread or contagious the virus is. The duration and extent of the epidemic indicates that this virus will not be weakened through the chain of infection. Its epidemiological reproduction rate (R_0) in this outbreak is estimated at 1.6–2.0, with an incubation period of 15 days (1), although this is based on measurements that were taken while containment measures were still functioning.

At present the capacity of the medical support network allows only a small proportion of those infected to be cared for. It is likely that local communities will themselves implement countermeasures to contain contagion. I saw one group from a local community who had had their faces painted white to indicate that they were suspected Ebola patients. If the crisis gets much worse, there is every reason to fear that more drastic measures may be put in place. Unless the global community manages to mobilise the necessary resources swiftly enough, in the worst case the poorest countries could experience an epidemic of huge proportions accompanied by a humanitarian catastrophe resulting from the disintegration of social structures, lawlessness and a halt in production, imports and food distribution.

Promising vaccines
The Ebola virus is classified into several subtypes, and the virus in question in West Africa is the Zaire Ebola virus. Untreated, the mortality rate from this subtype is 80–90 %, but survival can be somewhat improved by supportive care (2). In addition to attempting to combat the epidemic by contact tracing and isolation, it would be advantageous to be able to administer vaccines and to provide antiviral treatment. An expert panel discussion arranged by WHO on 11 August 2014 concluded that in this situation the initiation of experimental interventions on patients could be accepted for drugs that do not have a scientifically documented effect and that are not fully validated with regard to safety and adverse effects in humans. The expert panel set

several requirements: such use was to follow the ethical rules (including informed consent), the distribution of such treatment had to be carried out fairly, and all data involved in the treatment were to be systematically gathered to enable professionals to learn from them (3). They did not explicitly mention that this should be done in the form of placebo-controlled clinical trials, even though – as was concluded in a subsequent commentary in *The Lancet* (4) – this is the best way of avoiding confounding factors.

A vaccine developed by GlaxoSmithKline (GSK) and the National Institute of Allergy and Infectious Diseases (NIAID) is now ready for phase 1 trials in the UK, Gambia and Mali as soon as ethical approval has been granted. It is hoped that the vaccine's safety will be clarified before the end of this

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year so that clinical trials can then be initiated on populations in the areas at risk. This vaccine is based on a live viral vector, the chimpanzee adenovirus type 3 (ChAd3), with genetic material from the Ebola virus. According to a press release from GSK, studies on primates that were infected with the Ebola virus show promising protection (5).

Another promising Ebola vaccine platform, developed by the Public Health Agency of Canada among others, is based on the recombinant vesicular stomatitis virus (rVSV) (6). A trial of various rVSV vaccines provided 100 % protection against the Ebola virus pre-exposure in primates, but did not elicit cross-immunity between the Zaire Ebola virus and the Sudan Ebola virus (7). Surprisingly enough, the vaccines could also be used post-exposure. In experiments with the Marburg virus – a virus in the same taxonomic family as the Ebola virus – five out of six primates survived when the vaccine was administered 24 hours after they had been given a fatal dose of the virus, and two out of six survived when it was administered 48 hours afterwards (8).

Bavaria Nordic is also working on an

Ebola vaccine, and is planning to start phase 1 studies in 2015 (9). The possibility of vaccinating healthcare workers, hygiene staff and infected contact persons against the Ebola virus will represent a large step forward, although time is against us in this particular epidemic. Ultra-fast ethical approval of the trials by WHO and national health authorities will be crucial.

Drug therapy
There is no registered antiviral medication with documented effect against the Ebola virus in humans. A publication from 1999 demonstrated the effect of a number of nucleoside analogues (S-adenosylhomocysteine hydrolase inhibitors) on the Ebola virus in cell cultures. One of them, Ca-c3Ado, was tested on mice. With the Ebola virus dose that was given, all the untreated mice died after five to seven days, while all those that were given more than 0.7 mg/kg Ca-c3Ado from day 0–1 survived. Survival rates when treatment was started on days 2 and 3 were 90 % and 40 % respectively (10). The fact that these findings have not been followed up illustrates that so far the Ebola virus has been a low-priority field.

The nucleoside analogue BCX4430, which acts on both the Ebola virus and the Marburg virus, was given to primates one hour, 24 hours and 48 hours after they were infected with the Marburg virus. Seventeen out of 18 primates in the treatment group survived, while all six in the control group died. Consideration is now being given to starting phase 1 trials of BCX4430 (11, 12). Yet another drug – TKM-Ebola, based on siRNA – is at the phase 1 trial stage (13). Another treatment principle could be glucosidase inhibitors, which hinder the morphogenesis of the virus (14).

In two studies, specific monoclonal antibodies had an effect on primates that started the medicine one hour and 24 hours respectively after they were infected with the Ebola virus (15, 16). This drug has been given to Ebola patients under the name of ZMapp as so-called compassionate treatment. As far as I have been able to ascertain from the media coverage, only seven people with the Ebola virus infection have so far been given ZMapp. Five have survived, of whom at least two were already getting better when they were given the drug. As yet it is impossible to say whether it has any effect. Stocks have now run out, and it will take a long time to produce more. A drug

that is so complicated to produce will of necessity be extremely expensive, and it is difficult to believe that it will ever be used for large outbreaks in countries with few resources.

At an expert panel meeting on 5 September 2014 WHO decided to attempt to give infected patients transfusions of blood from people who had survived the Ebola virus infection (17). The only scientific publication on this is a report from the Democratic Republic of the Congo that describes how seven out of eight Ebola patients who were given blood from convalescent patients survived (18). Treatment involving blood transfusions will generate considerable logistic problems in a disaster situation where there is hardly sufficient capacity to take care of the dead. In the long term it may be possible to develop an anti-Ebola virus immunoglobulin antibody.

New rules

A potentially fruitful approach is to seek efficacy against the Ebola virus among drugs that have already been registered and tried out and where adverse effects and safety for human beings have already been well validated. Madrid and his colleagues found that chloroquine has an anti-Ebola virus effect, with nine out of ten mice in the treatment group surviving (19). The mice were given a far higher dose of chloroquine than that used in the treatment of malaria. Another study tested oestrogen receptor inhibitors in vitro and in a mouse model (20). It was found that 90 % of the mice survived if they were injected with chlomiphene one hour after being given an injection of a fatal dose of the Ebola virus. Chlomiphene is normally used to correct anovulation. It has been on the market so long that there are now generic substitutes, and it is therefore cheap and easily available.

A new Japanese antiviral – T-705 (favipiravir) – is currently undergoing phase 3 trials for use against influenza. When this medicine was tested on mice, all the mice that were treated on day 6 after they were infected with the Ebola virus survived (after signs of the disease had begun to be apparent), while all the mice in the control group died. The mice that received treatment from day 8 did not show a significantly better survival rate than the control group (21).

In my opinion the global community should now assign high priority to testing more drugs that are already available for their possible effect against the Ebola virus. This would allow trials of combination therapies to be initiated as quickly as possible to avoid resistance development.

Ideally drug efficacy should be tested on primates with the Ebola virus infection before a clinical trial is implemented in humans. Antivirals' point of attack is the virus rather than the host organism. Experiments on mice will therefore be more relevant with regard to use in humans than if, for example, blood pressure medicine is being tested. The main differences will apply to pharmacokinetics, the adverse-effect profile and toxicity. Experiments with primates are resource-intensive, somewhat risky and take time to prepare. The question must also be raised as to whether in this case it is more ethical to infect primates with the Ebola virus than to give some Ebola patients a chance. The Ebola epidemic situation is so precarious and the time factor so critical that in my view changing the rules can be defended for the public good. WHO's decision to now allow the use of experimental Ebola treatment directly in human beings seems to be a wise one.

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