NATURE | NEWS: EXPLAINER

Should experimental drugs be used in the Ebola outbreak?

***Nature* examines the risks and benefits of unproven Ebola treatments, as World Health Organization says it is ethical to use them in West African crisis.**

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Michael Duff/AP/Press Association Images

In Freetown, Sierra Leone, preventing Ebola is a top priority: when might vaccines and drugs be part of the effort?

Two Liberian doctors are set to become the first Africans to receive an experimental drug against the Ebola virus. Once they are treated, existing supplies of the drug, ZMapp, will be exhausted. The news comes as the World Health Organization (WHO) concludes that it is ethical to use unproven treatments in the current outbreak in West Africa, the biggest outbreak of Ebola since records began, which had killed 1,013 people by 9 August.

The debate about experimental drugs intensified after two US health workers infected with Ebola received the drug ZMapp, made by Mapp Biopharmaceutical of San Diego, California. That prompted some public-health leaders to argue that the drug should also be made available in Africa, where the majority of patients are dying. Others fear that this will provoke a backlash if the drugs cause side effects or are not effective.

In response, the WHO convened a panel of experts on 11 August to discuss the ethics of using experimental drugs more widely in the current outbreak, which was declared a global health emergency last week.

The group released a statement on 12 August, concluding that “it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention”. The group adds: “Ethical criteria must guide the provision of such interventions. These include transparency about all aspects of care, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community.”

In a phone conference with reporters, WHO assistant director-general Marie-Paule Kieny said that it is not the number of people affected that led the group to take this unusual position, but the fact that usual prevention and infection control measures are not working to contain the outbreak.

The WHO group plans to reconvene at the end of the month to discuss the much thornier ethical question of how to go about

prioritizing the use of the drugs, including whether ethics dictates that health-care workers receive limited doses of treatments before the general community. For the time being, Kieny said, the WHO will act as a "broker" by putting communities in touch with drug developers, although the agency itself has no authority to decide who should get which drug and when. Liberia received the last doses of ZMapp because it requested them, she said. "I don't think there could be any fair distribution of something that exists in such small quantities."

***Nature* special:** Ebola outbreak in West Africa

The WHO group also says that there is a "moral obligation" to ensure that data on the safety and efficacy of any experimental drugs used in the current outbreak are collected, shared and evaluated scientifically. "If we don't do proper evaluation, we will never know," Kieny said.

So what are the risks and benefits of using experimental treatments? Here we answer your questions.

What treatments and vaccines exist for Ebola fever?

Several are under development but none has been fully tested in humans. In addition to ZMapp, another drug — TKM-Ebola, made by Tekmira in Burnaby, British Columbia — is also under consideration. Ebola vaccines, meanwhile, are being developed at biotechnology company Profectus Pharmaceuticals in Baltimore, Maryland, and under programmes sponsored by the US government. The WHO says that it also wants to investigate the use of serum from people who had Ebola and survived, because their blood now contains a high concentration of antibodies against the virus.

Do they work?

Nobody knows. Although the two US ZMapp recipients seem to be recovering, it is impossible to know whether this is due to the drug itself, to good health care or to other treatments; one of the patients was also infused with blood from a boy who recovered from an Ebola infection, which may have provided infection-fighting antibodies. "There is a lot of excitement over ZMapp, but there is no evidence that it actually worked," says Amesh Adalja, an infectious-disease physician at the University of Pittsburgh Medical Center in Pennsylvania. A Spanish priest who was also due to be treated with ZMapp has died, although it is yet unclear whether he received the treatment first. A vaccine made from a vesicular stomatitis virus (VSV) — a modified version of which is used in the Profectus vaccine — saved the lives of monkeys with Ebola virus in 2005, which is a promising sign. TKM-Ebola, meanwhile, has only ever been given to healthy people.

Are the drugs and vaccines safe?

Because the drugs have been used in so few people, this is another unknown. ZMapp contains a cocktail of immune proteins called monoclonal antibodies. Such antibodies are already used to treat diseases such as cancer and arthritis, and can have side effects similar to those seen in an allergic reaction, such as rashes, fever, nausea, diarrhoea, vomiting and, rarely, life-threatening shock. The VSV-based vaccine, meanwhile, contains pieces of Ebola protein embedded in a virus and has been given to a single healthy person without serious side effects. TKM-Ebola was tested in a handful of healthy people before the US Food and Drug Administration (FDA) stopped the trials in July because of safety concerns. Tekmira's drug was said to have the potential to trigger a condition called cytokine release syndrome, which can cause symptoms similar to those seen with monoclonal antibodies. But the FDA has clarified its position in the wake of the current outbreak, and said on 7 August that the drug could potentially be used in Ebola patients, but not in healthy volunteers.

Aren't the side effects worth it in the case of a deadly disease like Ebola?

It might seem so, but side effects could complicate things. Health-care workers in outbreaks may not be equipped to handle a very rare side effect if it occurs, and the death of a patient due to a side effect could deepen fear and mistrust of health-care workers and slow the development of Ebola medicines and other research. "I do worry about a '*Constant Gardener*' scenario, where you have concerns that Western companies are experimenting on Africans," says Adalja, referring to the John Le Carré novel, which also became a film, about a man who uncovers a secret drug trial run by a Western company in Africa. "There may be political ramifications if a drug that has no safety data is given and causes side effects," Adalja says. He recommends indemnifying the companies that might provide experimental Ebola treatments, which would protect them from lawsuits brought on behalf of patients who experience side effects. This is already done for makers of childhood vaccines in countries such as the United States.

What precedent is there for using untested drugs in special cases?

The FDA approved the use of an unapproved antiviral drug called peramivir during the 2009 H1N1 influenza epidemic. And individual patients are often provided with unapproved drugs under 'compassionate use' guidelines; a US Marine, for instance, was treated with

two unapproved drugs in 2009 to treat a runaway infection with vaccinia virus after a routine vaccination against smallpox. Usually, however, the medicines given in these situations have been proved to be safe in healthy people: “It’s very uncommon to use a drug that hasn’t undergone safety testing in humans, in ill volunteers,” says Jesse Goodman, head of the Center on Medical Product Access, Safety and Stewardship (COMPASS) at Georgetown University Medical Center in Washington DC. That’s because it is difficult to tell the side effects of a medicine from the normal course of a disease, and because ill people might be more vulnerable to side effects from an experimental drug.

What are the ethical obstacles to using the drugs in the current outbreak?

A major question is whether patients with a fatal disease can make a well-informed decision about using unapproved treatments. “Dying people grasp at straws,” says physician Armand Sprecher of Médecins Sans Frontierès (also known as Doctors Without Borders), who is fighting the current outbreak. He recommends gaining consent from affected communities, not just individuals, to boost understanding of the research. “This is a setting where people are already accusing the infection-control agencies of all sorts of nefarious things — stealing organs, spreading disease, performing nefarious research,” Sprecher says. “You would want to be really transparent in your actual research to make sure nobody misunderstands.”

Is there any scientific or medical downside?

Some public-health experts have argued that the debate about the treatments is distracting from the public-health measures necessary to end the Ebola outbreak. “If people think they can hold out for this drug and not use the public-health measures that have worked in past Ebola outbreaks, this disease will just spread,” Adalja says. The WHO worries too about the public response to the existence of a treatment: if there is not enough to go around, health-care workers suspected of having a cure could be in danger. And a promising treatment that ends up not working could erode hopes and trust in public-health workers. Communication, the WHO says, will be essential.

Would scientists learn anything from using the treatments in the current outbreak?

Experts have argued that using experimental treatments during an outbreak might be the best way to determine whether they actually work. “While we can likely provide safety data from anywhere in the world, we can only assess whether a vaccine or drug works for Ebola by using it in affected countries with the consent of individuals and communities concerned,” says tropical-medicine physician Jeremy Farrar, head of the UK-based Wellcome Trust, who was one of the 12 experts chosen for the WHO ethics panel.

If they are used more widely, who would take Ebola drugs?

Patients infected with Ebola would be first in line for ZMapp. If the drug works, it could have benefits beyond saving the lives of those patients, says Sprecher, by helping to gain the trust of affected communities, some of which have been mistrustful of health-care workers, hindering efforts to contain Ebola. “It could be a really strong tool. All these people that are not feeling good about coming into the treatment unit might change their minds if you start producing survivors instead of bodies,” he says.

What about the vaccines?

Health-care workers caring for Ebola patients would probably be among the first to receive a vaccine. Because some workers are refusing to care for patients with Ebola-like symptoms, patients with treatable illnesses such as malaria and dysentery are probably dying as a result, so an effective vaccine would be welcome. “It would save a lot of lives if you could return health-care delivery to normal by vaccinating health-care staff,” says Sprecher. But, cautions John Eldridge, the chief scientific officer of Profectus, it is unlikely that a vaccine would be used in health workers before it undergoes rigorous human safety testing, which has not yet begun. “The risk-to-benefit ratio is for a normal healthy adult,” he says, “and someone suspected of being infected is radically different.” Kieny said that two vaccines are likely to be put on the fast-track to begin first trials in people by the end of September.

Can any of the treatments be made available in large quantities before the outbreak ends?

According to the WHO, after doses are given to the two Liberian doctors, existing supplies of ZMapp will be exhausted. Mapp Biopharmaceutical says that it will take months to make more. Kieny is hopeful about prospects for speeding up the availability of treatments: “There is so much effort from so many people to move as quickly as possible,” she said. Thomas Frieden, director of the US Centers for Disease Control and Prevention in Atlanta, Georgia, said on 7 August that it will be at least three months until the epidemic ends.

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Updates

Updated: This story contains additions since it was first posted to incorporate reporting from a subsequent World Health Organization press conference.