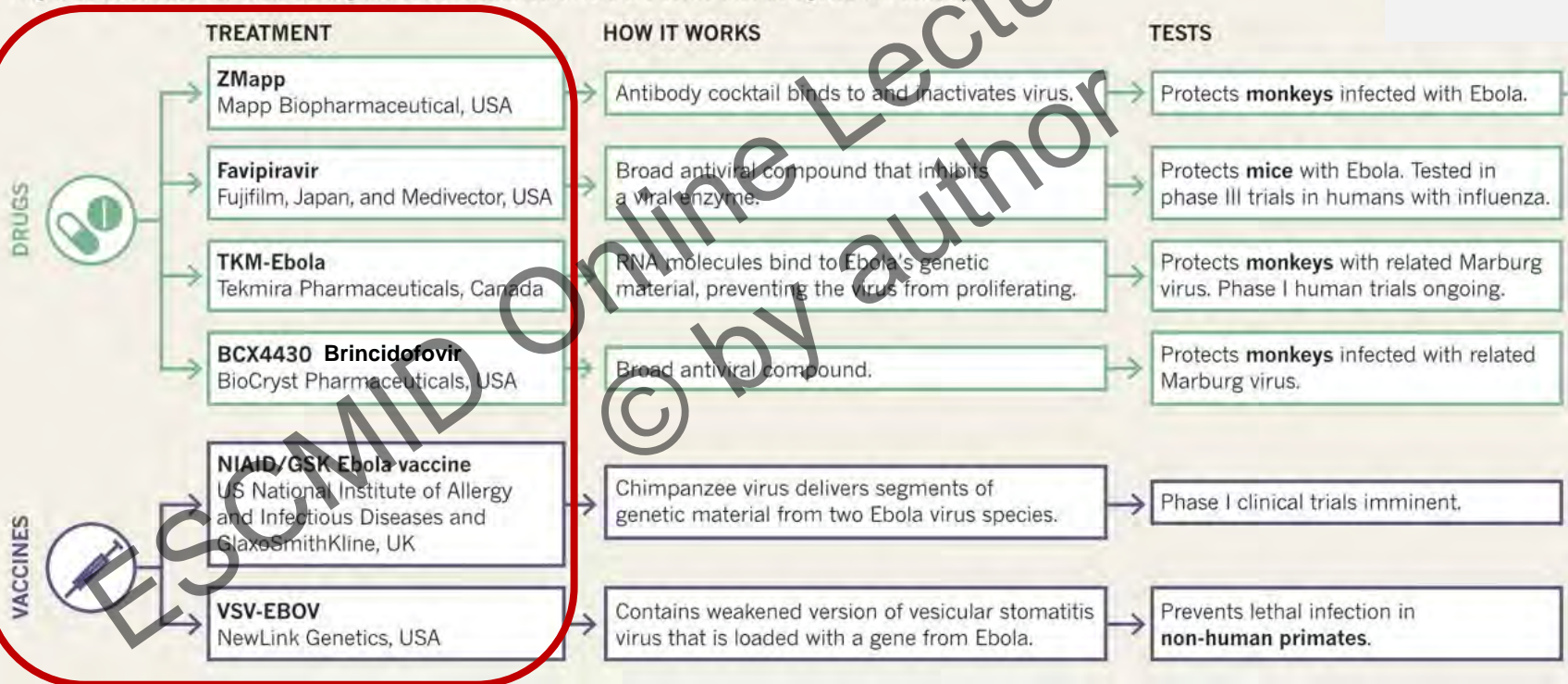


## Over the past decade, several experimental strategies have shown promise in treating EBOV-challenged nonhuman primates (NHPs) after infection.

- Recombinant human activated protein C (rhAPC)<sup>3</sup>
- Recombinant nematode anticoagulant protein c2 (rNAPc2)<sup>9</sup>
- Small interfering RNA (siRNA)<sup>10</sup>
- Positively-charged phosphorodiamidate morpholino oligomers (PMOplus)<sup>11</sup>
- The vesicular stomatitis virus vaccine (VSVΔG-EBOVGP)<sup>12</sup>
- The monoclonal antibody (mAb) cocktails MB-003 (consisting of human or human–mouse chimaeric mAbs c13C6, h13F6 and c6D8)<sup>13</sup>
- The monoclonal antibody (mAb) cocktails ZMAb (consisting of murine mAbs m1H3, m2G4 and m4G7)<sup>14</sup>
- **Only the antibody-based candidates have demonstrated substantial benefits in NHPs when administered >24 h past EBOV exposure.**
- Follow-up studies have shown that MB-003 is partially efficacious when administered therapeutically after the detection of two disease “triggers”<sup>15</sup>, and ZMAb combined with an adenovirus-based adjuvant provides full protection in rhesus macaques when given up to 72 h after infection<sup>16</sup>.

## DRUGS AND VACCINES TO WATCH

This week the World Health Organization is convening a meeting to discuss Ebola drugs and vaccines that might be prioritized for trials during the current outbreak. Here are some that delegates will consider.



# Convalescent plasma

## State of research

Studies suggest blood transfusions from EVD survivors might prevent or treat EV infection in others, but the results of the studies are still difficult to interpret. It is not known whether antibodies in the plasma of survivors are sufficient to treat or prevent the disease. More research is needed.

## Safety

Safe if provided by well-managed blood banks. Risks are like those associated with the use of any blood products, such as the transmission of blood-borne pathogens that cause disease. There is a theoretical concern about antibody-dependent enhancement of EVD infection, which can increase infectivity in the cells.

## Availability/feasibility

Blood transfusion is culturally acceptable in West Africa. Potential donors are Ebola survivors, but the logistics of blood collection are an issue. Options to conduct studies in patients are being explored. The first batches of convalescent plasma might be available by the end of 2014.

# Zmapp: Cocktail of three chimeric mousehuman monoclonal antibodies



## State of research

The three antibodies in this mixture block or neutralize the virus, by binding to or coating a different site on the covering or “envelope” of the virus. Studies in monkeys showed a strong survival up to five days after infection, when virus and/or fever were present.

*Company: Mapp Biopharmaceutical Inc. Type: Monoclonal antibodies. Three murine mAbs selected from MB-003 and ZMAb (13C6, 13F6 and 6D31) engineered with human constant regions targeting non-overlapping Ebola virus epitopes (the mucin-like domain as well as the 6D31 and core epitopes of GP1) manufactured in transgenic N. benthamiana lacking plant-specific N-glycan residues. Sci. Trans. Med. 5, 199ra113 (2103)*

## Safety

There have been no formal safety studies in humans. Very small numbers of EVD-infected people have been given ZMapp on a compassionate basis, and no safety issues have been reported to date. Clinical effectiveness is still uncertain.

## Availability/feasibility

A very limited supply (fewer than 10 treatment courses) has been deployed to the field. Efforts to scale up production may yield increased supplies of potentially few hundred doses by the end of 2014.



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## Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp

Xiangguo Qiu, Gary Wong, Jonathan Audet, Alexander Bello, Lisa Fernando, Judie B. Alimonti, Hugues Fausther-Bovendo, Haiyan Wei, Jenna Aviles, Ernie Hiatt, Ashley Johnson, Josh Morton, Kelsi Swope, Ognian Bohorov, Natasha Bohorova, Charles Goodman, Do Kim, Michael H. Pauly, Jesus Velasco, James Pettitt, Gene S. Olinger, Kevin Whaley, Bianli Xu, James E. Strong, Larry Zeitlin *et al.*

Affiliations | Contributions | Corresponding authors

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National Laboratory for Zoonotic Diseases and Special Pathogens, Public Health Agency of Canada, Winnipeg

Here we show that a combination of monoclonal antibodies (ZMapp) is able to rescue 100% of rhesus macaques when treatment is initiated up to 5 days post-challenge. ZMapp exceeds the efficacy of any other therapeutics described so far, and results warrant further development of this cocktail for clinical use.

High fever, viraemia and abnormalities in blood count and blood chemistry were evident in many animals before ZMapp intervention. Advanced disease could be reversed leading to full recovery.

ELISA and neutralizing antibody assays indicate that ZMapp is cross-reactive with the Guinean variant of Ebola.

# TKM-100802 Lipid Nanoparticle Small interfering Ribonucleic acid (siRNA) (Tekmira)



## State of research

TKM targets two essential viral genes to stop the virus from replicating. Effective in guinea pigs and monkeys. In monkeys 83% survival if administered 48 hours after infection, and 67% survival 72 hours after infection.

*Tekmira Pharmaceuticals. Type: small particle. Lipid nanoparticle delivery of anti-Marburg virus nucleoprotein-targeting small interfering RNA (siRNA). Sci Transl Med. 2014 Aug 20;6(250):250ra116.*

## Safety

A single-dose study in healthy volunteers found side effects including headache, dizziness, chest tightness and raised heart rate at high doses. At lower doses projected to be the dose used for treatment, drug was better tolerated

## Availability/feasibility

The FDA has authorized emergency use in EVD-infected patients. A limited number of treatment courses are potentially available. There is potential for the production of 900 courses by early 2015.

# Favipiravir/T-705 (Avigan)

## State of research

Effectiveness against EVD in mice, but in animal monkey study only one out of six survived. Another study of animals using a different dose regimen is underway.

*Company: MediVector. Type: Small molecule. Avigan (favipiravir) broad spectrum 6-fluoro-3-hydroxy-2-pyrazinecarboxamide nucleoside analog inhibitor of RNA-dependent RNA polymerase. Active against influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease virus as well as other flaviviruses, arenaviruses, bunyaviruses and alphaviruses. J. Antiviral Res. 82, 95–102 (2009)*

## Safety

Approved in Japan for influenza treatment under special circumstances. Remains under study in other countries. Has been tested in more than 1000 people, with no major adverse effects reported. But the dose proposed for treatment of EVD could be 2-5 times higher than that tested so far and duration of treatment might be longer than in current influenza studies. It should not be used during pregnancy due to potential birth defects. It has not been studied in humans for EVD

## Availability/feasibility

Use for field post-exposure prophylaxis is under discussion. More than 10,000 treatment courses may available, pending determination of the therapeutic dose

# BCX4430 (Brincidofovir)

## State of research

Studies of this anti-viral in animals indicate 83% to 100% survival in rodents with EVD. It is also effective in animals 48 hours after infection with the lethal Marburg virus. Testing for EVD in monkeys is underway.

*Company: BioCryst Pharmaceuticals. Type: Small molecule. Lipid conjugate of cidofovir that is converted intracellularly into the active antiviral, cidofovir diphosphate, BCX-4430 adenosine analog inhibitor of RNA-dependent RNA polymerase. Julander et al. 2nd Antivirals Congress, 0:14, 17:12–17:24, November 12, 2012, Cambridge, Mass., USA.*

## Safety

No human safety studies or data available. Safety studies are planned.

## Availability/feasibility

Has been approved by the FDA for use in treating EVD patients through an Emergency Investigational New Drug (EIND) application. No material is currently available for field use.



# AVI 7537 (Sarepta) Phosphorodiamidate oligonucleotide.

## State of research

In monkey studies, doses of 14 to 40 mg/kg for 14 days showed typical survival ranging from 60% to 80% when given at the time of infection

*Company: Sarepta Therapeutics. Type: Antisense oligonucleotide. Piperazine-modified phosphorodiamidate morpholino antisense oligos against Ebola VP24 and VP35 transcripts. Nat. Med. 16, 991–994 (2010)*

## Safety

Human tolerability has been demonstrated in early studies.

## Availability/feasibility

The active pharmaceutical ingredient is available for 20 to 25 courses by mid-October. Potential production of approximately 100 treatment courses by early 2015.

# Interferons

## State of research

Induces an antiviral state in exposed cells and regulates the immune system. A study showed delayed time to death in monkeys but no overall increased survival. Early administration enhances the effectiveness of treatment in animals and lengthens the time after the viral infection at which antibodies show effectiveness.

## Safety

Various forms approved for treating chronic hepatitis and multiple sclerosis. Higher doses are associated with increased adverse effects but no greater efficacy.

## Availability/feasibility

Commercially available. There are several types of interferons. Decisions regarding which one to use, when to use, and the dose regimen need careful consideration.

# cAd3-ZEBOV: Chimpanzee adenovirus serotype 3 vaccine

## State of research

Uses a chimpanzee adenovirus that does not grow, containing the gene for EVD surface protein. In a study of animals given a lethal dose of EVD, all 16 were protected by a single dose of the vaccine.

*Company: GlaxoSmithKline. Type: Viral vaccine. **Contains genes for a surface protein from two different strains of Ebola stitched into a harmless chimpanzee adenovirus that serves as a vector.** Recombinant Chimpanzee adenovirus delivering non-disclosed Ebola genes. *Sci. Transl. Med.* 4, 115ra24 (January 2012)*

## Safety

More than 1,300 people have received these vaccines for other diseases, including over 1000 people in Gambia, Senegal, Burkina Faso, and Kenya. These other vaccines seem safe so far, but as yet there is no safety information on an EVD vaccine in humans.

## Availability/feasibility

There is no information from human trials. An early trial of an EVD vaccine containing two EVD strains, Zaire and Sudan, is planned to start in September 2014 in the US. A vaccine against Zaire EVD may be evaluated in the UK, and then in one or two African countries in 2014. The earliest availability depends on results of trials and manufacturing timelines. Approximately 15000 doses might be available by the end of 2014.

# rVSV-ZEBOV: Recombinant Vesicular Stomatitis Virus vaccine

## State of research

The rVSV vaccine aims to induce EVD-specific immune responses. The vaccine protected all 20 animals from a lethal dose of EVD. Animals with weakened immunity were not harmed by rVSV-EVD. The vaccine was safe when injected directly into the brain of animals. Could be very durable

*Company: Profectus BioSciences. Type: DNA vaccine . **Contains the Ebola surface protein gene inside a weakened version of vesicular stomatitis virus (VSV)**, Prime boost combination of plasmid DNA vaccine expressing Ebola/Marburg surface antigens together with a recombinant vesicular stomatitis viral vector expressing same epitopes. J. Virol. 81, 5257–5269 (2007)*

## Safety

It is unknown if rVSV-EVD will grow in humans, especially in people with weak immunity. Too little growth could make a weak vaccine, while too much could cause illness. The consequences of spreading rVSV-EVD to unvaccinated people or animals are unknown. One laboratory worker was given rVSV after a needle stick injury, and remained well. This does not prove the vaccine will be safe or protective. The laboratory worker had a small but detectable amount of vaccine in plasma for a short time after rVSV-EVD vaccine injection.

## Availability/feasibility

Safety, efficacy and duration of protection are unknown. An early trial is due to start soon in the US. Eight hundred doses are currently available.



BACKGROUND DOCUMENT  
POTENTIAL EBOLA THERAPIES AND  
VACCINES

DRAFT

THIS DOCUMENT INCLUDES  
PROPOSED ELEMENTS TO CONSIDER DURING THE DELIBERATIONS TO DEVELOP A FRAMEWORK  
TO ASSIST DECISION MAKING AT GLOBAL AND NATIONAL LEVEL

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