Ebola Vaccines and Treatments
Current Prevention and Treatment

- Isolation of cases
- Stringent infection control
- Contact tracing
- Surveillance
- Risk communication
- Treatment options limited
- Supportive therapy centred on:
  - Fluid resuscitation
  - Correction of electrolyte abnormalities
  - Prevention and treatment of concomitant infections
  - Prevention complications of shock
Treatment options for Ebola virus disease

• At present, there is no licensed specific therapeutic drug or vaccine available for Ebola virus disease (EVD)

• Number of drugs and vaccines under development which have demonstrated promising results in animal models

• Pressure to expedite clinical trials in light of current outbreak
• The gold standard animal model for Ebola vaccine and drug testing is the non human primate (NHP)

• Macaques, African green monkeys, baboons
WHO CONSULTATION ON POTENTIAL EBOLA THERAPIES AND VACCINE

GENEVA, SWITZERLAND
4-5 SEPTEMBER 2014
Potential Ebola Vaccines
Ebola vaccines - historically

- Debate about requirement for vaccine previously
  - Rarity of disease
  - Lack of interest from pharmaceutical industry
  - Potential cost

- View has changed in recent years
  - Increasing frequency of outbreaks with high case fatality rates
  - Number of imported cases of viral haemorrhagic fever and laboratory exposures
  - Potential misuse of EVD as bioterrorism agent
Who to vaccinate?

• Valuable for:
  – Medical personnel
  – First responders
  – Military personnel
  – Researchers
  – Ring vaccination in outbreak
What’s in the pipeline?

• Several candidate vaccines being developed
• **Two** identified as being at the most advanced stage of development
• Both are recombinant vector vaccines
  1. Chimpanzee adenovirus serotype 3 (cAd3-EBO)
  2. Recombinant vesicular stomatitis virus (rVSV-EBO)
• Both are being fast-tracked but data on safety and efficacy are limited
1. Chimpanzee adenovirus serotype 3 (cAd3-EBO)

- Based on recombinant adenovirus 3 (cAd3) technology
  - a surface protein gene of Ebola virus is inserted into a modified chimpanzee adenovirus
  - resulting virus cannot replicate in humans, but is intended to induce an immune response

- Adenovirus causes common cold
- Pre-existing immunity in humans may be a problem, impairing vaccine efficacy
- However, cAd3 is a rare adenovirus serotype, with most humans not having pre-existing immunity
1. Chimpanzee adenovirus serotype 3 (cAd3-EBO)

- cAd3-EBO tested in 16 NHPs and found to be 100% protective (Stanley et al 2014)
- Phase 1 human trials began in September in US and Oxford
- Being developed by GlaxoSmithKline and US National Institute of Health
2. Recombinant vesicular stomatitis virus vaccine (rVSV-EBO)

• VSV causes mild flu-like illness in humans

• Gene for surface glycoprotein of Ebola inserted into VSV - this recombinant virus is then intended to induce an immune response in humans to Ebola virus

• Jones et al (2005)
  – 100% protective against Zaire Ebola virus (ZEBOV) in NHPs after a single vaccination
2. Recombinant vesicular stomatitis virus vaccine (rVSV-EBO)

  – demonstrated varying degrees of protection post-exposure in NHPs if vaccine given up to 24 hours after exposure to a lethal dose of Ebola virus

• Given to lab worker exposed to ZEBOV following needle stick injury in Hamburg, 2009
  – VSV viraemia but did not develop EVD
  – It’s not possible to know if treatment was effective or if patient was never infected
2. Recombinant vesicular stomatitis virus vaccine (rVSV-EBO)

• Phase 1 human trials began this autumn

• Being developed by Public Health Agency of Canada, NewLink Genetics
Potential Ebola Treatments
Potential Ebola Treatments

1. Antibody therapy
   a. Convalescent whole blood and plasma
   b. Monoclonal antibodies (ZMapp)

2. Antiviral therapy
   a. RNA-based drugs
   b. Brincidofovir (CMX-001)

3. Immunomodulators

4. Coagulation modulators
1a. Convalescent Whole Blood and Plasma

- Blood or plasma transfusions from Ebola survivors might prevent or treat infection in others
- Studies not conclusive
- Theoretical and anecdotal evidence
- Used in small number in current outbreak
- Well-managed blood banks critical with thorough screening to ensure
  - No pathogens being transmitted via transfusion
  - Blood types match
1b. Monoclonal Antibodies - ZMapp

- Cocktail of 3 monoclonal antibodies
  - c13C6 and c2G4 and c4G7
- Manufactured in tobacco plants
- Targets Ebola virus glycoprotein
- Attaches to the virus and block its infective potential
1b. ZMAPP: What’s the Evidence?

- Qiu et al (2014)
  - Study of 21 rhesus macaques
  - ZMAPP able to rescue 100% of macaques infected with lethal dose of EBOV when treatment initiated up to 5 days post lethal Ebola challenge
  - Some NHPs with advanced disease fully recovered
1b. Monoclonal Antibodies - ZMapp

- Not yet tested in human trials
- Small number of cases from current outbreak given drug on compassionate basis with variable results
- Current supplies of drug exhausted
- Efforts being made to scale up production, task difficult due to its complex production processes

Phase 1 clinical trials planned
2a. RNA-based drugs

- Interfere with translation of Ebola virus mRNA to protein
- Prevent virus from replicating
2a. RNA-based drugs

Favipiravir (T-705)

• Orally available

• Approved for influenza treatment in Japan

• Efficacy against Ebola in mice (Oestereich et al 2014)

• However, in study of monkeys only 1 out of 6 survived (Wong et al 2014)

• Higher dose regimens (2-5 influenza dosing) being evaluated in NHP models

• Potential benefit in current outbreak, supplies should be readily available as already in late stage trials in US for influenza
2a. RNA-based drugs

**TKM-Ebola**

- Intravenously available
- It is a small interfering RNA (siRNA), affecting 3 of Ebola’s 7 proteins
- Limited safety and efficacy data are available
- Clinical hold on phase 1 trials in early 2014, because of increased cytokine levels in healthy individuals
- FDA has approved the emergency use of TKM-Ebola during the current outbreak
- Risk versus benefit should be estimated when deciding whether to use this agent
2a. RNA-based drugs

**AVI-7537**

- Intravenously available
- In early stage development for treatment of Ebola virus
- It is an antisense phosphorodiamidate morpholino oligomers (PMO) that inhibits VP24 protein of Ebola virus
- Efficacious in NHP studies (Geisbert et al 2010; Iversen et al 2012)
- Studies ongoing in NHPs and humans to further evaluate safety, efficacy and dosing
2b. Brincidofovir (CMX-001)

- Orally available
- It is early and late clinical trails for a variety of DNA viruses (e.g. adenovirus, cytomegalovirus, smallpox as a biodefence agent)
- Brincidofovir is a prodrug of cidofovir but fewer renal side-effects than cidofovir
- In vitro tests have shown its potential for treatment of EVD, paradoxical as Ebola not a DNA virus
- 6 October 2014, received approval for emergency use in this outbreak and used in treatment of cases in Dallas, Nebraska and New York
- 16 October 2014, received approval to commence phase 2 clinical trials to assess safety, efficacy and tolerability in patients with Ebola

Brincidofovir to be evaluated in a clinical study in patients with confirmed Ebola in West Africa
3. Immunomodulators

Interferons

• Commercially available
• Efficacy in rodents
• Delayed time to death but no overall increased survival in NHPs (Smith et al 2013)
4. Coagulation Modulators

- Severe coagulation disorder occurs in EVD
- Disseminated intravascular coagulation (DIC) picture
5. Coagulation Modulators

- **Recombinant Activated Protein C**
  - Inhibits clotting factors
  - Levels of protein C low in EVD

- **Recombinant Nematode Anticoagulant Protein**
  - Inhibits clotting factors (tissue factor pathway)

- Limited success with both in NHP studies (Hensley et al 2007; Geisbert et al 2003)
Ethical Questions

• How much emphasis should be placed on experimental interventions in response to this outbreak?

• If experimental drugs and vaccines become available, what are the ethical considerations relating to their use?
Therefore, on 11 August 2014, WHO convened a consultation to consider and assess the ethical implications for clinical decision-making of the potential use of unregistered interventions.

In the particular circumstances of this outbreak, and provided certain conditions are met, the panel reached consensus that it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention.

Ethical criteria must guide the provision of such interventions. These include transparency about
Take Home Messages

• Ebola outbreak in West Africa continues to escalate
• Mounting pressure to expedite clinical research
• WHO meeting in Switzerland Sept 2014
• Promising results in NHPs but limited data on safety and efficacy in humans

• Two potential recombinant vaccines
  • CAd3 – based
  • VSV – based
Take Home Messages

• **Potential Treatments**
  — Convalescent whole blood and plasma
  — Monoclonal antibodies (ZMapp)
  — Antiviral drugs (Brincidofovir and TKM-Ebola have FDA emergency use approval)
  — Immunomodulators
  — Coagulation modulators

• Use of experimental interventions raises ethical questions

• Should not distract from public health measures needed to curb outbreak
References


References

• Tuffs A. Experimental vaccine may have saved Hamburg scientist from Ebola fever. BMJ. 2009;338:b1223

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