Ebola Virus Epidemic, 2014
Halftime Adjustments, Lessons Learned

Alan Schmaljohn, PhD
Professor of Microbiology and Immunology
University of Maryland School of Medicine, Baltimore, MD

Associate Member, Institute of Human Virology
Affiliate Member, Global Virus Network

Disclaimer: All views presented or discussed are my own, not necessarily endorsed by M&I, SOM, IHV, or GVN
Ebola Virus Epidemic, 2014
Halftime Adjustments, Lessons Learned

OUTLINE FOR THIS TALK

1. Vaccines and therapies: Where are we, why do some things take so long, how do we move things faster in a time of crisis?

2. Aerosol transmission and Other Risks: What’s true? What are known unknowns? Why is the communication -- and therefore public understanding -- so flawed? What is fixable, and what is sadly embedded in our traditions?

3. What good may come from this catastrophe in West Africa, a global health threat we anticipate will be relatively short-lived?
A woman looks at an Ebola mural in Monrovia.
Ahmed Jallanzo, European Pressphoto Agency
Volunteers bury the body of a person who died from Ebola in Waterloo, Sierra Leone.
Florian Plaucheur, AFP/Getty Images
Nowa Paye is taken to an ambulance after showing signs of the Ebola infection in Freeman Reserve village near Monrovia, Liberia. Jerome Delay, AP
Size Comparison, Filovirus & Erythrocyte

Scanning electron micrographs of Marburg virus, courtesy of Ron Taylor, UVA
Cutaway Illustration of a Single Ebola Virion

- Lipid envelope derived from host cell
- Glycoprotein spike (for attachment & entry)
- Ca. 80 nm diameter
Relative Simplicity of Filovirus Genomes

Genome size is around 19 kilobases: 7 or 8 genes

(for comparison, bacteria have a few thousand genes)

Marburg:
- 3’ NP 35 40 GP 30 24 L 5’
- 38% identity

Ebola:
- 3’ NP 35 40 GP 30 24 L 5’
- 41 KDa soluable sGP
- RNA edit
- 74.5 KDa sGP
- furin

GP0

74.4 KDa
furin
GP1 GP2
GP2 = 27 KDa

Marburg GP2 = 20 KDa

32% 25% 29% 30% 35% 47%
identity

32% 25% 29% 30% 35% 47%
identity

(soluble)
Ebola Vaccines

Three Relatively New Vaccine Technologies

Replication-defective Adenovirus
(enters human cell, makes proteins including Ebola GP, does not spread to new cells)

Live-Attenuated Recombinant VSV
(enters human cell, makes proteins including Ebola GP, spreads, is cleared by host immunity)

Replication-defective Alphavirus
(enters human cell, makes proteins including Ebola GP, does not spread to new cells)

There's a big difference between mostly dead and all dead. Mostly dead is slightly alive.
- Miracle Max
### Ebola and Marburg Virus Vaccines Containing Glycoprotein (GP)

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Comments</th>
<th>Principal Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>killed filovirus</td>
<td>Early vaccine efforts and recent proofs of concept; inadequate efficacy in NHP</td>
<td>safety; potency; observed disease exacerbation</td>
</tr>
<tr>
<td>live attenuated filovirus</td>
<td>Only as proofs of concept with natural or passaged viruses; high risk could theoretically be mitigated by reverse genetics approach</td>
<td>live vaccine safety; incomplete attenuation or reversion</td>
</tr>
<tr>
<td>live vaccinia vectored</td>
<td>Proof of concept, deprioritized along with other live pox-vectored vaccines</td>
<td>vaccinia safety; vector immunity; potency</td>
</tr>
<tr>
<td>expressed protein, bacuolvirus</td>
<td>Incomplete efficacy in guinea pigs, no reported efficacy in NHP</td>
<td>potency, adjuvant requirement; altered glycosylation</td>
</tr>
<tr>
<td>defective VEE replicon</td>
<td>Excellent rodent efficacy, first demo of NHP efficacy against MARV, potency of $10^8$ IU near “tipping point” in NHP</td>
<td>vector immunity; safety at doses high enough to achieve potency</td>
</tr>
<tr>
<td>DNA</td>
<td>Adequate in rodents; incomplete NHP efficacy with MARV and none reported with EBOV; touted for immunological priming</td>
<td>potency</td>
</tr>
<tr>
<td>defective adenovirus</td>
<td>Excellent rodent and NHP efficacy at high doses (e.g. $10^{10}$ VP). First demo of NHP efficacy and single-shot efficacy with EBOV in NHP</td>
<td>vector immunity, safety at doses high enough to achieve potency</td>
</tr>
<tr>
<td>virus-like particles</td>
<td>Good rodent efficacy, no robust efficacy yet reported with NHP</td>
<td>potency; adjuvant requirement</td>
</tr>
<tr>
<td>live recombinant vesicular stomatitis virus, VSV</td>
<td>Excellent rodent and NHP efficacy with both MARV and EBOV. Single shot vaccine, rapid immunity. No overt illness from live vaccine itself. In recombinant, filovirus GP replaces VSV GP</td>
<td>live vaccine; balance of safety &amp; potency; environmental release</td>
</tr>
<tr>
<td>live recombinant parainfluenza</td>
<td>Good efficacy against Ebola in guinea pigs, contains both parainfluenza and EBOV glycoproteins</td>
<td>live vaccine; balance of safety &amp; potency; environmental release</td>
</tr>
</tbody>
</table>

---

How Ebola and Marburg viruses battle the immune system Mansour Mohamadzadeh, Lieping Chen, and Alan L. Schmaljohn, nature.com/reviews/immunol
Vaccines and Therapies

Where are we?

Short answer: Reasonably good shape
- thanks to prior funding of the scientific foundations for vaccines and therapies. - several agencies, many reasons

• Ebola Vaccines in or very near human testing (others to follow):
  * Two varieties of VSV-vectored vaccines (live-attenuated)
  * One cAd3-based monovalent vaccine (mostly dead = slightly alive)
  * One cAd3-based bivalent vaccine (mostly dead = slightly alive)

• Ebola antibody-based therapies in human testing:
  * Zmapp (extraordinarily effective in NHP, too early to discern human efficacy)
  * Convalescent plasma (probably harmless, but weak rationale, and irreproducible)

• Promising Antiviral Drugs in or near human testing:
  * Two varieties of RNA polymerase inhibitors (Favipiravir/T-705, BCX4430)
  * Anti-sense approaches (TKM-Ebola, siRNA; AVI-7537, antisense...
Vaccines and Therapies
What Takes So Long?

Short answer: Complexity and Money

• **Complexity:**
  * Vaccine development isn’t rocket science ... it’s harder, not like science fiction.
  * We (rightly) self-impose regulatory requirements that add complexity.
  * Added complexities of biosafety, biosecurity.

• **Money:**
  * Almost no private investment for an “orphan” disease that mostly afflicts the financially impoverished.
  * Transition from laboratory proof-of-concept and/or reduction to practice (i.e., patent) to production (efficient, high-quality, large-scale) is exceedingly costly in both time and dollars.
  * Government has a predictably hard time prioritizing big-money expenditures, winnowing choices.

Alan Schmaljohn, PhD
Vaccines and Therapies
How do we move things faster in a time of crisis?

Short answer: Prioritize and Accept More Risk

• Expedited review at FDA – already being done
  * Non-emergencies are back-burnered, something else will slow down

• Find and Disburse the Money
  * Mostly federal money, little incentive for private sources
  * Typically taken from somewhere else, while Congress fiddles.

• Indemnification as Needed:
  * Manufacturers reluctant to be ruined by trying to do the right thing.

• Accept Some Low-Risk Unknowns in Current Product:
  * Expect that FDA won’t acknowledge any lowering of standards
  * Some genetic instability of inserted vaccine genes may be acceptable or simply unknown. This may even be “a feature, not a bug.”
  * In the face of epidemic high-mortality disease, reduce the demand on proofs of long-term safety for vaccines and drugs. (e.g., interactions, HIV)

• BARDA’s raison d'être (Biomedical Advanced Research and Development Authority)
Aerosol Transmission and Other Risks: What’s true?

Short answer: Consider Relative Risks, Avoid Dogmatic or Absolute Statements

• Close contact with the gravely ill or deceased is HIGH RISK.
  * Especially blood, which has highest levels of infectious virus.
  * Infection can occur via any skin-break, mucosal surface including oral
  * Direct contact or fomite

• Aerosol transmission (person-to-person) EXCEEDINGLY LOW RISK.
  * Has not been convincingly demonstrated in humans or any species.
  * Many anecdotes suggest transmission at up to a few meters distance, but simplest explanation (Occam’s razor) always points to fomites or droplets generated by pressurized water (room and cage cleaning).

• Mechanical aerosols (e.g. centrifuge accident, some medical procedures) are highly infectious, and HIGH RISK.
  * This is why Ebola is Biosafety Level 4 (highest aerosol containment).
  * This is one reason Ebola is a Select Agent (highly controlled access).
Much is Known (Data Example):
Neither PCR nor Antigen-Detection Reveal Ebola Virus in Blood Before Onset of Symptoms (Aligns with Epidemiological Data)

Data from 18 survivors and 27 non-survivors. (Sudan species of *Ebolavirus* shown, but concordant with Zaire data elsewhere.)

“...no cases were identified by PCR or antigen capture prior to the onset of symptoms...”

From Towner et al., JOURNAL OF VIROLOGY, Apr. 2004, p. 4330–4341
Aerosol Transmission and Other Risks: What are known unknowns?

Short answer: There are unknowns, especially in the realm of low-risk, low-probability events.

- Likelihood of major genetic change in virus, \( \uparrow \) transmissibility.
  * Presumptively very low, and arguably without historical precedent.
  * Many mutational events probably required (and recombination?).
  * However, every new human infection exerts natural selection.

- Half-life of Ebola infectivity in a city (chlorinated) water system.
  * Ebola is among the easiest viruses to inactivate, deemed low-risk in \( \text{H}_2\text{O} \)
  * Experimentally difficult (impossible?) to address question directly.
  * In an abundance of caution, chem. decontaminate before flushing toilet.

- Ebola behavior in high-density human populations

- Countless unknowns in scientific details

Alan Schmaljohn, PhD
Aerosol Transmission and Other Risks: Why is the communication -- and therefore public understanding -- so flawed?

Short answers:

**Errors** – Learning curve on unprecedented situations

**Oversimplifications** – inartful messaging at times

**Second-guessing** – an American tradition

**Doubt of authorities** – another American tradition

**Infotainment News** – conflict and fear increase audience

**Puffery** – unhelpful pundits and publicity seekers

**Partisans** – incentive to stoke fear, confusion, anger
Aerosol Transmission and Other Risks:  
What is fixable, and what is sadly embedded in our traditions?

Short answers:

Errors – Fixable, trending in right direction
Oversimplifications – Partly fixable, partly necessary
Second-guessing – embedded in our nature
Doubt of authorities – embedded, and not a bad thing
Infotainment News – aggravatingly embedded
Puffery – tied to infotainment news patterns
Partisans – embedded in our chosen form of democracy
What good may come?
Despite catastrophe in West Africa, and a global health threat we anticipate will be relatively short-lived.

Some Examples:

• Good “systems test” for when THE BIG ONE comes.
  * Opportunity to learn and adjust.

• Reminder of the value (money, lives, ROI) of knowledge-base, scientific preparation for low-probability catastrophes.

• Reminder of global interdependence and the long view
  * Many already know “we’re all in this together”
  * Too many still suppose a lifeboat mentality, i.e., “every man for himself”

• Vindications of federal funding, federal response in some areas.

• Opportunity to reconsider the military’s role in peacemaking and global security by other-than-usual means.
End