<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Date</td>
<td>April 2015</td>
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</tbody>
</table>
Ebola

Jake Dunning
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@outbreakjake

BHIVA Annual Conference, April 2015
An Ebola talk? At BHIVA?!

- Overview of Ebola and the current outbreak
- Personal perspective
- Clinical trial challenges
- Links with HIV Medicine
A long, long time ago...

- **June-Nov 1976: Nzara, Sudan**
  - Unknown infection
  - 284 infected, 151 died (53%)

- **Yambuku village, Zaire (DRC)**
  - Ebolavirus identified for first time
  - Peter Piot, CDC et al.
  - 318 infected, 280 died (88%)
  - Belgian nuns, IV vitamins
  - Field epidemiology; public health; IPC

http://www.bbc.co.uk/news/magazine-28262541
<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
<th>Principal Reservoir/Vector</th>
<th>Geographic Distribution of Disease</th>
<th>Annual Cases</th>
<th>Disease-to-Infection Ratio</th>
<th>Human-to-Human Transmissibility</th>
<th>Case Fatality</th>
</tr>
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<tbody>
<tr>
<td><strong>Filoviridae</strong></td>
<td></td>
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<tr>
<td>Ebola</td>
<td>Ebola HF</td>
<td>Fruit bat (&quot;Egyptian fruit bat&quot; or <em>Rousettus aegyptiacus</em>, perhaps others)</td>
<td>Sub-Saharan Africa</td>
<td>~</td>
<td>1:1</td>
<td>High</td>
<td>25–85% depending upon species</td>
</tr>
<tr>
<td>Marburg</td>
<td>Marburg HF</td>
<td>Fruit bat (&quot;Egyptian fruit bat&quot; or <em>Rousettus aegyptiacus</em>, perhaps others)</td>
<td>Sub-Saharan Africa</td>
<td>~</td>
<td>1:1</td>
<td>High</td>
<td>25–85%</td>
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<tr>
<td><strong>Arenaviridae</strong></td>
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<tr>
<td><strong>OLD WORLD</strong></td>
<td></td>
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<tr>
<td>Lassa</td>
<td>Lassa fever</td>
<td>Rodent (&quot;multimammate rat&quot; or <em>Mastomys natalensis</em>)</td>
<td>West Africa</td>
<td>30 000–50 000</td>
<td>1:5–10</td>
<td>Moderate</td>
<td>25%</td>
</tr>
<tr>
<td>Lujo</td>
<td>Lujo HF</td>
<td>Unknown. Presumed rodent</td>
<td>Zambia</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Moderate-to-high</td>
<td>80%</td>
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<tr>
<td><strong>NEW WORLD</strong></td>
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<tr>
<td>Junin</td>
<td>Argentine HF</td>
<td>Rodent (&quot;corn mouse&quot; or <em>Calomys musculinus</em>)</td>
<td>Argentine pampas</td>
<td>&lt;50</td>
<td>1:1.5</td>
<td>Low</td>
<td>15–30%</td>
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<tr>
<td>Machupo</td>
<td>Bolivian HF</td>
<td>Rodent (&quot;large vespertine mouse&quot; or <em>Calomys callosus</em>)</td>
<td>Beni department, Bolivia</td>
<td>&lt;50</td>
<td>1:1.5</td>
<td>Low</td>
<td>15–30%</td>
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<tr>
<td>Guanarito</td>
<td>Venezuelan HF</td>
<td>Rodent (&quot;cane mouse&quot; or <em>Zygodontomyus brevicauda</em>)</td>
<td>Portuguesa state, Venezuela</td>
<td>&lt;50</td>
<td>1:1.5</td>
<td>Low</td>
<td>30–40%</td>
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<tr>
<td>Sabiá</td>
<td>Brazilian HF</td>
<td>Unknown. Presumed rodent</td>
<td>Rural area near Sao Paulo, Brazil?</td>
<td>~</td>
<td>1:1.5</td>
<td>Low?</td>
<td>33%</td>
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<tr>
<td>Chapare</td>
<td>Chapare HF</td>
<td>Unknown. Presumed rodent</td>
<td>Cochabamba, Bolivia</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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<tr>
<td><strong>Bunyaviridae</strong></td>
<td></td>
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<tr>
<td>Crimean-Congo HF</td>
<td>Crimean-Congo HF</td>
<td>Wild and domestic vertebrates/tick (primarily <em>Hyalomma</em> species)</td>
<td>Africa, Balkans, southern Russia, Middle East, India, Pakistan, Afghanistan, western China</td>
<td>~500</td>
<td>1:1–2</td>
<td>High</td>
<td>15–30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Strain</th>
<th>Cases</th>
<th>Deaths</th>
<th>CFR</th>
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<tbody>
<tr>
<td>1976</td>
<td>Sudan</td>
<td>Sudan</td>
<td>284</td>
<td>151</td>
<td>53%</td>
</tr>
<tr>
<td>1976</td>
<td>Zaire</td>
<td>Zaire</td>
<td>318</td>
<td>280</td>
<td>88%</td>
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<tr>
<td>1979</td>
<td>Sudan</td>
<td>Sudan</td>
<td>34</td>
<td>22</td>
<td>65%</td>
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<tr>
<td>1994</td>
<td>Gabon</td>
<td>Zaire</td>
<td>52</td>
<td>31</td>
<td>60%</td>
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<tr>
<td>1995</td>
<td>Zaire</td>
<td>Zaire</td>
<td>315</td>
<td>254</td>
<td>81%</td>
</tr>
<tr>
<td>1996</td>
<td>Gabon</td>
<td>Zaire</td>
<td>37</td>
<td>21</td>
<td>57%</td>
</tr>
<tr>
<td>1996-7</td>
<td>Gabon</td>
<td>Zaire</td>
<td>60</td>
<td>45</td>
<td>75%</td>
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<tr>
<td>2000-1</td>
<td>Uganda</td>
<td>Sudan</td>
<td>425</td>
<td>224</td>
<td>53%</td>
</tr>
<tr>
<td>2001-2</td>
<td>Gabon/RC</td>
<td>Zaire</td>
<td>122</td>
<td>96</td>
<td>79%</td>
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<tr>
<td>2002-3</td>
<td>RC</td>
<td>Zaire</td>
<td>143</td>
<td>128</td>
<td>90%</td>
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<tr>
<td>2003</td>
<td>RC</td>
<td>Zaire</td>
<td>35</td>
<td>29</td>
<td>83%</td>
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<tr>
<td>2004</td>
<td>Sudan</td>
<td>Sudan</td>
<td>17</td>
<td>7</td>
<td>41%</td>
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<tr>
<td>2007</td>
<td>DRC</td>
<td>Zaire</td>
<td>264</td>
<td>187</td>
<td>71%</td>
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<tr>
<td>2007-8</td>
<td>Uganda</td>
<td>Bundibugyo</td>
<td>149</td>
<td>37</td>
<td>25%</td>
</tr>
<tr>
<td>2008-9</td>
<td>DRC</td>
<td>Zaire</td>
<td>32</td>
<td>14</td>
<td>45%</td>
</tr>
<tr>
<td>2012</td>
<td>Uganda</td>
<td>Sudan</td>
<td>24</td>
<td>17</td>
<td>71%</td>
</tr>
<tr>
<td>2012</td>
<td>DRC</td>
<td>Bundibugyo</td>
<td>77</td>
<td>36</td>
<td>47%</td>
</tr>
</tbody>
</table>
The old Ebola paradigm

• Ebola only affects remote villages
• Outbreaks relatively small
• Outbreaks self-limiting or easy(ish) to halt
• Not much point in developing vaccines or treatments
• Extreme public perception…
There are no “tears of blood”

- Myths about disease manifestations
- “The one infection you really don’t want to catch”
- “One of the most infectious pathogens”
- “Fatal infection”
- “Could become airborne”*

*Aerosol-generating procedure risk; aeroplanes!
How did the current outbreak begin?

- Probably started Dec 2013
- 2 year-old boy in Meliandou, southern Guinea
- Hunting/butchering bats? Environmental exposure?
- No die-offs in wildlife
- “Rain of bats” when hollow tree burned, March 2014
- Bat DNA found in stump

Baize et al. NEJM 2014; 371 1418-1425
How did the outbreak escalate?

• Alert March 2014
• Cross-border travel
• Illness behaviour
• Funeral practices
• Reluctance to accept
• Resistance/unable to tackle effectively
• Late global response
Novel, wider reach of Ebola

- Via flights – 1\textsuperscript{st} time
- Transmission outside Africa – 1\textsuperscript{st} time
- Rapid response in Nigeria, Mali and Senegal $\rightarrow$ control
- Travellers and returning workers elsewhere
Ebola virus (EBOV)

- Filovirus, ssRNA
- Zaire, Sudan, Bundibugyo, Tai Forest, (Reston)
- Zoonotic; human-human spread
- 2014 Guinea virus
  - Zaire strain
  - Multiple substitutions
  - Some evolution in humans – significance?
Transmission

Ebola viruses:
- Ebola virus (formerly Zaire virus)
- Sudan virus
- Tai Forest virus
- Bundibugyo virus
- Reston virus (non-human)

Following initial human infection through contact with an infected bat or other wild animal, human-to-human transmission often occurs.

Human-to-human transmission is a predominant feature of epidemics.
Ebola Virus Disease (EVD)

- Variable symptoms after 2-21 days
- Flu-like initially, then often D&V
- Haemorrhage uncommon
- Multiple clinical phenotypes
- Reported CFR in treatment centres typically 30-55%
  - NB: case selection bias; staff-patient ratios
- Mortality probably 70% throughout
Pathogenesis

- **Limited information** – mice, guinea pigs, non-human primates (NHPs)
- **Virus**: Blood, urine, semen, saliva, breast milk (sweat), (tears)
- **Entry** via mucous membranes/broken skin/parenteral macrophages and dendritic cells
- **Proinflammatory response** but \( \downarrow \) type I IFN
- **Organ necrosis**, vascular leak, coagulopathy
A spectrum of illness

• Gastrointestinal symptoms
• Personal observations (n>100)
  • Sometimes profound anergia
  • Some do have a “vacant” look
  • Some surprising sudden deaths
  • Some surprising recoveries
  • Hiccups ring alarm bells
  • Have never seen the rash
  • Did see shocking cases

Photo: Dan Bausch (Manson’s)
“Ebola is nothing compared to malaria, HIV, TB…”

Leading causes of death in Africa
(deaths in thousands)

Source: WHO 2012 (Ebola 2014)
• Projections using Demographic and Health Surveys data

• Up to 3.5 million extra untreated cases of malaria

• Up to 11,000 additional malaria deaths
Global Response Efforts

- MSF staff were there from the beginning
- Dedication & sacrifices of National Workers
- An abundance of ETCs (eventually!)
- + Command help; Epidemiology; Public Health
- Help came too late…
- 9 of 11 US centres unused
What is it like inside an ETC?
Why I got involved

• Wanted to help
• Interest in dangerous pathogens/zoonoses
• Finished PhD & SpR training in Oct 2014
• Natural progression from recent work (pH1N1, H7N9, MERS-CoV)
• Clinical research important component of response
• Convinced friends, family, partner…
When standard care is not enough

- Standard care: variable; untested; unproven; resource-influenced
- Rehydration, antibiotics, antimalarials, nutritional support, symptom control
- Modest survival advantage seen with intense IV fluid – FLUID BALANCE
- Mortality remains very high in ETCs (~55%)
- Vaccines long time coming
- DEMAND FOR SPECIFIC TREATMENTS
Potential treatments

• WHO statement on ethics of unproven therapies: “go ahead (within reason)”
• Some “Wild West” medicine e.g. lamivudine
• WHO expert committee formed to consider options
• Over 200 suggestions…
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<tbody>
<tr>
<td>ZMapp</td>
<td>mAb cocktail</td>
<td>✓</td>
<td>✓ NHP</td>
<td>Limited</td>
<td>IV x 3</td>
<td>X</td>
</tr>
<tr>
<td>TKM-100802</td>
<td>siRNA</td>
<td>✓</td>
<td>✓ NHP</td>
<td>Limited</td>
<td>IV x 7d</td>
<td>X</td>
</tr>
<tr>
<td>Survivor plasma/blood</td>
<td>hAb</td>
<td>✓</td>
<td>X</td>
<td>Some (other infections)</td>
<td>IV</td>
<td>✓ (Dec)</td>
</tr>
<tr>
<td>Brincidofovir</td>
<td>Small molecule antiviral</td>
<td>✓</td>
<td>X Mice</td>
<td>&gt;1000 (CMV; adenoviruses)</td>
<td>Oral (6 tabs over 2 weeks)</td>
<td>✓</td>
</tr>
<tr>
<td>Favi-piravir</td>
<td>RNA-d RPI</td>
<td>✓</td>
<td>✓ Mice (NHP)</td>
<td>Licensed for flu</td>
<td>Oral (++ tabs)</td>
<td>✓</td>
</tr>
</tbody>
</table>

NB: other agents (antivirals, immunomodulators) considered – see WHO website
Trials and Tribulations: To randomise or not?

- Up to 70% mortality and only modest improvement with standard care
- Equipoise argument
- INSERM & RAPIDE Trials: historical control data
- RCTs take longer (even adaptive RCTs)
- No MedEvac’d HCWs enrolled to RCTs (until March 2015)
- BIG ongoing debates: “NIH/FDA vs. Europeans”
Conclusions

- MSA discards ineffective treatments quickly
- MSA reliably provides evidence concerning effective treatments
- With 100 new cases per day, MSA 6% and 15% greater reductions in mortality over first 100d for *highly effective* treatments compared to SRCT
- MSA appropriate for clinical evaluation of potential EVD treatments
Feasibility Visit Oct 2014
The first RAPIDE Trial: BCV

- MSF ELWA-3
- Liberia PI: Stephen Kennedy
- Chief Investigator: Peter Horby
- Field Team deployed Nov 2014
- THREE ethics approvals
- L-MHRA approval
- Bridge-building with partners
- Community engagement…
Happy Christmas

DON’T GIVE EBOLA
THIS CHRISTMAS!
NO TOUCHING, NO HUGGING, STAY SAFE
• RAPIDE-BCV Trial launched 01 Jan 2015
• Started planning sites in Sierra Leone
RAPIDE-BCV progress

• 30 Jan 2015: Chimerix announce their withdrawal from all Ebola trials
• Small number of patients recruited
• Impossible to continue trial – close down Feb 2015
• BCV Trial experience being published
RAPIDE-TKM

• GOAL ETC, Port Loko
TKM-130803 (Tekmira)

- Small interfering RNA within lipid nanoparticle
- Targets LP, VP35, VP24
- Modified for current virus
- Supportive in vitro and animal (NHP) data
- Predecessor given to MedEvac’d HCWs & healthy controls
Clinical trial platform – setup

*from protocol 1st draft

TKM-Ebola 9 weeks*
FPFV 11/3/15

Brincidofovir 12 weeks*
FPFV 2/1/15

cumulated Cases, Guinea
cumulated Cases, Liberia
cumulated, Sierra Leone

*from protocol 1st draft
RAPIDE-TKM:

• IV infusion – min 2h – once daily for 7 days
• Safety monitoring – risk of cytokine release
• At least 7 Red Zone entries per day
• Requires operational randomisation
• Two cohorts:
  – Standard care + TKM
  – Standard care only (observational)
• Primary outcome: D14 survival
Stopping rules for the TKM trial

Survivors

D14 assessments completed
RAPIDE-TKM: Progress

• Trial opened 10 March 2015
  – Ebola outbreak at Base Camp

• Case numbers have dropped in SL (great news!)

• Recruitment is ongoing
Current status of outbreak

• Guinea remains problematic
• 100 cases last 21 days
  • Guinea: 70
  • Sierra Leone: 30
  • Liberia: 0
• Halt in decline to zero
• Contacts <50%
Current status of trials

- Guinea: Favipiravir; IFN; Convalescent plasma (CP)
- Sierra Leone: TKM; Zmapp; convalescent plasma
- No combination antiviral trials
- No immunomodulator trials
- Multiple vaccine trials – W Africa & elsewhere
- Competing groups
The Ebola aftermath

- We MUST reach zero cases
- Recovery, restoration, capacity building, investment
- Support survivors:
  - Stigma and rejection
  - Sequelae – musculoskeletal, ophthalmological, neurological, psychological…
  - Financial help
  - Semen positive 6 months
Support >10,000 orphans
Okay, so what about HIV?

• August 2012: SSAT educational visit to Uganda

• Just as an Ebola outbreak started…

• “Do you want to see an Ebola patient?”

• Phone call to me: “Help! What do I do?”

• “But they are Lanvin, with a patent toe…”
Ebola and HIV

- No known relationship/experience
- Sierra Leone HIV Ab (15-49y): 1.6% [1.2% - 2.0%]
  - 52,000 HIV-infected adults [41,000 - 67,000]
- Virtually no HIV testing of ETC patients
  - Implications of retrospective sample testing?
- Impact of Ebola outbreak on HIV programmes?
- Effect of pre-existing immunosuppression on Ebola?
- Effect on clearance of EBOV?
Can HIV inform Ebola response?

- Fighting fear & stigmatisation
- Educate and inform
- In for the long-term: prevent new cases
- Empowerment, capacity building
- Funding *and* human resources required
- Pharmaceutical development and trial ethics?
So what I have learnt?

- Expect the unexpected
- Do something different
- I can do a clinical trial ANYWHERE now
- “No touch” is a sound policy for staff
- Never give up – outbreak research gets closer each time…
What has the world learnt?

- Expect the unexpected
- Global cooperation needed
- *Prepare* in advance— including research
- Think ahead – can we have a global task force?
- Understand & empower countries
- Humility and contrition (WHO)
21st Annual Conference of the British HIV Association (BHIVA)

21–24 April 2015

The Brighton Centre, Brighton, UK
Professor Martin Fisher
21st Annual Conference of the British HIV Association (BHIVA)

21–24 April 2015

The Brighton Centre, Brighton, UK