WHO R&D Blueprint:
—Scientific strategies from recent outbreaks to help us prepare for Pathogen X

Designing Trials During Outbreaks—
What have we learned so far?

Prof Thomas Fleming
Univ of Washington, Seattle
WHO R&D Working Group
Therapeutics for Ebola Virus Disease (EVD)

• The 2014–’15 major outbreak of EVD in West Africa ⇒ ‘urgent’ need for more effective approaches, both for prevention of spread and for treatment

• In treatment settings, 28-day mortality appeared to be substantially impacted by ‘optimized Standard of Care’ (e.g., aggressive IV fluid resuscitation, hemodynamic monitoring & support, point-of-care diagnostic modalities, other aspects of critical care medicine)

• Considerable interest in experimental interventions (e.g., monoclonal antibodies & antiviral drugs)

• Debate:

  *Is randomization ethical in a public health emergency?*
Guiding Considerations

“Medical interventions must be evaluated in a manner that is ethically acceptable, efficient, and reliable.

Ethical considerations relate to safeguarding the interests of study participants, and to achieving timely and reliable insights about interventions to enhance the health of the public.

While we strive to achieve efficiency by reducing financial costs, number of participants, burdens on medical personnel and study duration, these efforts should not lead to diminished reliability;

The goal of clinical research is not simply to provide those pursuing safe and effective interventions a ‘choice’, but rather an ‘informed choice’.”

Therapeutics for Ebola Virus Disease (EVD)

“Randomized trials are the preferable approach, and unless there are compelling reasons not to do so, every effort should be made to implement randomized trial designs.”
NAM (2017);  WHO R&D Working Group (2018)

“PREVAIL II”

ZMapp (Monoclonal Antibody)  
Optimized Standard of Care (oSOC)

Primary Endpoint: 28-day Mortality

Sample Size: Beginning in March 2015, 200 participants to be enrolled from the outbreak in Liberia, Guinea, & Sierra Leone
**“PREVAIL II”**
**Therapeutics for Ebola Virus Disease**

<table>
<thead>
<tr>
<th></th>
<th>ZMapp (Monoclonal Antibody)</th>
<th>Optimized Standard of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Deaths</td>
</tr>
<tr>
<td>ZMapp</td>
<td>36</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Control</td>
<td>35</td>
<td>13 (37%)</td>
</tr>
</tbody>
</table>

(Intended **100/arm** not reached, when outbreak waned in late 2015 in Liberia, Guinea, and Sierra Leone)

**NIH October 13, 2016 Press Release**

“Study finds Ebola treatment ZMapp holds promise, although results not definitive”
At the end of an outbreak, the release of promising but inconclusive results from partially completed trials may support the belief that confirmatory trials comparing the investigational agents against the previously accepted placebo or standard-of-care comparator could no longer be conducted.

Reference: “Accumulating evidence from randomized clinical trials across outbreaks”

NEJM: Under Review

(WHO R & D Working Group)

Accumulating evidence... across outbreaks

“A new clinical trial paradigm is needed...

To avoid premature release of data, master protocols specify that efficacy data from a trial that has not yet been completed due to insufficient enrollment should not be released.

After an outbreak has ended at a given site, the study would be paused...
Importantly, under the master protocol, the investigators would remain blinded to any results of analyses;
the study data would only be released if the trial were either stopped on the basis of a recommendation from the monitoring committee or had reached its targeted number of endpoints.”
### WHO MEURI and PALM RCT for 2018-19 EVD Outbreak in DRC Case Fatality Rate

<table>
<thead>
<tr>
<th>Intervention Group</th>
<th>MEURI 20 Sept 2019</th>
<th>PALM RCT 9 Aug 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Died/N   CFR%</td>
<td>Died/N   CFR%</td>
</tr>
<tr>
<td>mAb114</td>
<td>81/252   32%</td>
<td>43/127   34%</td>
</tr>
<tr>
<td>REGN-EB3</td>
<td>73/232   31%</td>
<td>32/112   29%</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>113/221  51%</td>
<td>70/131   53%</td>
</tr>
<tr>
<td>ZMapp</td>
<td>24/51    47%</td>
<td>63/129   49%</td>
</tr>
</tbody>
</table>
## Therapeutics for COVID-19 Hospitalized Patients

### RECOVERY

<table>
<thead>
<tr>
<th>Therapy</th>
<th># Patients</th>
<th>OS Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Convalescent Plasma</td>
<td>11,560</td>
<td>0.93</td>
</tr>
<tr>
<td>* Hydroxychloroquine</td>
<td>4,290</td>
<td>1.09</td>
</tr>
<tr>
<td>Lopinavir-Ritonavir</td>
<td>4,480</td>
<td>1.03</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>6,853</td>
<td>1.00</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>5,711</td>
<td>0.83</td>
</tr>
<tr>
<td>(On ventilator: 0.65; On oxygen only: .80; Other patients: 0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>4,116</td>
<td>0.86</td>
</tr>
</tbody>
</table>

### WHO SOLIDARITY THERAPEUTICS

<table>
<thead>
<tr>
<th>Therapy</th>
<th># Patients</th>
<th>OS Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Remdesivir</td>
<td>5,451</td>
<td>0.95</td>
</tr>
<tr>
<td>* Hydroxychloroquine</td>
<td>1,853</td>
<td>1.19</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>2,771</td>
<td>1.00</td>
</tr>
<tr>
<td>Interferon</td>
<td>4,100</td>
<td>1.16</td>
</tr>
</tbody>
</table>
**Virologically Confirmed Symptomatic Covid-19 Disease**

**Vaccine**
- SARS-CoV-2 Vaccine
- Placebo or Active Comparator

**Risk of Exposure**

**Immune Protective Mechanisms**
- Neutralizing Antibody titre
- Binding Antibody titre
- IgG & IgA Mucosal Antibody
- CD4+ T-cells & CD8+ T-cells
- Memory B-cells

**Immunologic Biomarker**
- SARS-CoV-2 Vaccine

**Unintended effects**

**Virologically Confirmed Symptomatic Covid-19 Disease**

**Other Immunologic Biomarkers**

The vaccine’s effect on the **Immunologic Biomarker** could **underestimate** or **overestimate** the vaccine’s true clinical efficacy.
Covid-19 Vaccine Trial: Key Design Considerations

Even in Public Health Emergencies, “Randomized trials are the preferable approach, and unless there are compelling reasons not to do so, every effort should be made to implement randomized trial designs.”

NAM (2017); WHO R&D Working Group (2018)

Primary Endpoint:
Virologically Confirmed COVID-19 Symptomatic Disease and Severe Disease
Designs of Monkeypox Therapeutics Trials

Even in Public Health Emergencies, “Randomized trials are the preferable approach, and unless there are compelling reasons not to do so, every effort should be made to implement randomized trial designs.”

NAM (2017); WHO R&D Working Group (2018)

Monkeypox Therapeutics

Placebo (or Active Comparator)

Primary Endpoint: Duration/Severity of Symptoms
Designs for Evaluating Monkeypox Therapeutics

- Experimental Monkeypox Therapeutic (EXP) vs. Placebo
  1° Endpoint: Duration/Severity of Symptoms

- Teomirimat or Brincidofovir + EXP vs. Teomirimat or Brincidofovir + Placebo
  1° Endpoint: Duration/Severity of Symptoms

- Experimental Monkeypox Therapeutic (EXP) vs. Active Comparator (AC)
  1° Endpoint: Duration/Severity of Symptoms

- Efficient design
- Results that are: Interpretable & Reliable
- Could use factorial design
- If complementary MOA
- Results that are: Interpretable & Reliable
- Lack of non-inferiority margin ⇒ need to establish superiority
Some Principal Issues in Pursuit of Interventions for Pathogen X

✓ Safe and effective interventions will be needed in a timely manner to more effectively address the outbreaks on an international scale

✓ **Randomized clinical trials** provide reliable & interpretable results regarding whether experimental interventions are safe & provide worthwhile efficacy
  • **Clinical endpoints** provide increased relevance & reliability
  • Assessments of **safety** are of key importance
  • RCTs using **Placebo Controls** have enhanced efficiency & interpretability
  • When randomization against Placebo Controls is not possible, use of **Active Controls** might enable a reliable evaluation of efficacy and safety

✓ Outbreaks of limited size & duration, in diverse clinical settings ⇒ creative approaches
  • **Master Protocols** enable accumulating evidence from RCTs across outbreaks