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?

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R&DBlueprint
Powering research to prevent epidemics

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’.”*

***** Fleming TR, Ellenberg SS. Evaluating Interventions for Ebola: The Need for Randomized Trials. *Clinical Trials* 2016; 13: 16-19

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"

R — 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 Leonne

"PREVAIL II"

Therapeutics for Ebola Virus Disease

	N	Deaths
ZMapp	36	**8 (22%)**
Control	35	**13 (37%)**

$2p = 0.18$

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

NIH October 13, 2016 Press Release

"Study finds Ebola treatment ZMapp holds promise, although results not definitive"

The Master Protocol

Reference: "Accumulating evidence from randomized clinical trials across outbreaks"

NEJM: Under Review

(WHO R & D Working Group)

Natalie E. Dean, Pierre-Stéphane Gsell, Ron Brookmeyer, Forrest W. Crawford, Christl A. Donnelly, Susan S. Ellenberg, Thomas Fleming, M. Elizabeth Halloran, Peter Horby, Thomas Jaki, Philip R. Krause, Ira M. Longini, Sabue Mulangu, Jean-Jacques Muyembe-Tamfum, Martha C. Nason, Peter G. Smith, Rui Wang, Ana Maria Henao Restrepo, Victor De Gruttola

"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."

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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

Intervention Group	MEURI 20 Sept 2019		PALM RCT 9 Aug 2019	
	Died/N	CFR%	Died/N	CFR%
mAb114	**81/252**	**32%**	**43/127**	**34%**
REGN-EB3	**73/232**	**31%**	**32/112**	**29%**
Remdesivir	**113/221**	**51%**	**70/131**	**53%**
ZMapp	**24/51**	**47%**	**63/129**	**49%**

World Health Organization

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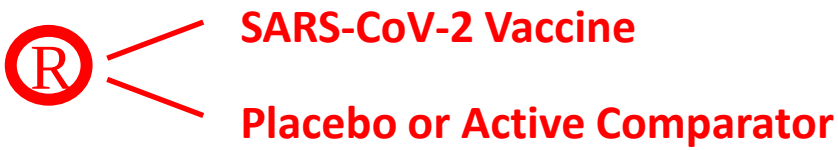
Therapeutics for COVID-19 Hospitalized Patients

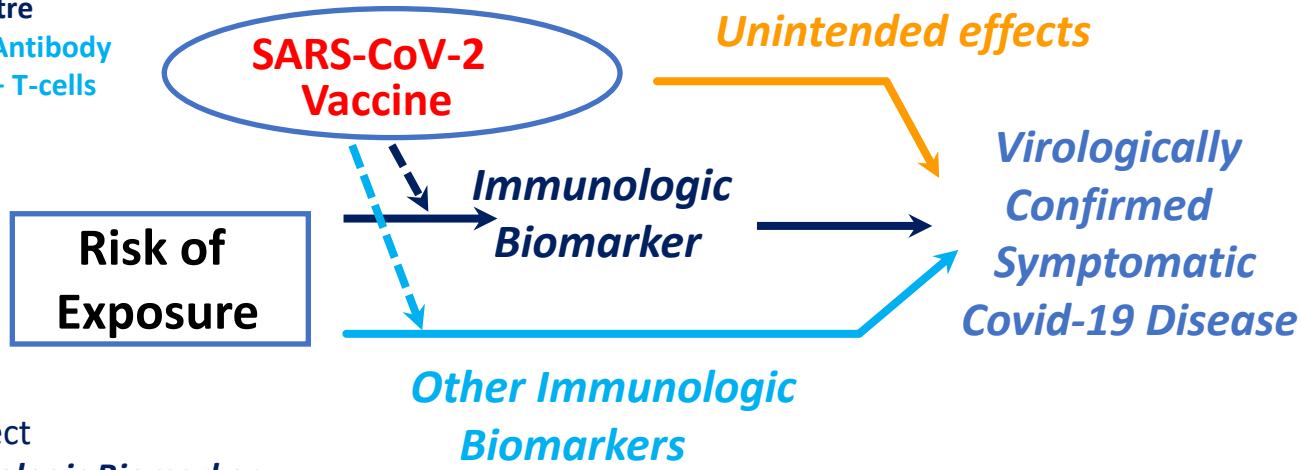
RECOVERY	# Patients	OS Hazard Ratio
• * Convalescent Plasma	11,560	0.93
• * Hydroxychloroquine	4,290	1.09
• Lopinavir-Ritonavir	4,480	1.03
• Azithromycin	6,853	1.00
• Dexamethasone	5,711	0.83
(On ventilator: 0.65; On oxygen only: .80; Other patients: 0.93)		
• Tocilizumab	4,116	0.86

WHO SOLIDARITY THERAPEUTICS		
• * Remdesivir	5,451	0.95
• * Hydroxychloroquine	1,853	1.19
• Lopinavir	2,771	1.00
• Interferon	4,100	1.16



Immune Protective Mechanisms

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

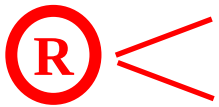


The vaccine's effect on the ***Immunologic Biomarker*** *could* ***underestimate*** *or* ***overestimate*** *the vaccine's true clinical efficacy*

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)



COVID-19 Vaccines

Placebo (or Active Comparator)

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***."

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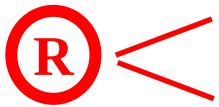


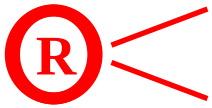
Monkeypox Therapeutics

Placebo (or Active Comparator)

Primary Endpoint:

Duration/Severity of Symptoms

Designs for Evaluating Monkeypox Therapeutics



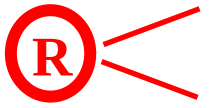
Experimental Monkeypox Therapeutic (EXP)

Placebo

1º Endpoint: **Duration/Severity of Symptoms**

- ✓ Efficient design
- ✓ Results that are: Interpretable & Reliable

- ✓ Could use factorial design

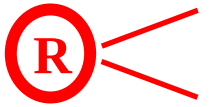


Tecomirimat or Brincidofovir + EXP

Tecomirimat or Brincidofovir + Placebo

1º Endpoint: **Duration/Severity of Symptoms**

- ✓ If complementary MOA
- ✓ Results that are: Interpretable & Reliable



Experimental Monkeypox Therapeutic (EXP)

Active Comparator (AC)

1º Endpoint: **Duration/Severity of Symptoms**

- ✓ 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