


Evolution of Preparedness and Emergency Research Response: Ebola 2014 to Marburg 2024

A Defining Decade— What Have We Learned About How to Do it??

WHO R&D Blueprint Consultation:
Integration of Rigorous Research into Outbreak Response to Accelerate Medical Countermeasures Licensure

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10 Year Evolution in ERR & GHS

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Vision: Ideal end state
Essential Role MCMs for advancing global health security

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Key paradigm shifts and learnings from the last decade of preparedness and emergency research response using exemplars, Ebola, SARS-CoV-s, Mpox etc

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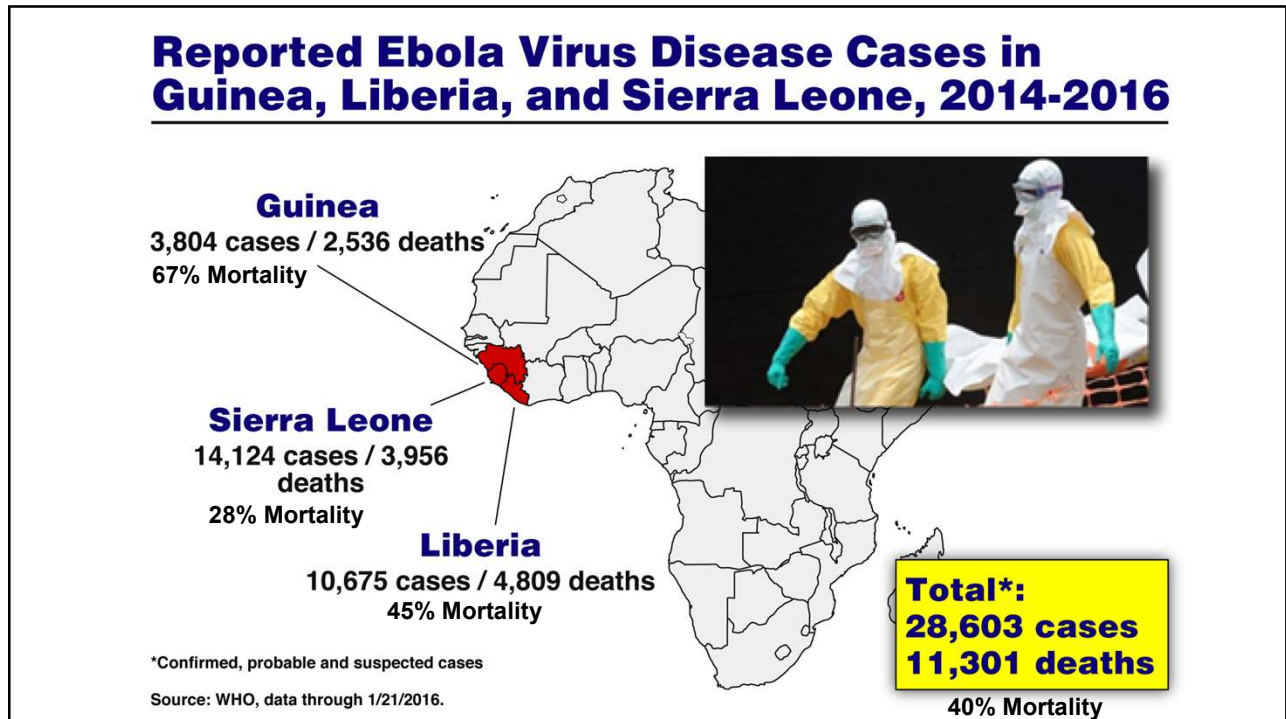
Global Ecosystem changes
Greater chance of success than ever before
Multisectoral solutions

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Collective Vision: Ideal Global Health Security End state

Outbreaks quickly detected and contained at their source	Licensed vaccines, therapeutics, and diagnostics (medical countermeasures or MCMs) available for infectious diseases with known outbreak and pandemic potential
Candidate MCMs for viral families (prototype pathogen approach) & pathogen X	Countries & regions prepared, partnered, and accountable for rapid response to contain outbreaks and initiate research when needed

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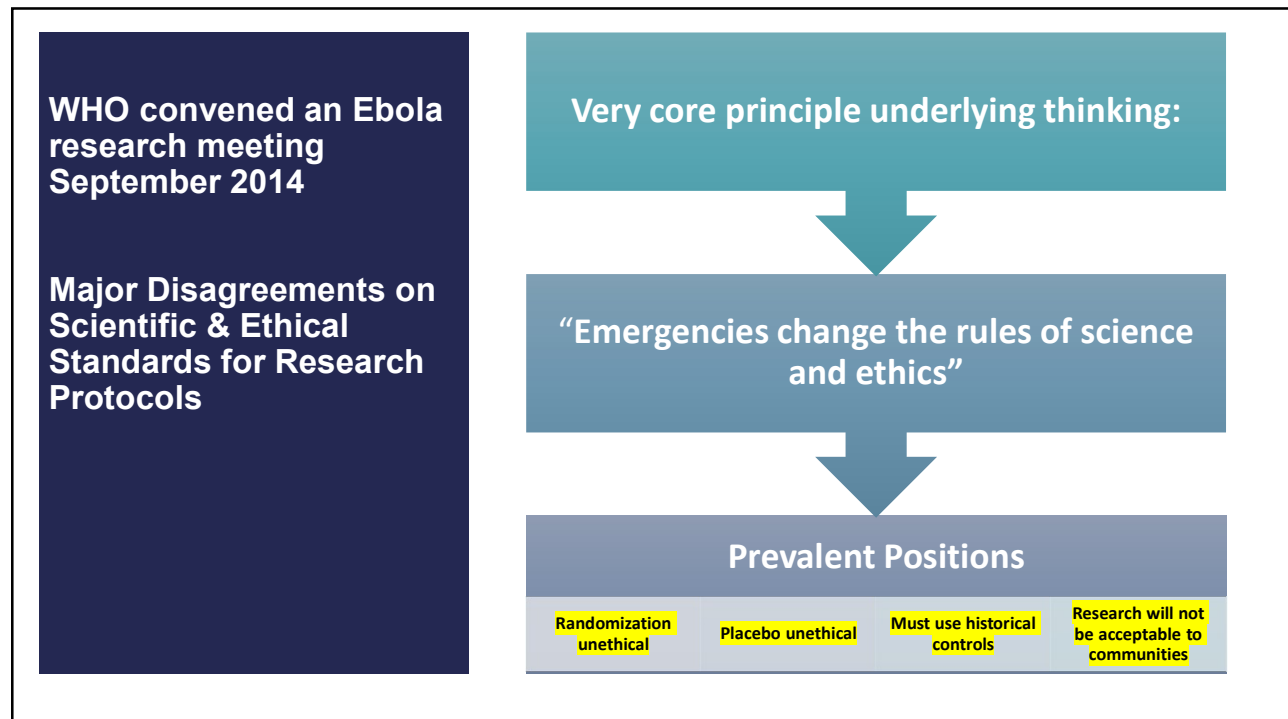


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Status of Preparedness & Emergency Research Response 2014: **Unprepared**

- Research **not** viewed as part of emergency response
 - viewed by many as an encumbrance
- WHO not organized for health emergency
- No global ecosystem for health security nor equity

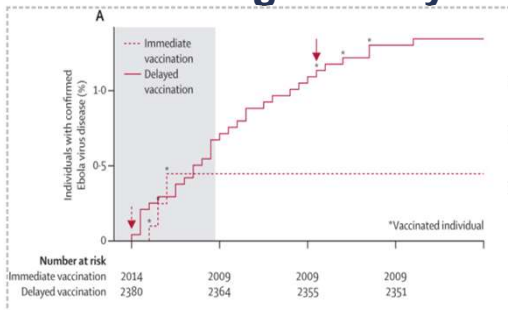
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Protocols Advancing Ebola Vaccines in the 2014-16 Outbreak

Prevail 1: Phase 2 randomized, placebo-controlled trial of two candidate Ebola virus vaccines in Liberia → **Phase 3 Ring Trial in Guinea: Cluster randomized ring trial showing efficacy**



Emergency Use Authorization based on the enabled use in Guinea & Sierra Leone and helped bring the outbreak to an END

2018-2020 Hundreds of thousands of doses were administered during the 2018 North Kivu Ebola virus outbreak. Helping end transmission

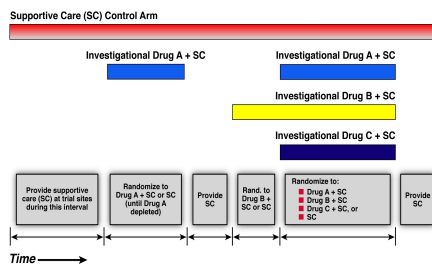
Lancet. 2015 Aug 3. pii: S0140-6736(15)61117-5. doi: 10.1016/S0140-6736(15)61117-5.

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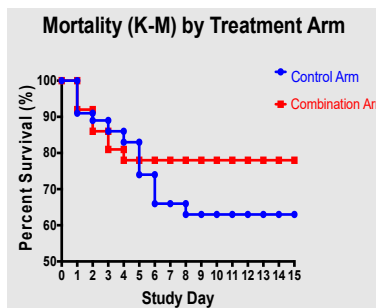
Protocols Implemented During the 2014-16 Ebola Outbreak

▪ **Prevail 2: A randomized, oSOC controlled regional trial of therapeutics for Ebola virus disease.**

An Adaptive Trial to Study Treatment for Ebola Virus Disease



LE Dodd, et al. JID 2016



<https://www.nejm.org/doi/full/10.1056/NEJMoa1604330>

- A randomized, controlled trial could be conducted regionally in the setting of an outbreak
- ZMapp, while not proven to be better than control (8/36 vs. 13/35); was not inferior to control and enabled it as the control for the next trial
- All deaths occurred by day 10 suggesting it as a good surrogate for day 28 all-cause mortality

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Changing Mortality for Ebola Virus Infection Over 6 Months

Date	N	Site	Mortality	Change from Prior Interval	Change from May-June
May-June, 2014*	106	Kenema, Sierra Leone	74%	-	-
Sept.-Oct., 2014**	151	Freetown, Sierra Leone	48%	-35%	-35%
Oct.-Nov., 2014**	126	Freetown, Sierra Leone	32%	-33%	-55%
Nov.-Dec., 2014**	304	Freetown, Sierra Leone	23%	-28%	-69%

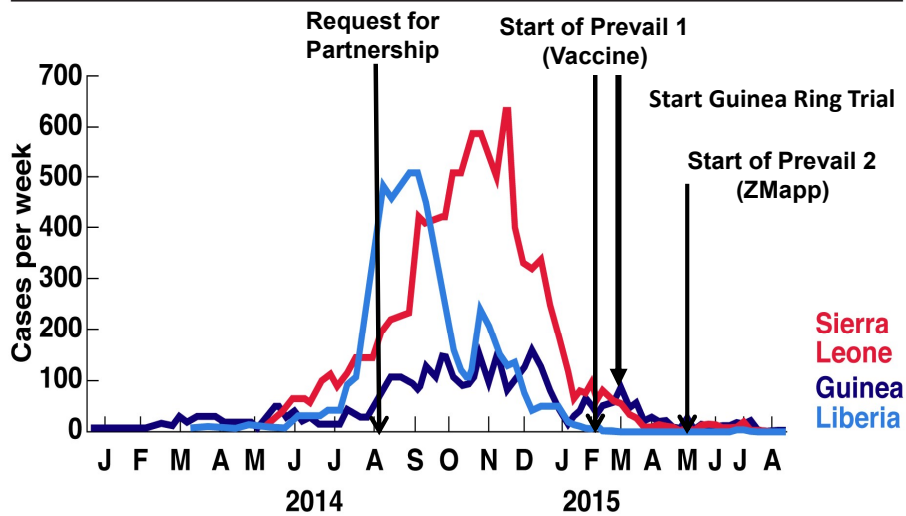
Settled Debate over Concurrent Controls

*Schieffelin JS, et al. *New Eng J Med* 371:2092-100, 2014
 **Ansumana R, et al. *New Eng J Med* 372:587-88, 2014

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New Confirmed and Probable Cases of Ebola Infection per Week


Too Late!




Source: WHO, The Economist

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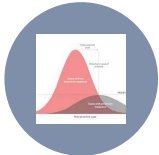
Global Lessons Learned From Ebola Outbreak




Clinical Research can be a critical element of response to a public health emergency



It is possible to conduct regulatory level randomized, controlled trials in the setting of an outbreak of a life-threatening disease for which there is no known treatment. Concurrent randomization necessary.



Essential to start quickly if one wants to get the most effective interventions to the greatest number of individuals, available IP



Inclusion of Community: Good Participatory Practices- (SMC) is not optional, rather essential in a health emergency

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Global Ecosystem Scientific/Policy Shifts Following 2014 West African Ebola Outbreak

WHO Creates the Health Emergencies Program & Established the R&D Blueprint May 2015

Goal to start trials in 4 months May 2015

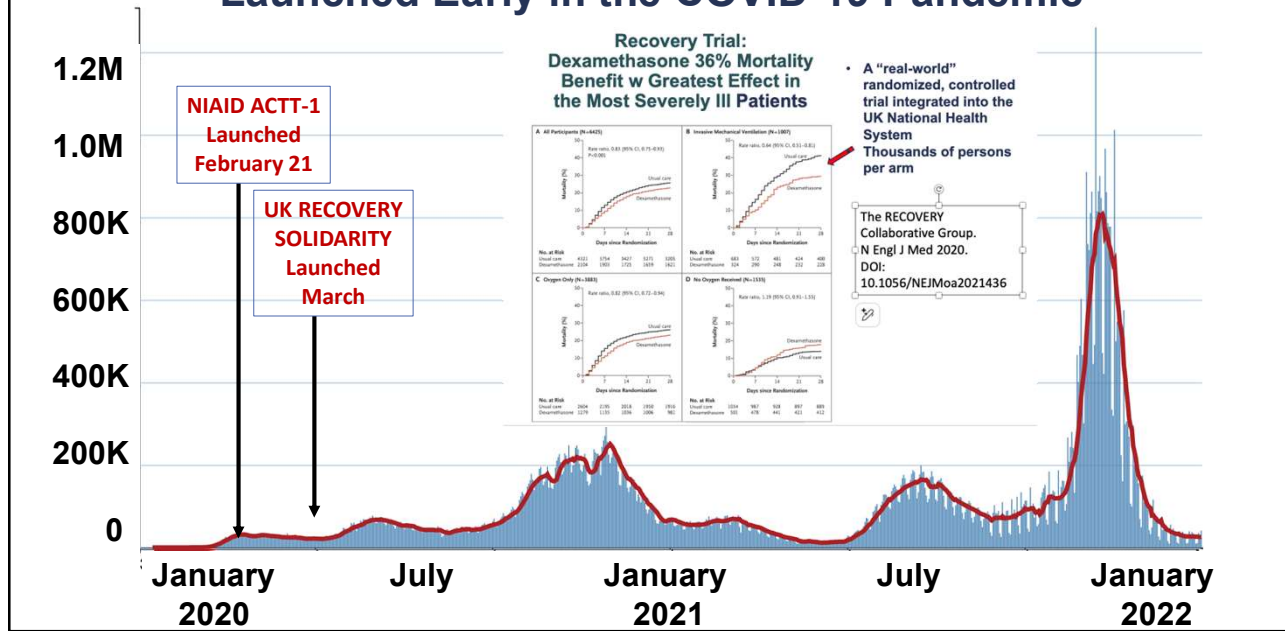
US National Academies Report: Core principals of clinical science do not and should not change during an outbreak. RCTs are ethical and the most appropriate efficient study design to determine safety and efficacy

NIAID Emphasis on prototype pathogen approach for Pathogens with Pandemic Potential

Countries Lead Outbreak Coordinated by IMS

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Applied Lessons: Large, Platform Trials Were Launched Early in the COVID-19 Pandemic



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Differences in Mortality Rates in Control Arms

Study (Intervention)	Recruitment	Date of Last Enrollment (n)	Mortality for Mechanically Ventilated Patients
ACTT-1 (Remdesivir)	Academic Centers	March 2020 (154)	19.3%
RECOVERY (Dexamethasone)	Healthcare System	June 2020 (683)	41%

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Global Policy Changes & Learnings From COVID-19

Rigorous Research Response Imperative: G7 Clinical Trials Charter

"Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination." WHA 75.8-avoid research waste

Pandemic Preparedness economically, socially, politically, necessary:
Pandemic Accord (WHA 2025)

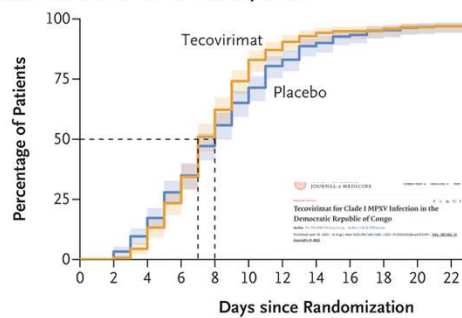
Equity-clinical trials, social value coming from trials: ACT

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MPOX PEHIC Value of Negative Studies— Fallacy of Therapeutic Misconception

Expanded Access Programs in Place Early 2022
"Since 2012, the CDC has maintained an expanded access Investigational New Drug (EA-IND) protocol for tecovirimat, and "with increasing mpox cases, supplies of oral tecovirimat were prepositioned across the country from August 2022 through February 2023 for use in accordance with the EA-IND protocol."

Lesion Resolution in the Overall Population

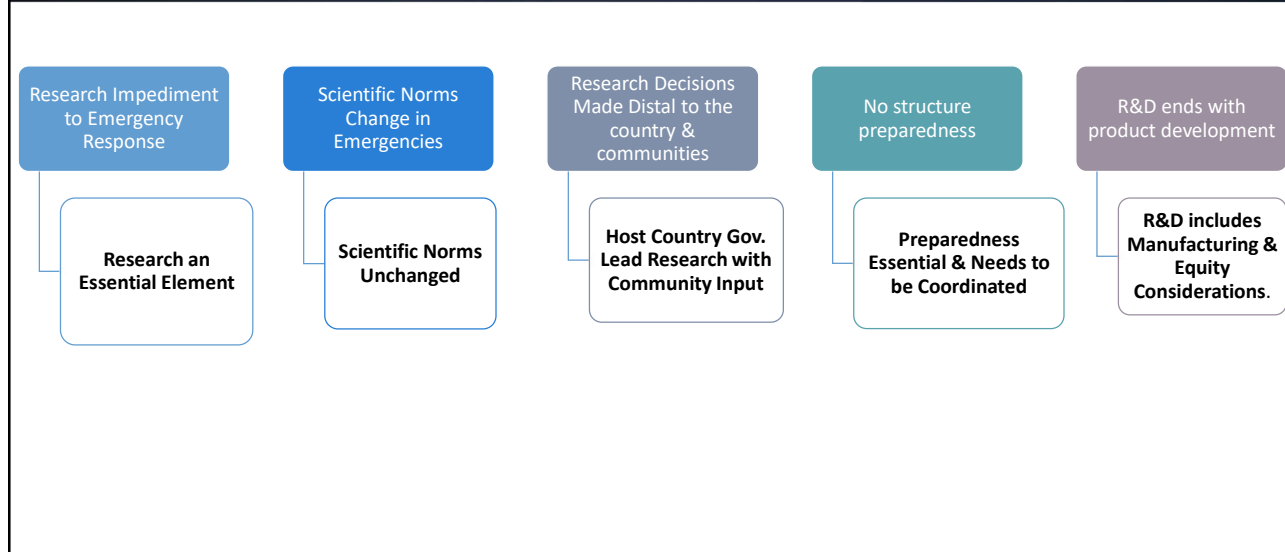


Days since Randomization	Tecovirimat	Placebo
0	295	302
2	294	302
4	281	272
6	225	217
8	144	159
10	76	105
12	38	59
14	21	34
16	15	22
18	14	15
20	10	11
22	9	9

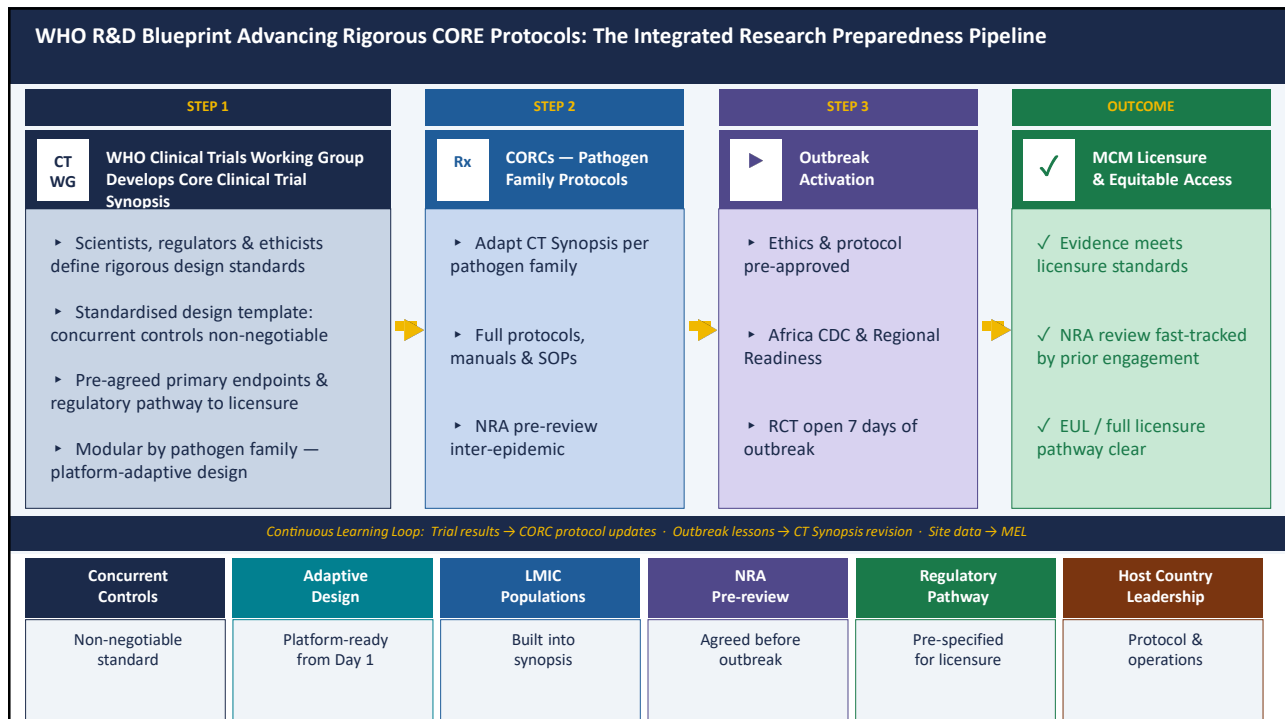
- Three RCTs: PALM (clade 1), UNITY and STOMP clade 2b— tecovirimat was safe but did not reduce the time to lesion resolution
- CDC no longer recommends tecovirimat for treatment of mpox unless severely IC.
- **Key Lesson: Cannot Assume Therapeutic Efficacy from Animal Rule in Humans**

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Summary: A Decade of Paradigm Shifts in Preparedness & Research Response.



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Summary—Over the last Decade

- Established collective understanding of the imperative of rigorous clinical research design elements, randomization, concurrent controls etc. to advance licensure and access for MCMs
- Global Coordination Around Pathogen Families via CORCs for CORE protocols— ensure preparedness phase 1, 2a and rapid implementation of CORE protocols.
- Facilitating development of national, regional, and continental research capacities to respond to outbreaks, containing them at their source, and advancing MCM licensure

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Greatest Chance of Advancing GHS by Building on What We Have Learned!

- Thank you to the many investigators, participants, countries, regulatory authorities, pharmaceutical companies, and manufacturers involved in research studies
- Thank you to policy makers for integrating rigorous research into outbreak response.

Additional information & learnings in open access textbook:
“Principles and Practice of Emergency Research Response”
Springer 2024 <https://link.springer.com/book/10.1007/978-3-031-48408-7>

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