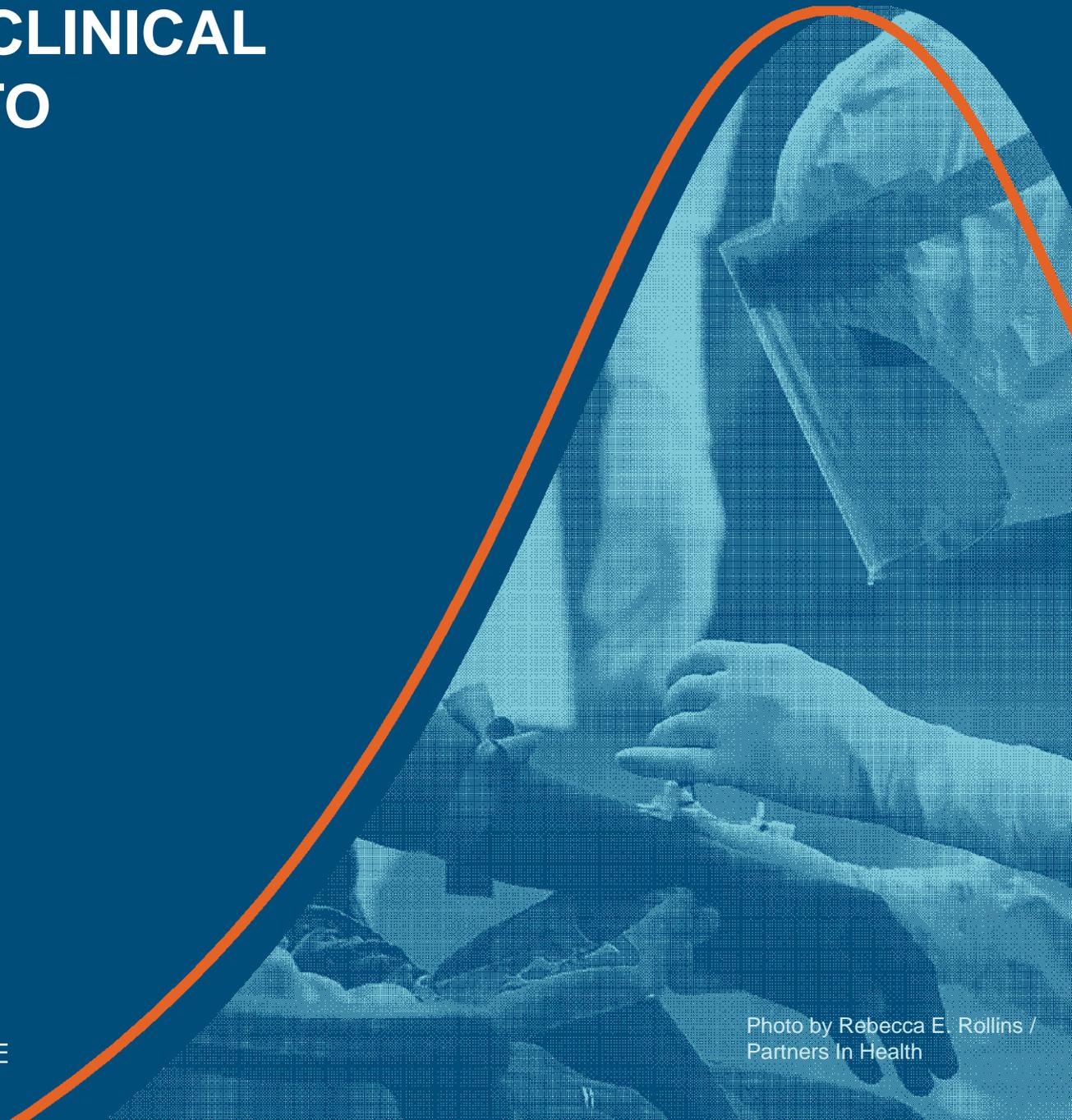


INTEGRATING CLINICAL RESEARCH INTO EPIDEMIC RESPONSE

THE EBOLA EXPERIENCE

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Photo by Rebecca E. Rollins /
Partners In Health



Key Messages

- Research must be integrated into epidemic response
- Research and response both begin before an outbreak occurs
- Community engagement and participation is critical
- Messages must come from trusted messengers
- Learn from the past but adapt to the context
- It is ethical and feasible to conduct clinical research during an epidemic
- Research must be scientifically rigorous and designed to produce useable information

Key Messages, continued

- Capacity building spans health care, public health, and research
- Local-national-international action must link to a coordinated agreed-upon plan
- Investment now is critical to improve future performance – pay now or pay much more later
- Better coordination and cooperative engagement among research and development agencies (both within US and internationally) can help assure these goals will be achieved

Report Details

Study Sponsors

- U.S. Assistant Secretary for Preparedness and Response
- U.S. Food and Drug Administration
- U.S. National Institute of Allergy and Infectious Diseases



Committee on Clinical Trials during the 2014-2015 Ebola Outbreak

- **GERALD KEUSCH** (Co-Chair), Boston University Schools of Medicine and Public Health
- **KEITH McADAM**, (Co-Chair), London School of Hygiene and Tropical Medicine
- **ABDEL BABIKER**, Medical Research Council Clinical Trials Unit at University College London
- **MOHAMED BAILOR BARRIE**, The Wellbody Alliance, Sierra Leone
- **JANICE COOPER**, The Liberia Mental Health Initiative, The Carter Center
- **SHEILA DAVIS**, Partners In Health
- **KATHRYN EDWARDS**, Vanderbilt University School of Medicine
- **SUSAN ELLENBERG**, University of Pennsylvania
- **ROGER LEWIS**, Harbor–UCLA Medical Center
- **ALEX JOHN LONDON**, Carnegie Mellon University
- **JENS LUNDGREN**, University of Copenhagen, Denmark
- **MICHELLE MELLO**, Stanford University School of Medicine, School of Law
- **OLAYEMI OMOTADE**, University of Ibadan, Nigeria
- **DAVID PETERS**, Johns Hopkins Bloomberg School of Public Health
- **FRED WABWIRE-MANGEN**, Makerere University School of Public Health, Uganda
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Consultants

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Charge to the Committee

Assess the Ebola clinical trials performed in West Africa during 2014-2015 and make recommendations to improve and speed up clinical research during future infectious disease outbreaks.

Methodology:

- 3 public workshops in Washington DC, London and Monrovia, Liberia
- 6 closed committee meetings from February to November, 2016
- Comprehensive literature survey and review of written submissions to the committee
- Extensive external and internal review
- Our primary goal: to improve future performance

Context

- The outbreak was recognized in January 2014 but not identified and confirmed to be Ebola until March
- MSF, influenced by experience on the ground, declared the outbreak was out of control
- WHO, influenced by past experience, declared this was a level two (moderate) event
- Delayed designation of Public Health Emergency of International Concern (PHEIC) in August 2014 resulted in late international mobilization for response

Result: Largest Ebola Outbreak Ever

Mainly affected Guinea, Liberia, and Sierra Leone

28,652

PEOPLE INFECTED

11,325

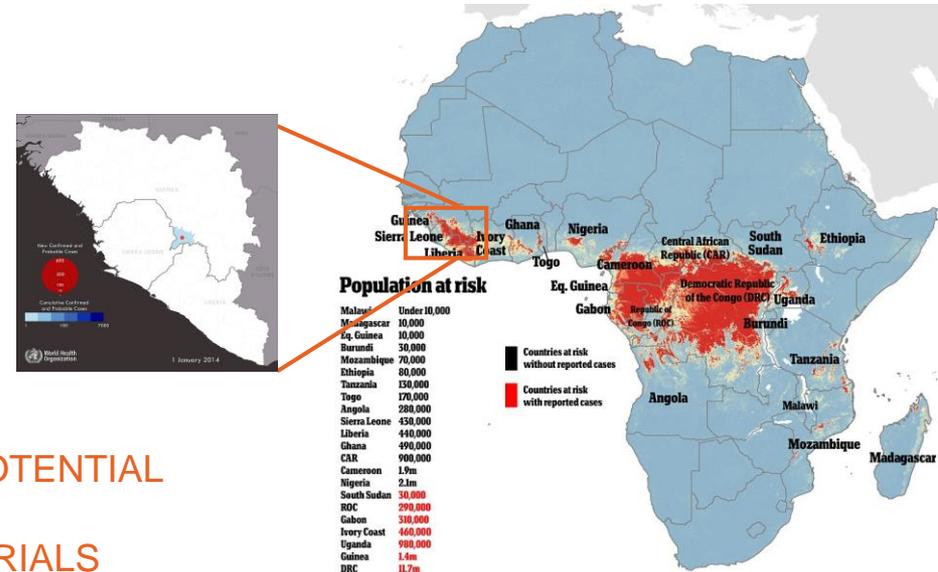
LIVES CLAIMED

ZERO

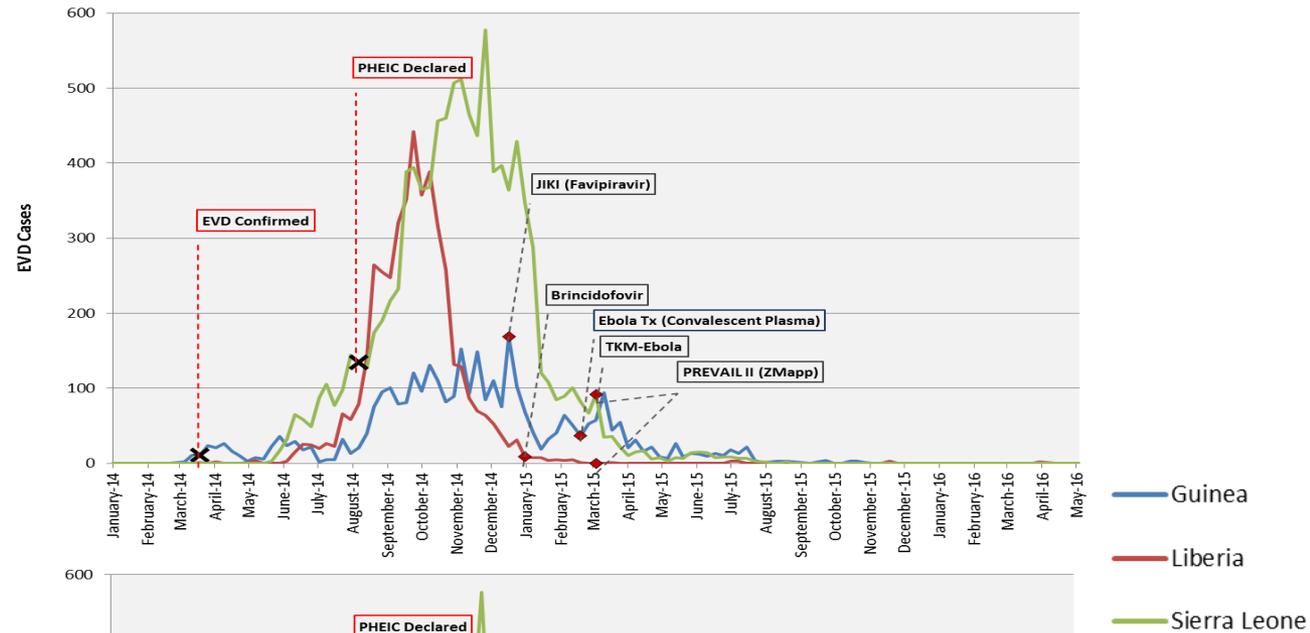
APPROVED EBOLA-SPECIFIC VACCINES OR TREATMENTS AT THE OUTSET

~20

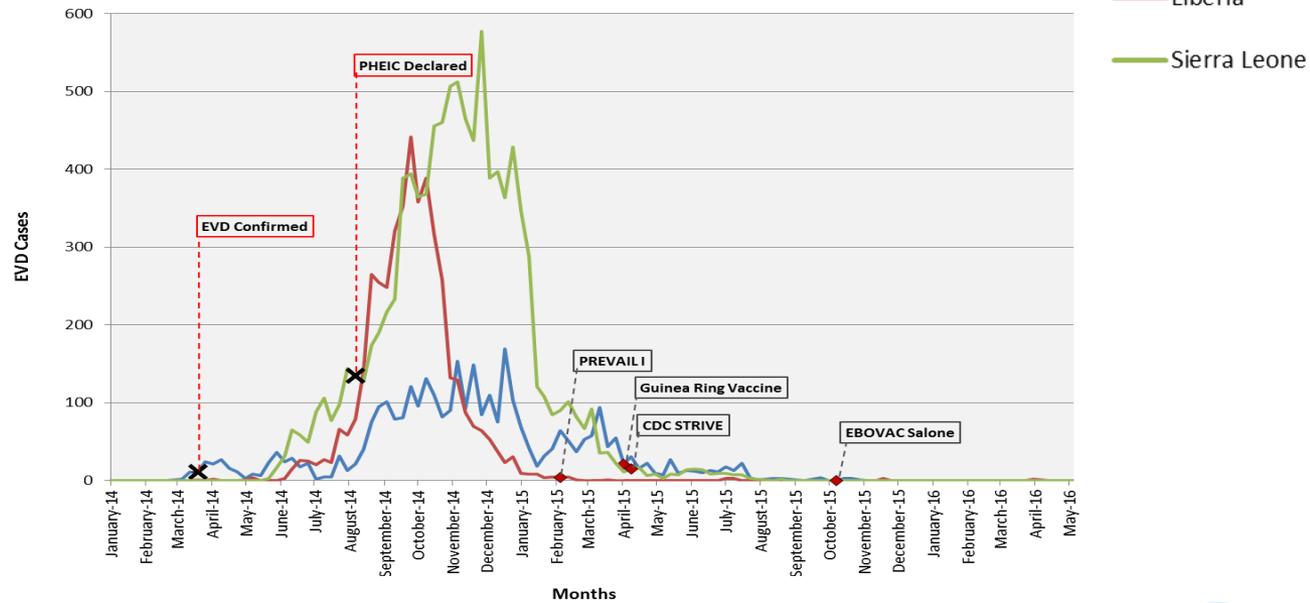
WHO LIST OF POTENTIAL CANDIDATES FOR CLINICAL TRIALS



Ebola Therapeutic Trials Timeline



Ebola Vaccine Trials Timeline



Source: WHO situation reports

Challenges to Rapid Implementation

- Post declaration of PHEIC, **chaotic clinical and public health needs** clashed with research goals with no consensus on what or how to study it
- **Lack of local capacity** or experience with Ebola or clinical research
- Early **missteps in messaging** and control efforts and a **failure to engage community** led to fear, rumors, mistrust, and violence
- **Expanded access** to experimental therapeutics for international responders led to therapeutic misconceptions
- **Disagreements** about priority for patient care versus research
- Stakeholders disagreed whether it was **ethical and feasible to conduct randomized, controlled trials**
- **Poor coordination** among multiple research groups, competition for trial approval and sites as cases dwindled

Is it ethical to do research during outbreaks?

Randomized, Controlled Trials During Epidemics: Both Ethical & Preferable

- **Seven Principles** considered by Committee
 1. Scientific and social value
 2. Respect for persons
 3. Community engagement
 4. Concern for participant welfare and interests
 5. Favorable risk–benefit balance
 6. Justice in the distribution of benefits and burdens
 7. Post-trial access
- Longstanding substantive requirements for **ethical research** apply to research in emergency contexts but assessment and approval can be expedited
- Randomization is necessary in most cases to get **interpretable results** – a fundamental ethical requirement. RCTs are the fastest way to identify beneficial treatments and vaccines while minimizing risk
- Trials without concurrent, randomized controls do not allow for **incremental learning** about moderate efficacy, the reality of most clinical trials

Assessment of Therapeutic Trials

“Thin Scientific Harvest”¹

Trial Name (investigational agent)	Country	Number Enrolled	Trial Design	Results
JIKI (Favipiravir)	Guinea	126	non-random, historical controls	Inconclusive
RAPIDE-BCV (Brincidofovir)	Liberia	4	non-random, historical controls	Inconclusive
RAPID-TKM (TKM-100802)	Sierra Leone	14	non-random, historical controls	Inconclusive
Ebola Tx (Convalescent plasma)	Guinea	99	non-random, historical controls	Inconclusive
Prevail II (Z-MAPP)	Guinea, Liberia, Sierra Leone, United States	72	Randomized, controlled (optimized standard of care)	Suggests some benefit

- No trials reached conclusive results
- One RCT was implemented (it is feasible)—results suggest some benefit but further study is needed
- Single arm trials: a gamble, usually a losing gamble

Assessment of Vaccine Trials

Suggestive efficacy; more study needed

Trial Name (investigational vaccine)	Country	Number Enrolled	Trial Design	Results
Ring Vaccination (rVSV-ZEBOV)	Guinea	7,284	<ul style="list-style-type: none">• cluster-randomized ring trial• Immediate vs. deferred (21 days) vaccination	Suggestive efficacy, likely protective
CDC-STRIVE (rVSV-ZEBOV)	Sierra Leone	8,673	<ul style="list-style-type: none">• individually randomized• Immediate vs. deferred (18–24 weeks after enrollment)	Inconclusive, analysis ongoing
PREVAIL-I (rVSV-AZEBOV/ChAd3)	Liberia	1500	<ul style="list-style-type: none">• Individually randomized• saline placebo controlled	Vaccines are safe and immunogenic
EBOVAC-Salone (Ad26-EBOV/MVA-EBOV)	Sierra Leone	Ongoing	<ul style="list-style-type: none">• Prime-boost, staged phase 1-3 trial	Ongoing

- Ring design was appropriate for a high risk population
- Placebo-controlled RCT most appropriate for lower risk, general population
- Lack of coordination among researchers led to competition for participants and limited the sharing of resources

Nine Clinical Trials during Ebola Outbreak

First outbreak where formal trials were launched, but not quite in time

5

Therapeutic Trials

Zero

Conclusive Results

4

Vaccine Trials

One

Vaccine candidate with probable protective effect

Implementing Clinical Trials

Requires core clinical, public health, and research capacities and community engagement from the start

Integrate clinical research into response efforts from the beginning

- **Clinical care, public health, and research are linked**; optimally every country should have a well-integrated functional healthcare, public health, and health research system

Community engagement is essential

- Local communities can understand and accept research concepts like randomization and consent; but it takes time, an understanding of local beliefs, traditions and customs, and **the right message and the right messengers**

How can we do better next time?

- Recommendations address three main areas:
 - Capacity strengthening
 - Community engagement
 - International coordination and collaboration

Strengthen Capacity of Health and Research Systems

International Health Regulations & Beyond

Recommendations:

- Support, improve, and monitor capabilities for **sustainable surveillance, diagnostics, and basic epidemiology** in all countries
- **Integrate clinical research** into national clinical and public health systems, and emergency preparedness and response systems before the next outbreak
- Develop plans and provide resources to support the collection and **sharing of clinical, epidemiological, and research data**
- Ensure capacity strengthening **is not limited** to services that solely benefit study participants
- Establish **banks of experts** to advise on ethics review and negotiation of legal agreements and develop template agreements for clinical trials

National Governments, Research Institutions, Development Agencies,
Humanitarian Organizations, International and Regional Bodies

Prioritize community engagement

Recommendations:

- **Engage** with key community representatives from outset to end
- Include **social scientists** on research teams to work with communities
- **Coordinate** with national authorities and other research and response teams on social mobilization
- Provide support and training to **local leaders and organizations**
- Fund **training and research** into **community engagement, cultural competency, and communications**

National Governments, Research Institutions, Humanitarian Organizations, Public Health Agencies

Advance Planning and International Collaboration are key when the “Rubber Hits the Road”

Recommendations:

- A **Coalition of Stakeholders** should work during the inter-epidemic period on planning to prepare for a future outbreak: priority pathogens for R&D, trial design templates, collaboration agreements, list of experts to be deployed when an outbreak strikes. Must be independent, expert, free of conflicts of interest, and able to make timely decisions.
- At the start of an epidemic, a **Rapid Research Response Workgroup** should be established to: appraise and prioritize candidates for trial, select the optimal design, monitor and evaluate trials conducted

For the next epidemic, we need a **fast, nimble mechanism** with the **right expertise** and **representation** to set research priorities and agenda. This mechanism must be **established in advance** of the next outbreak

Model Governance Structure for International Coordination

Inclusive, autonomous, and independent

Inter-epidemic planning

International Coalition of Stakeholders (ICS)

governments | foundations | academic institutions | researchers | pharmaceutical companies | humanitarian NGOs | WHO | community representatives

OUTBREAK DECLARED

Epidemic action

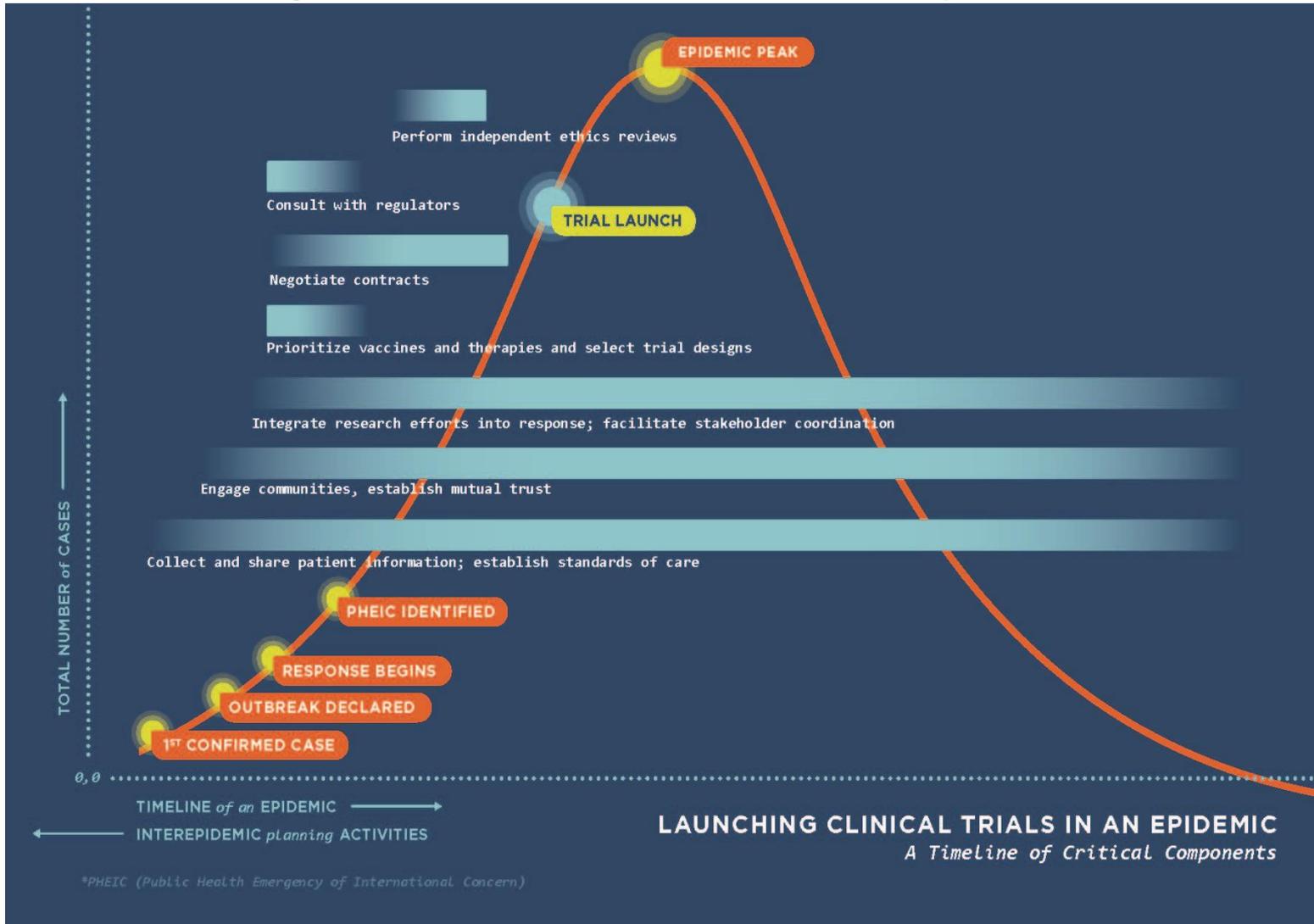
Rapid Research Response Workgroup (R³W)

Expertise in: pathogen of concern | R&D of investigational interventions | clinical trial design | ethics and regulatory review | community representatives

Three models were considered:

1. WHO
2. Global Health Security Agenda (GHSA)
3. Coalition for Epidemic Preparedness Innovations (CEPI)
 - As a model, CEPI has the “right DNA for the job”

Launching Clinical Trials in an Epidemic



To Best Prepare the Global Community

- Research should be considered a **critical part of the response** from the beginning
- National and international researchers and other stakeholders should work together on a **collaborative and coordinated research agenda**
- Effective **community engagement** and **communication** strategies should be incorporated into research and response plans and local communities are included at every step
- **Funding needed to invest in global health capacity and security** needs to be identified

Next Steps

Further dissemination events to diverse audiences

Free PDF available

nationalacademies.org/EpidemicClinicalTrials

