INTEGRATING CLINICAL RESEARCH INTO EPIDEMIC RESPONSE

THE EBOLA EXPERIENCE

In 2014 “little was known about how to best manage patients to improve survival, and there were no approved therapeutics or vaccines”

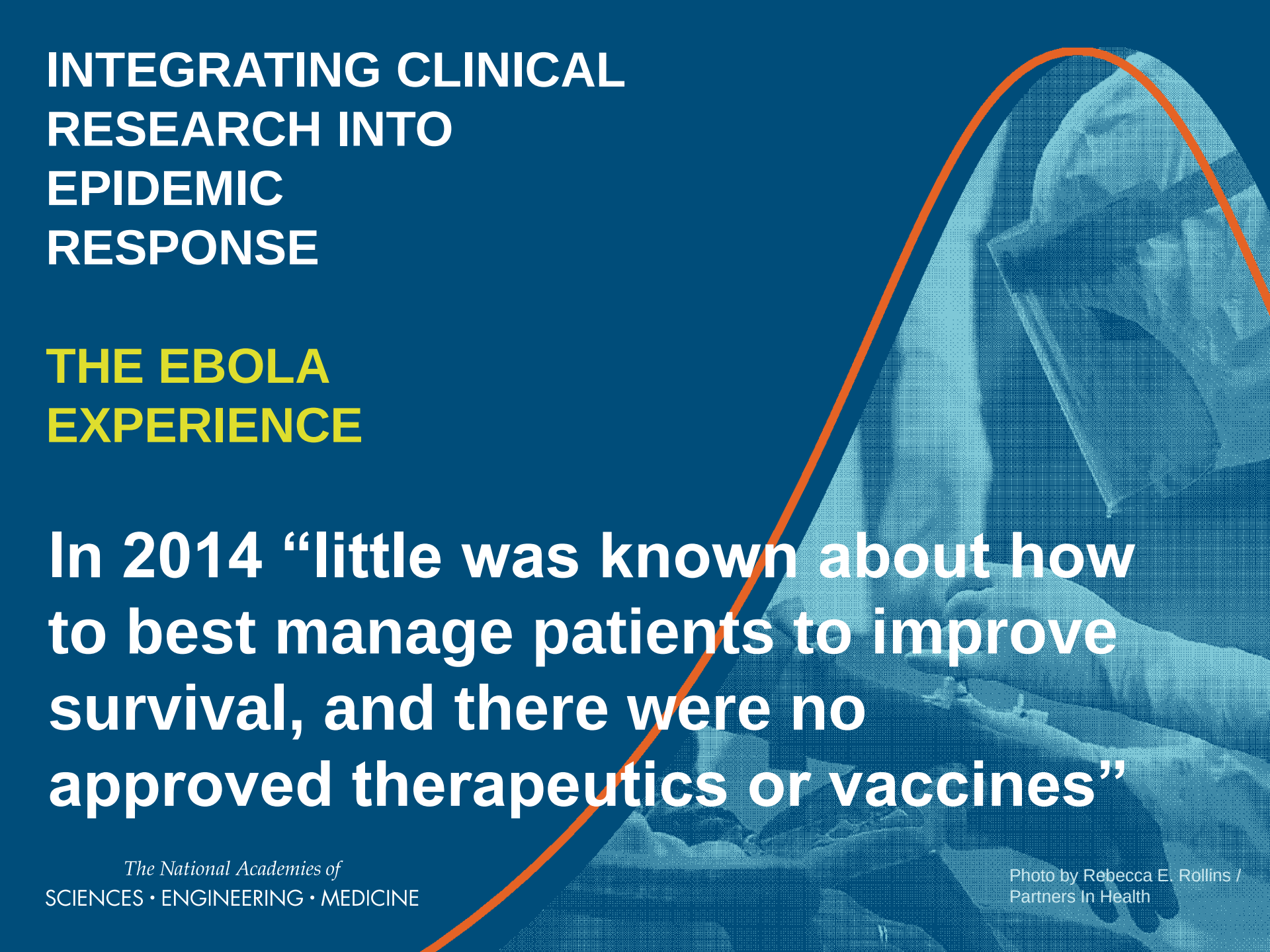

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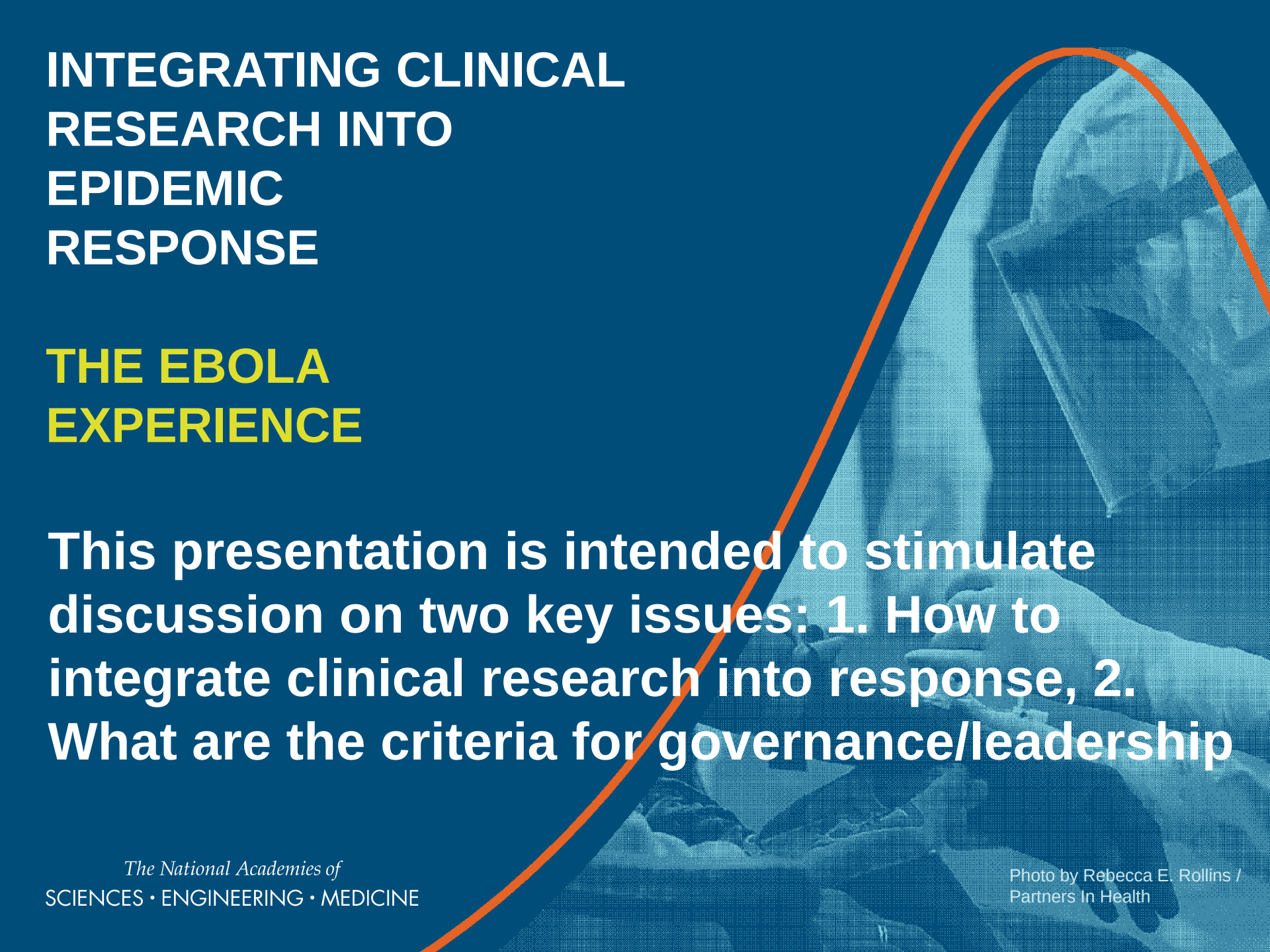
Photo by Rebecca E. Rollins / Partners In Health

INTEGRATING CLINICAL RESEARCH INTO EPIDEMIC RESPONSE

THE EBOLA EXPERIENCE

This presentation is intended to stimulate discussion on two key issues: 1. How to integrate clinical research into response, 2. What are the criteria for governance/leadership



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How are new drugs and vaccines developed?

- Upstream basic science research to identify targets (microbial, host) and candidate products
- Extensive development to determine efficacy and safety in animal models, including modifications of candidates to increase efficacy and safety
- Favorable data from more than one animal model
- Regulatory approval for early Phase 1 (safety) trials in humans, followed by small Phase 2 studies to determine if the candidates perform as expected, & Phase 3 human challenge infections if indicated
- If warranted, large scale efficacy/safety trials – most candidates fail along the way and are discarded

Why is research during an Ebola epidemic different from Measles, cholera, or Dengue?

- Because of its high mortality as well as the lack of proven treatment, experimental human infection models are impossible. An outbreak is the only opportunity for human trials
- Measles has a highly effective highly safe vaccine
- Cholera is readily treated with fluids and antibiotics and there is already an effective vaccine
- There is no approved drug or vaccine for dengue, but it is not hard to conduct trials during outbreaks because special containment is not needed

Why do research during Ebola epidemics?

- Collect basic clinical data **to learn how to best care for infected patients**
- **To assess** investigational drugs and vaccines for **safety and efficacy in humans** because animal models do not reliably predict human results
- Because safe, effective and accessible vaccines can **enhance public health measures** (e.g. safe burial practices) to **control or prevent future epidemics**
- Because safe, effective, accessible **drugs are needed to treat sick people** when public health measures are not enough to prevent an outbreak from spreading

Why do clinical research during epidemics?

- To **advance medical knowledge and patient care** when clinicians don't know if or how well new approaches will work in people, which are better and safer, for whom, and in what settings
- Because knowing drugs/vaccines are safe and effective is necessary for **approval/licensing** and for manufacturing, distribution, and use
- To expand access to promising new approaches that are shown to work, and **to benefit future patients** by adding to scientific knowledge

Charge to the Committee

The National Academies were asked to assess the clinical trials in West Africa during 2014–2015 Ebola outbreak and recommend improvements during future outbreak emergencies

Sponsors:

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

Methodology:

- 16 member expert committee from the U.S., Europe, Africa
- 3 public workshops, 6 closed committee meetings, comprehensive literature review, frequent conference calls and email exchanges
- Extensive external and internal review

Context of the outbreak and its progression

- The outbreak was recognized in early January 2014 but not identified as Ebola until mid- March – International Health Regulations (IHR) failed; *what are the IHR's? Core capacities to detect, assess, notify and report outbreaks*
- MSF, influenced by their clinical experience on the ground, declared the outbreak was out of control
- WHO, influenced by past experience, declared this was a level two (moderate) event, needing moderate support, run by WHO Country Office under regional office supervision
- The delayed designation of the highest level of concern, a Public Health Emergency of International Concern, until August 2014 resulted in late international response response
- Only then was the possibility of clinical trials raised

2014-15: Largest Ebola Outbreak Ever

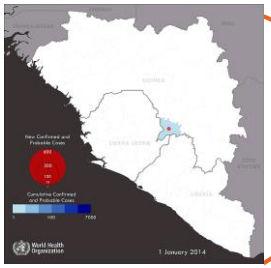
Mainly affected Guinea, Liberia, and Sierra Leone

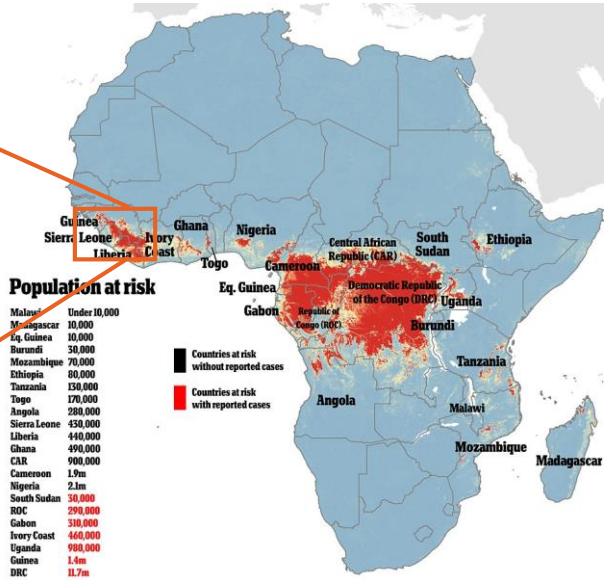
28,652

PEOPLE INFECTED

11,325

LIVES CLAIMED





Population at risk

Malawi	Under 10,000
Madagascar	10,000
Eq. Guinea	10,000
Burundi	30,000
Mozambique	70,000
Ethiopia	80,000
Tanzania	150,000
Togo	170,000
Angola	280,000
Sierra Leone	430,000
Liberia	440,000
Ghana	490,000
CAR	900,000
Cameroon	1.9m
Nigeria	2.1m
South Sudan	30,000
ROC	290,000
Gabon	310,000
Ivory Coast	460,000
Uganda	980,000
Guinea	1.4m
DRC	11.7m

ZERO

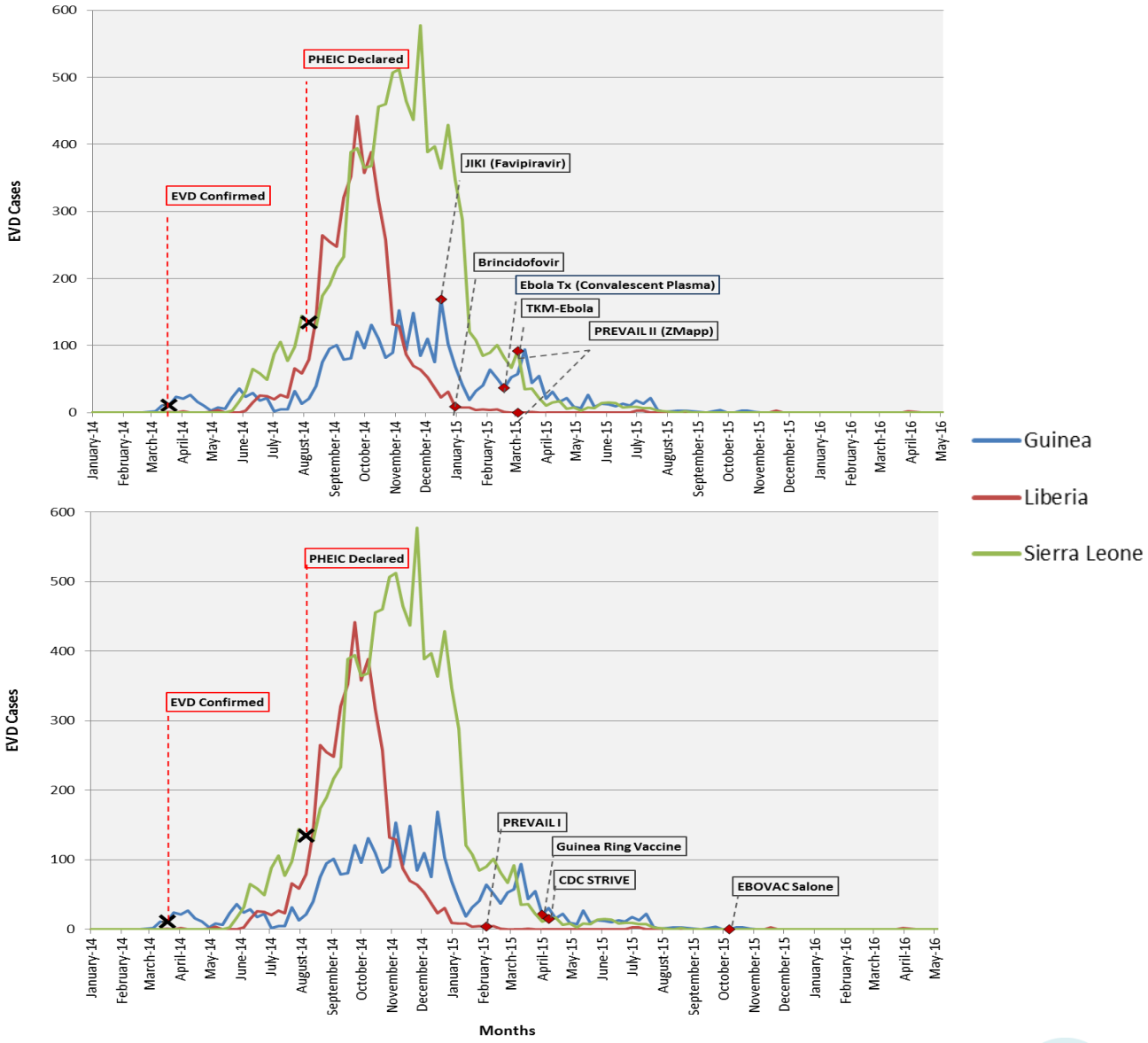
APPROVED EBOLA-SPECIFIC VACCINES OR TREATMENTS AT THE OUTSET

~20

WHO LIST OF POTENTIAL CANDIDATES FOR CLINICAL TRIALS

Ebola Therapeutic Trials Timeline

Ebola Vaccine Trials Timeline



Source: WHO situation reports

Nine Clinical Trials during Ebola Outbreak

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

5

Therapeutic Trials

Zero

Conclusive results, with one possibly effective product

4

Vaccine Trials

One

Vaccine candidate with probable protective effect

Challenges to Rapidly Starting Trials

- Post PHEIC chaotic conditions so **humanitarian clinical and public health needs clashed with research goals**
- **No consensus on what to study** or how to organize it
- **Limited local experience** with Ebola or clinical research
- Early **missteps in messaging/control efforts** and **failure to engage community** led to fear, rumors, and violence
- Access to untested therapy and **better outcomes for foreign responders** led to therapeutic misconceptions
- **Controversy about ethics** and feasibility of randomized controlled trials
- **Poor coordination** among research groups created competition for trial approval and sites as cases dwindled

Key Messages from Report

- Research is **necessary and should be integrated into epidemic response** – these can be organized to work together. The question is how to insure this happens?
- It is **ethical and feasible** to do clinical research during epidemics – research must be scientifically rigorous and designed to produce useful information
- Planning research and response **begins before an outbreak** occurs – requires international and national partners to coordinate and collaborate
- **Community engagement and participation** in planning is critical before and during outbreaks

Key Messages, continued

- **Capacity strengthening** in at-risk countries spans health care, public health, research, training, and improvement of health, public health, and research infrastructure
- **International/national investment now** is key to improved future performance – new outbreaks will occur, so we pay now or pay much more later
- **Coordination and cooperative engagement** among research and development agencies needs improvement to achieve these goals
- Optimal **leadership characteristics may differ** for the response and clinical research challenges

Limitations of IHR (2005)

- IHR has a clear hierarchical governance structure, led by WHO, with specific roles for national authorities, and other organizations, and ability to call on Roster of Experts for Emergency Committee & Review Committee

But

- **No enforcement mechanisms**, **little public accountability** over State or WHO performance
- **IHR mandate and governance arrangements do not include research**
- Need to **bridge practice and research** efforts in epidemics

Filling the Governance Gap: What should global governance for research in epidemics involve?

- Governance is defined as *"how societies make and implement collective decisions" (WHO 2016)*
- Sustainable Development Goal 16: **build effective, accountable and inclusive institutions**

- **Global governance** in health research involve **multi-stakeholder networks** with different **interests, capabilities, mandates, and power** → we need a governance model that recognizes these realities

Key stakeholders for research in epidemics

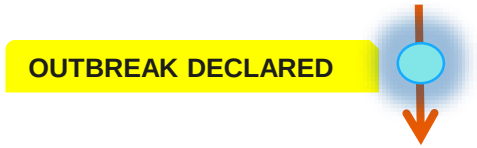
- National governments: Ministries of Health, Foreign Affairs, regulatory agencies, research agencies, and public health agencies
- Multilateral organizations: World Health Organization, World Bank, UNICEF
- Humanitarian organizations (international and national NGOs): MSF, PIH, etc. (>70 involved in Ebola outbreak).
- Academic and research organizations
- Health professions associations
- Foundations
- Pharmaceuticals and diagnostics companies
- Civil society organizations

Model Governance Structure for International Coordination From the Report: *Inclusive, autonomous, and independent*

Inter-epidemic planning

International Coalition of Stakeholders (ICS)

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



Epidemic action

Rapid Research Response Workgroup (R^3W)

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

Key issues to resolve in establishing governance arrangements

1. Clarity of **goals**, including commonalities and differences across **stakeholders**
2. Recognize the full range of **stakeholder interests, ideology, power and accountability**, with structures and processes to provide balance and maximize goals
3. Agree on **working principles**
4. Use **deliberative processes** that demonstrate **legitimacy, inclusiveness, authority, and public accountability** (both internationally and within nations)

How clear are the goals?

Apparent consensus by some key actors on “the importance of proactive, collaborative and coordinated research and development (R&D) efforts to save peoples’ lives and avert public health crises” (Chatham House Meeting Summary)

But are there accepted common goals on key issues?

1. Drug/vaccine **availability**
2. Scope of **research agenda** to address outbreaks
3. Role of **capacity strengthening**
4. **Accountability** goals?
5. **Sharing of benefits and costs** of research

How do we address different interests, ideology, power and accountability?

- All stakeholders have different **interests** (e.g. commercial, financial, institutional preservation/reputation, political)
  - WHO claims to have no vested interests (Lancet 2017), yet all organizations have financial and other interests
- **Ideologies** (values and beliefs)
  - What constitutes “evidence”; ownership of intellectual property; commitments to prior programs and normative decisions (e.g. approved clinical guidelines)
- **Power** (ability to act or have others act)
  - Who will pay for governance and implementation?
- **Accountabilities** -- stakeholders are accountable to different bodies, hold others accountable, and have different means of accountability.
  - Government agencies may be accountable to their citizens, taxpayers, &/or voters; Corporations to boards and shareholders; Multi-lateral agencies to boards or assemblies.

Is there agreement on working principles?

Many principles proposed for Global Coordination Mechanism (GCM)

- E.g. use of WHO Blueprint for top-priority pathogens, focus on evidence, ensure accountability …

But how important to address what's missing …

- Inclusiveness of stakeholders beyond government and scientific communities (civil society, NGO sector, industry)
- Who chooses who is should be involved? Why not China CDC, USAID, other universities and civil society organizations?
- How to avoid/reduce conflicts of interest accountabilities by design – i.e. balance and distribution of responsibilities and accountabilities

Deliberative processes: Do they have the legitimacy, authority and public accountability?

- Should governance be based on a single lead agency? E.g. incorporate into IHR led by WHO?
  - If so, how to avoid conflicts of interest in research roles?

- Should governance arrangements involve distribution of leadership and accountability across network “nodes”?

Do key actors have capabilities to perform and manage key research functions?

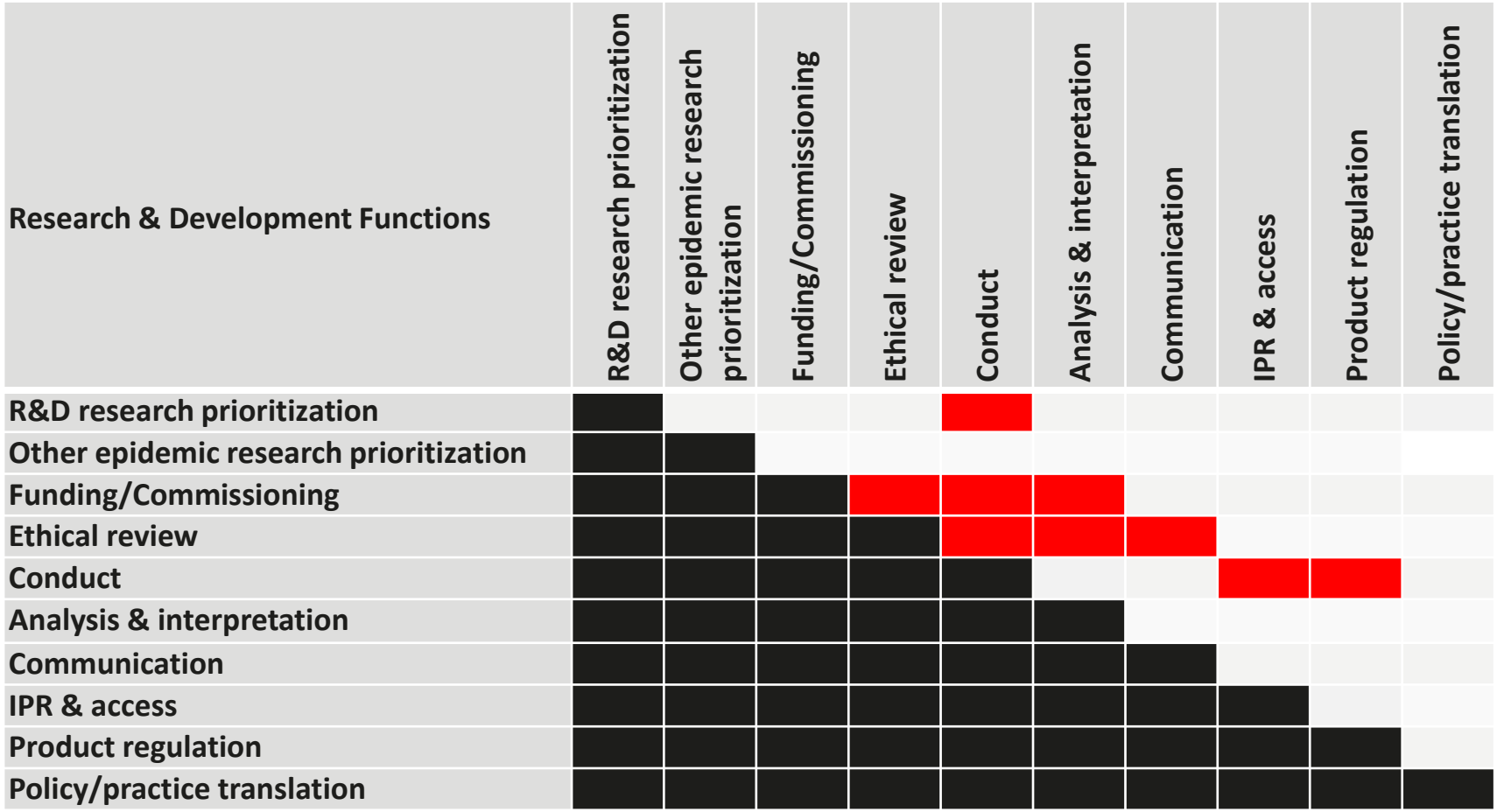
- R&D research prioritization
- Prioritization of other epidemic related research
- Funding and/or commissioning for clinical research
- Ethical review of research
- Conduct of field research
- Results analysis and interpretation
- Research communication
- Legal arrangements for IPR and access to products
- Regulation of clinical research products
- Translation of research to policy and practice

Should agencies play conflicting roles in research?

- In the EVD outbreak, WHO led prioritization efforts and commissioned vaccine research, but was also involved in …
  - Human subjects ethical review
  - Study implementation
  - Analysis of results
  - Communication of results and policy decisions
  - Access to products from research (e.g. access to vaccines and revenues)

- How can create a more balanced leadership role be created?

R&D leadership functions: Which are in conflict?



International Governance for Research in Epidemics - How can we do better?

1. Engage broader range of stakeholders for global coordination mechanism
   - Seek agreement on critical goals
2. Develop governance mechanisms that address network structure and the interests, ideologies, power and accountabilities of key actors
   - Develop and apply agreed principles and processes
3. Develop a roster of experts and sets of standing procedures to be able to assemble Rapid Response Research Workgroup for the next relevant outbreak.