Framework on accumulating evidence across outbreaks

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Figure 1. Total Ebola cases per week reported in Liberia are plotted in red, based on the reports from the Ministry of Health. Lines in orange, green, and blue show the breakdown of weekly reported cases that were classified as confirmed, probable, or suspected, respectively. On the right, the black dotted line shows the cumulative enrollment in the PREVAIL I vaccine trial, scaled to the axis on the right side of the graph. Below the figure, important events are shown to give a sense of the timeline as the epidemic unfolded.
Figure: Weekly incidence of Ebola in Guinea 2014–15, and key dates in the ring vaccination trial
A Brazilian mother holds her daughter, who was born in 2016 with microcephaly, a Zika-caused birth defect. MARIO TAMA/GETTY IMAGES

As massive Zika vaccine trial struggles, researchers revive plan to intentionally infect humans

By Jon Cohen  |  Sep. 12, 2018 , 12:30 PM

doi:10.1126/science.aav3996
FIGURE 7-1 A timeline of critical components: Launching clinical trials in an epidemic. The above figure represents an idealized timeline of activities necessary to launch a clinical trial and their relation to an epidemic curve. It should also be noted that each of these endeavors has inter-epidemic planning activities—if properly planned for these inter-epidemic activities will contribute to faster...
Confirmed global cases of MERS-CoV

Reported to WHO as of 18 Sep 2018 (n=2254)

Motivation

Outbreaks are of unpredictable size and duration

All outbreaks represent an opportunity to advance research and development efforts

There is considerable risk that trials will be underpowered and results from trials terminated due to low accrual will be inconclusive

Prejudgment of promising but inconclusive results can:
- Impact decision-making of caregivers and policy makers
- Jeopardize the conduct of future confirmatory trials
Recommended approach

We advocate for the use of a “master protocol” to preserve data confidentiality and trial integrity until the scientific aims have been reliably addressed.

**Master protocol** = conventional clinical trial designed to extend across multiple sites and outbreaks.

Trial results are released only following the advice of an independent data monitoring committee (e.g. stop for efficacy, futility, reached target # of endpoints) and not due to lack of recruitment.
Practical considerations

Multi-site trial in high-risk areas with opportunity to add sites responsively

Researchers and national representatives from affected countries should be engaged early on

Requires a clear and transparent mechanism for achieving consensus regarding elements of the protocol

For each successive outbreak, study teams should commit to collaborating on existing, ongoing protocols, rather than starting new independent trials
Statistical considerations

“Standard” sequential monitoring plan based on information fraction
- Number of endpoints in vaccine trial
- Number of participants in therapeutic trial

Pre-specified analyses or flexibly timed to occur when outbreaks end
Lassa therapeutics

~400 participants needed to have 80% power to detect a reduction in CFR from 20% to 10%

- Uncertainty in oSOC CFR
- Planned sample size adjustment based on aggregated “internal pilot” data
- Sample size may increase to $\hat{N}$ or remain at 400
- Information fraction is based on adjusted sample size

Planned interim look at halfway point or after first season

- If first season outbreak is very large, may look before season ends
- If first season outbreak is modest, may look at the end of the season
- If first season outbreak is small, may wait until further data accrue
What is needed...

Practical guidance on when to conduct interim analyses

- When enough information has accrued to take a look
- Maximum number of looks
- Minimum spacing between looks
- Strategies to integrate epidemic forecasting into decision-making
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