Experimental challenges of humans with pandemic infectious agents --
What is needed for them to make a greater contribution?

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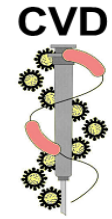
Precedent



Challenge studies with pandemic pathogens

- *Shigella dysenteriae* 1 (Shiga bacillus)
  - Strain from Central America Shiga dysentery pandemic (1967-1971)
- *Vibrio cholerae* O1 classical biotype (6th pandemic)
- *Vibrio cholerae* O1 biotype El Tor (7th pandemic)
- *Vibrio cholerae* serogroup O139 (pseudopandemic)
- A(H3N2)/Hong Kong/8/68 influenza virus
- A/H1N1/pdm09
- SARS-CoV-2
- *Monkeypox*?

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Volunteer challenge studies are a powerful and useful tool

Information challenges can:

- Establish pathogenicity
- Elucidate pathogenesis
- Identify host risk factors
- **Estimate infective inoculum**
- **Assess infection-derived immunity**
- **Characterize the immune response**
- **Assess vaccine efficacy (providing evidence for licensure)**
- **Identify correlates of protection**
- Assess efficacy of therapeutic agents

Is the pathogen amenable to a model?

- Clinical severity of natural disease?
- Is the illness treatable?
- Is the illness reliably self-limited?
- Risk to the community?
- Is physical containment required?
- Quarantine (compulsory isolation) required?
- Document subject's baseline health?
- Can subjects' follow-up be assured?
- Are there compelling questions answerable only (or best) by human challenge studies?

1974 – NIH funded the University of Maryland to establish a Research Isolation Facility where CHALLENGE STUDIES could be performed involving COMMUNITY VOLUNTEERS

- Ethical issues
- Bacteriologic/parasitologic/virologic issues
  - Challenge strain selection
  - GMP inoculum (free of extraneous agents)
  - Biosafety level required?
  - Realistic time to obtain the challenge inoculum
- Practical & logistical considerations
- Regulatory issues

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Ethics

- **Primum non nocere** (First, do no harm) –grappling with the physician's ethic
- **A CVD ethic:**
  - **Would I do this study?**
  - **Would I be comfortable with my family member doing the study?**
- Beware of financial conflict of interest
- Beware of "champions"
- "Ethics" change over time:
  - What was routine in 1967 was not so in 1977
- "Ethics" vary by country and culture

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Human Challenge Studies to Accelerate Corona Virus Licensure.

Nir Eyal, Marc Lipsitch, Peter G Smith.

Journal of Infectious Diseases 2020; 221:1751-1756

"By replacing conventional phase 3 testing of vaccine candidates, such trials may subtract many months from the licensure process, making efficacious vaccines available more quickly."

Why Challenge Trials of SARS-CoV-2 Vaccines Could Be Ethical Despite Risk of Severe Adverse Events

Nir Eyal.

Ethics & Human Research 2020; 42:24-34.

Extraordinary Diseases Require Extraordinary Solutions.

Stanley A Plotkin & Arthur Caplan.

Vaccine 2020; 38: 3987-3988

So much at stake: Ethical tradeoffs in accelerating SARS-CoV-2 vaccine development

Christine Grady, Seema Shah, Franklin Miller,et al.

Vaccine 2020; 38:6381-6387

For now, it's unethical to use human challenge studies for SARS-CoV-2 vaccine development

Jeffrey P Kahn, Leslie Melttzer Henry, Anna C Mastroianni, Wilbur H Chen, Ruth Macklin

Proc Nat'l Acad Sci, USA 2020; 117:28538-28542

Human Challenge Studies with Wild Type SARS-CoV-2 Violate Longstanding Codes of Human Subjects Research

Stanley M Spinola, et al.

Open Forum Infectious Diseases 2020

Musings on establishing an experimental monkeypox challenge model in humans

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Is monkeypox amenable to a volunteer challenge model?

- Clinical severity of natural disease? *Clade 2B has low case fatality.*
- Treatable disease? *Yes. There are two approved antivirals*
- Self-limited disease? *Yes.*
- Transmission risk to the community? *Low. But should be done under physical containment.*
- Physical containment required? *Depends on the site. It would be most conservative to use containment*
- Quarantine? *It would be most conservative to have quarantine.*
- Document subject's baseline health?
- Can subjects' follow-up be assured?
- Compelling questions answerable only with challenges? *To be discussed. Probably not.*

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Is monkeypox amenable to a volunteer challenge model?

- Clinical severity of natural disease? ***Clade 2B has low case fatality.***
- Treatable disease? *Yes.* ***There are two approved antivirals***
- Self-limited disease? ***Yes, in normal hosts****.*
- Transmission risk to the community? ***Low. But should be done under physical containment. Presumed risk for contacts with eczema***
- Physical containment required? ***Depends on the site. It would be most conservative to use containment***
- Quarantine? *Most conservative to have quarantine.*
- Document subject's baseline health?
- Can subjects' follow-up be assured?
- Compelling questions answerable only with challenges? *To be discussed. Probably not.*

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Public perception is fickle

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Thank you