

# **The ethics of challenge studies**

November 18, 2015

Faculty, Department of Bioethics

Joint appointment with the Division of AIDS

Head of Unit on International Research Ethics

National Institutes of Health

The opinions expressed are my own. They do not reflect any position or policy of the U.S. Government or the NIH.

# Overview

- History/background
- Are challenge studies different than other types of research?
- Ethical framework for challenge studies

# **HISTORY/BACKGROUND**

# What are challenge studies?

- Studies that deliberately exposing subjects to disease pathogens/infection
- Goal: To study pathogenesis of infection or test preliminary efficacy of vaccines or other prevention interventions
- High potential value: can get answers more quickly, expose fewer subjects to risk, and results easier to interpret

# History of challenge studies

- Long history of challenge studies
- Important scientific developments as a result
- Many have raised controversy (often retrospectively)

# Yellow Fever (1900)



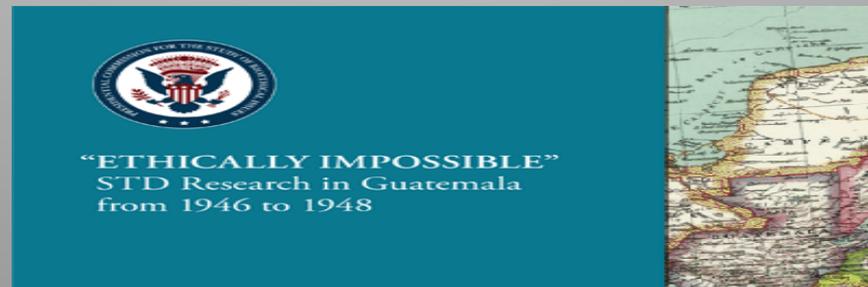
- Walter Reed sought to find out if mosquitoes transmit yellow fever
- Yellow fever can be mild or cause severe symptoms (e.g., fever, chills, nausea, bleeding, organ failure)
- Several phases of experimentation
- Subjects exposed to mosquitoes, received blood of infected patients, or housed w/ “fomites”
- Estimated mortality: 10-60%

# Protections & outcome

- Subjects gave informed consent
- Paid \$200 to participate (~\$8,000 today)
- Paid \$500 (~\$20,000 today) if infected, given to families if deceased
- Researchers served as subjects
- One researcher died; other subjects received supportive care, fully recovered

# Sexually transmitted infections

- 1940s: Inoculation experiments on syphilis, chancroid, gonorrhea conducted in Terre Haute prison & Guatemala
- Criticisms of Guatemalan experiments: Prisoners involved, infected through injections and exposure to commercial sex workers, lack of consent, transmitted infection to others, some not treated



# US apologizes for infecting Guatemalans with STDs in the 1940s

By the CNN Wire Staff

October 1, 2010 10:18 p.m. EDT



President Obama offers "profound apologies" to the Guatemalan president for the tests.

**Washington (CNN)** -- The United States apologized Friday for a 1946-1948 research study in which people in Guatemala were intentionally infected with sexually transmitted diseases.

A statement by Secretary of State Hillary Clinton and Secretary of Health and Human Services Secretary Kathleen Sebelius called the action "reprehensible."

*See also* Lynch HF, Journal of Medical Ethics 2012

# Criteria for U.S. Experiments

## QUALIFICATIONS FOR VOLUNTEERS

In the study, a total of 241 volunteers were employed. Each volunteer received a financial reward and an official certificate of participation, and a suitable notation was incorporated into the records of the institution. The following restrictions and qualifications governed the selection of volunteers:

1. Age between 21 and 45 years.
2. Freedom from all evidence of pre-existing gonococcal infection.
3. Negative culture findings in urine sediment on at least three occasions (once after prostatic massage) prior to being included in the study.
4. Freedom from anatomical abnormality of genital structures.
5. Completely negative history of arthritis of any type.
6. Reasonable assurance of availability for postexposure observation for a period of at least six months.
7. Freedom from intercurrent disease or debility which might exert an influence upon the course of the infection.
8. Assurance from the officials of the institution that the volunteer was acceptable from the standpoint of mental status and that the records of incarceration did not contain evidence indicative of the lack of ability to cooperate in the manner which would be required.
9. Assurance that the volunteer possessed a thorough understanding of the purpose underlying the study and the possible risks involved.

# Hepatitis

- 1950s-60s: At Willowbrook State School, “mentally deficient” infants and children inoculated with hepatitis
- Results: identified different types of hepatitis (A & B); injection of gamma globulin was protective
- Publication states that the decision to conduct study “not undertaken lightly”

# Hepatitis

- **Justifications given:**
  - Infectious hepatitis milder in young children
  - Agent used would produce mild disease
  - Residents likely to be exposed otherwise, received extra care in study
  - Parents gave consent
  - Serious uncontrolled endemic within the institution → knowledge was important
  - Research approved by state, federal officials

# Hepatitis

- Argued that:
  - Infectious hepatitis milder in young children
  - Agent used would produce mild disease
  - Residents likely to be exposed otherwise, received extra care in study
  - Parents gave consent
  - Serious uncontrolled endemic within the institution → knowledge was important
  - Research approved by state, federal officials

# Hepatitis

- Nevertheless, widely cited as ethically controversial research
  - Why not study hepatitis in adults first?
  - Risks were uncertain
  - Consent arguably deficient
  - Vulnerable population

Henry K. Beecher, “Ethics and Clinical Research,” *New England Journal of Medicine* 274 (1966):1354-60; Henry K. Beecher, *Research and the Individual: Human Studies* (Boston: Little, Brown, & Co., 1970); Stephen Goldby, “Experiments at the Willowbrook State School,” *Lancet* 1 (1971)

**ARE CHALLENGE STUDIES  
DIFFERENT THAN OTHER  
TYPES OF RESEARCH?**

# Challenge studies might be different in terms of:

- Goals
- Risks/benefits
- The “ick” factor

# Different in terms of goals?

- Goal of medicine to cure and prevent disease
- Challenge studies *infect* people with diseases
  - But in order to find ways to cure and prevent diseases in future patients
- Research generally exposes individuals to risk for the benefit of future patients

# Different in terms of risks?

- Trade-off between risks to participants and benefits for others in society occurs in all research at some level
- Not necessarily higher risk
  - E.g., first in human gene therapy trials, HIV cure research

# Different in terms of “ick” factor?

- Not necessarily, but may be in a class of research that seems “icky”
  - Immunology research on aborted fetuses
  - Testing artificial lungs in brain dead patients
  - Recruiting subjects to have sex to test experimental condoms
  - Toe amputation study
- But are our intuitions misfiring here?

# So are challenge studies different than other types of research?

- Hard to identify systematic, morally relevant differences between challenge studies and other types of research
- May be a category of research sometimes associated with cause for concern

# What made prior challenge studies so controversial?

- Other ethical issues arose in those studies:
  - Inadequate consent
  - Conducted on vulnerable/“disposable” populations
  - High risk
- No clear ethical framework in place for challenge studies at the time

# **ETHICAL FRAMEWORK FOR CHALLENGE STUDIES**

# Ethical framework

Acceptable  
scientific  
rationale?

Acceptable  
risks?

Vulnerable  
groups  
protected?

Solid informed  
consent  
process?

Appropriate  
level of  
compensation?

Right to  
withdraw  
respected?

Franklin G. Miller and Christine Grady, "The Ethical Challenge of Infection-Inducing Challenge Experiments," *Clinical Infectious Diseases* 33 (2001): 1028-33.

# Scientific rationale

- Compelling case for conducting a challenge study?
  - E.g., necessary to determine how infection is transmitted, will expedite vaccine development for important disease
- Ability to conduct prior animal research?

# Risks

- Limits on risk for vulnerable populations
- No clear upper limit on risk in research with consenting adults in US regulations
  - Implicit risk limit for many stakeholders\*
- Risks in challenge studies should be low, reversible, self-limiting, and/or treatable
- Minimize risk of infecting others—may need to keep subjects at research site for period of time

# Risks in malaria challenge studies

- Review of 18 studies with 118 subjects
  - No lasting adverse effects
  - Most frequent symptoms experienced
    - Arthralgia/myalgia (79%)
    - Malaise/fatigue (79%)
    - Headache (77%)
    - Chills (68%)
    - Fever >38C (61%); median duration of 2 days

Preston Church LW, et al. J Infect Dis 1997;175:915-20.

\*Slide courtesy of Frank Miller

# Risks in cholera challenge study

- 40 volunteers exposed to cholera
  - Antibiotic treatment administered in response to “severe” symptoms or after 4 days
  - 25% had “severe” diarrhea
  - 38% had fever  $>38^{\circ}\text{C}$

Sack DA, et al. *Infect Immun* 1998;66:1968-72.

# Vulnerable populations

- Populations chosen for ease and convenience, not scientific reasons
- Many definitions of vulnerability
- CIOMS: Decreased ability to protect one's own interests

CIOMS International Ethical Guidelines for Biomedical Research involving Human Subjects (2002)

# Vulnerable populations



# Vulnerability

- Challenge studies might require justification to include vulnerable populations
- &
- Tailored protections depending on *source* of vulnerability

(Denny C, Grady C, *JME* (2007); Hurst S, *Bioethics* (2008); Declaration of Helsinki 2013)

# Informed consent

- Could use heightened informed consent process
  - E.g., multiple steps to process, participants have to take initiative to enroll
  - Test-feedback shown to be effective

Flory & Emanuel, JAMA 2004

# Compensation

- Typical concern about undue inducement
- But we all rely on money as an incentive
- Some studies suggest participants motivated by money spent more time on risks, understood them better



Stunkel L, et al. Comprehension and informed consent: assessing the effect of a short consent form. *IRB*. 2010 Jul-Aug;32(4):1-9; Cryder CE et al, Informative inducement: study payment as a signal of risk. *Soc Sci Med*. 2010.

# Right to withdraw

- By regulation: “Subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled”
- May not always be safe to withdraw from challenge studies
- However, such restrictions not unique
  - E.g., experimental bone marrow transplantation

# \*Public trust in research

- Reason for risk limit may be to preserve public trust in research

London AJ, JLME 2012; Wertheimer A, J Law Biosci. 2014

- Challenge studies may be especially hard for public to understand
- More reason to communicate clearly about challenge studies, reasons for doing them

# Conclusions

- Long history of challenge studies
- Not necessarily different from other research in terms of risk, lack of direct benefit, “ick factor”
- Controversial when poor consent, vulnerable groups, high risk
- Existing ethical framework
- Some ethical issues more salient in challenge studies—such as risks to others, limits on right to withdraw, need to preserve public trust