Ethical framework for human challenge studies

(*or What I learned from chairing a committee on the ethics of Zika virus human challenge trials*)

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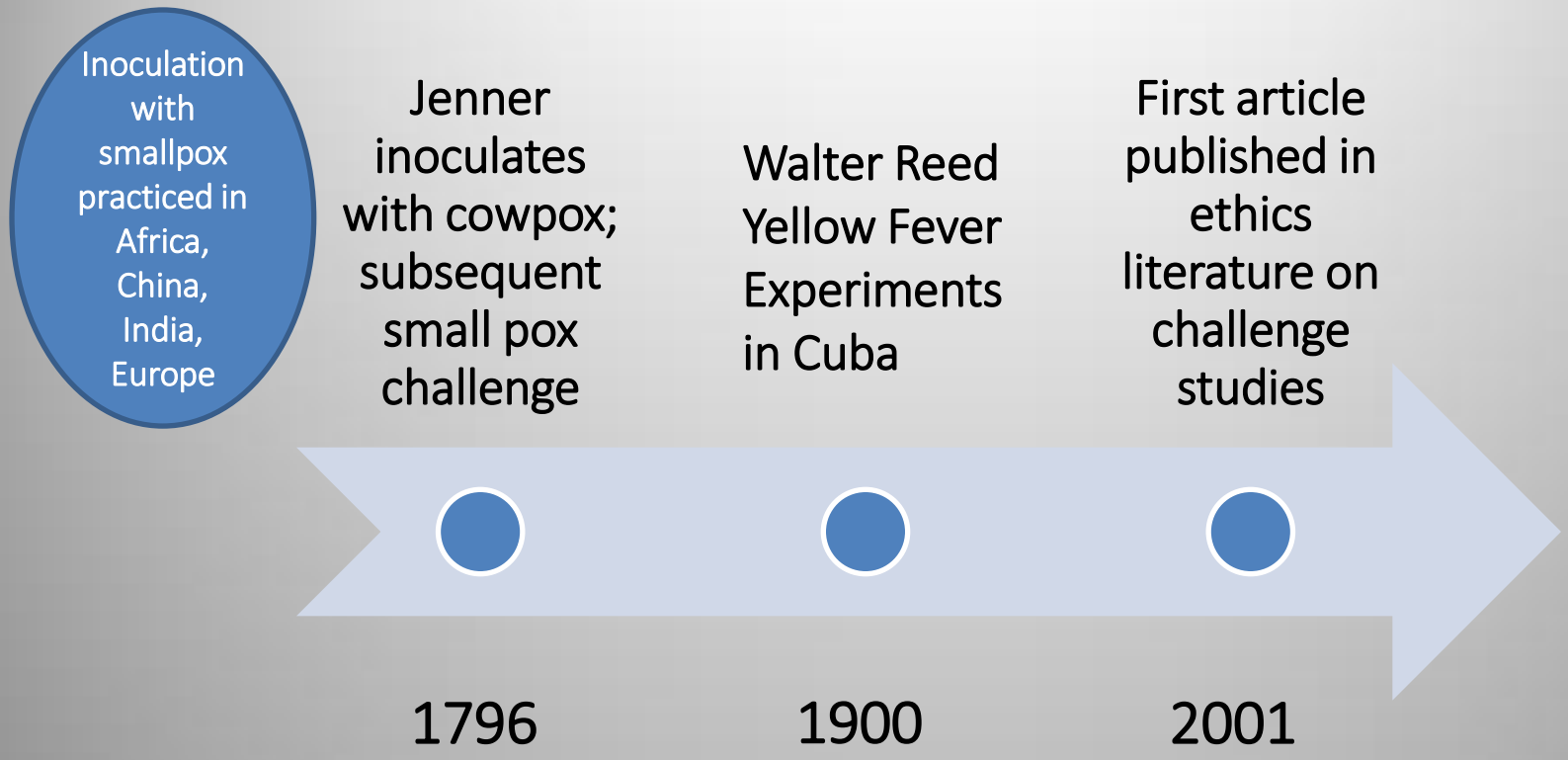
Brief background: History of human challenge studies



An abbreviated history

Walter Reed Yellow Fever Trials

- Substantial risk of mortality (~10-60%), one death
- Early use of subject protections:
  - Informed consent
  - Payment in gold
  - Self-experimentation
  - Supportive care

Lessons from history

- Several human challenge studies have been controversial (e.g., Guatemala STI studies, Willowbrook)
- Why?
  - Limited research oversight at the time
  - Research ethics not fully developed
  - Use of vulnerable populations without consent
  - May have been some rogue actors

Lynch HF, *J Med Ethics* 2012

Zika virus human challenge trial ethics consultation: Process

Recent consultation on Zika virus human challenge trials

- 2015: The National Institute of Allergy & Infectious Diseases (NIAID) received proposal to conduct a Zika virus human challenge model

Zika virus human challenge model consultation

- Recognizing the ethical complexity in a Zika virus human challenge model, NIAID and the Walter Reed Army Institute of Research (WRAIR) convened a consultation
  - Planning committee of stakeholders
  - Independent writing committee
  - One day meeting
  - Report and recommendations

Independent panel

Criteria

- Independence from funding/reviewing agencies
- Not planning to conduct a Zika virus human challenge trial
- Relevant cross-disciplinary expertise:
  - Research ethics
  - Gynecology
  - Neurology
  - Experience with challenge studies

Members

- Seema Shah (Chair)
- Frank Miller (Cornell)
- Jonathan Kimmelman (McGill)
- Annie Lyerly (UNC Chapel Hill)
- Holly Lynch (Petrie Flom Center, Harvard)
- Carlos Pardo (Johns Hopkins)
- Carmen Zorilla (U of Puerto Rico)
- Francine McCutchan (PATH)
- Ricardo Palacios (Butantan Institute)

Charge of consultation

Can a Zika virus human challenge trial be ethically justified?

If so, under what conditions?

Ethical framework for human challenge studies

VIEWPOINTS

The Ethical Challenge of Infection-Inducing Challenge Experiments

Franklin G. Miller and Christine Grady

Department of Clinical

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REVIEW ARTICLE

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RESEARCH ETHICS

Challenge studies of human volunteers: ethical issues

T Hope, J McMillan

Julie Rothstei
'Department of
and 'Department

See end of article for authors' affiliations

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The Academy of Medical Sciences

Microbial Challenge of Human Volunteers

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The rights and wrongs of research: contextualising inoculation study

Holly Fernandez Lynch

ABSTRACT

In its recent review of the US Public Health Service Sexually Transmitted Disease Inoculation Study, conducted in Guatemala from 1946 to 1948, the Presidential Commission for the Study of Bioethical Issues identified a number of egregious ethical violations, but failed to adequately address issues associated with the intentional exposure research design in particular. As a result, a common public misconception that the study was wrong because researchers purposefully infected their subjects has been left standing. In fact, human subjects have been exposed to disease pathogens for experimental purposes for centuries, and this study design remains an important scientific tool today. It shares key features with other types of widely accepted research on human subjects and can be conducted

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PATH VACCINE SOLUTIONS

PUBLIC HEALTH ETHICS VOLUME 9 • NUMBER 1 • 2016 • 92–103

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May 2015

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Ben Bambery*, Monash University
Michael Selgelid, Monash University
Charles Weijer, Western University
Julian Savulescu, University of Oxfo
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committees in negotiating the distinct issues rai
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in other areas of medical research, we conclude
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mentation of measures to protect the public fro
system for compensation for harm. We hope th
practice and help to safeguard public confidenc

Infectious Disease Challenge Studies: Ethical Issues in Causing Disease for Medical Knowledge

Daniel Kavanagh, PhD | Curren MacDonald, MD, CIP | Lindsay McNair, MD, MPH, MSB

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Summary of literature

- Challenge studies aren't different in kind from other types of research (e.g., phase I studies in healthy volunteers)

- Some diseases should not be used in human challenge—conditions without cures or that are not likely to resolve without lasting effects (e.g., HIV)

- Several ethical considerations to apply

Ethical considerations

(1) Are risks and discomforts identified, minimized, determined to be reasonable, and justified by social value?

(2) Is scientific rationale and social value acceptable?

(3) Is there a system for compensation for research related injury?

(4) Are vulnerable populations enrolled?

(5) Is informed consent process adequate?

(6) Is level of compensation adequate or undue?

(7) Can right to withdraw be respected?

(8) Will appropriate community engagement occur?

Frank Miller & Christine Grady, *Clinical Infectious Diseases* 33 (2001): 1028-33;
Bambery B, Selgelid M, Weijer C, Savulescu J, Pollard A. *Public Health Ethics* 9(1):92-103 (2016)

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1. RISKS

Risks

- Risk = chance * severity of harm
- Standard view in research ethics: Risks should be **reasonable**, **minimized**, and **justified** by benefits to individuals or society
- No clear upper limit on risk in research with consenting adults in US regulations
  - Why not let people do what they want?

One argument: Preserving public trust

- Risky research "can inadvertently undermine forms of broader, longer-term collaboration that sustain the production of socially valuable medical knowledge"

London AJ, Kimmelman J, Emborg ME, *Science* (2010)

Risk limits in literature on CHIM

- Agreement in literature that risk cannot be too high
  - Many argue disease should be treatable/curable or "self-limiting"
  - And no risk of irreversible harm

- But limited argument for this risk limit, so we did not see it as a showstopper for a Zika CHIM

Risk levels in existing research

In phase I and malaria human challenge research:

- Mild/moderate risks not uncommon
- But serious adverse events, risks to third parties very rare

→If Zika virus human challenge trials are comparable, risks should not pose a barrier

Emanuel E, et al. BMJ 2015 (n=4620); Johnson R, et al. *Clinical Trials* 2016 (n=27,185); Preston Church LW, et al. J Infect Dis 1997;175:915-20.

Minimizing risks

- Small numbers of participants may allow for:
  - More creative and rigorous inclusion/exclusion criteria
  - More intensive informed consent process
  - More confidence in participants' precautions

Minimizing risks in Zika CHIM

- Minimizing risks to third parties:
  - Risk of microcephaly/neurological damage for fetuses, spread to others outside research
  - Suggestions:
    - Agreement to use long acting, reversible contraception
    - Could enroll women anticipating lower rate of sexual transmission, more ability to ensure precautions taken
  - But unclear how long protections would need to be in place, or how to identify all at risk

What we do not know about Zika virus

All modes of transmission

- Breastmilk, organ/tissue transplantation, other fluids?

How long people are infectious

Longer term effects

Full spectrum of disease, rate of complications

Effects of infection with another flavivirus

2. SOCIAL VALUE

Social Value

- To be ethical, clinical research should lead to improvements in health **or** advancement in generalizable knowledge

- Little consensus on what does and doesn't count, how to operationalize this concept

How to evaluate the social value of a human challenge study?

- There is usually more than one way to answer a given scientific question
- Alternatives involve trade-offs:
  - Time
  - Certainty/rigor
  - Risk to participants
  - Delay in interventions to future patients

Social value of CHIM

- "Best way to answer valuable scientific question that offers substantial benefits, in terms of human mortality or morbidity averted, over all ethically permitted alternatives"
  - Could be met if a CHIM very likely to lead to approval of promising vaccine candidate
  - May not be met if field trials will take place anyway, CHIM would make little difference

Barnhill A, Joffe S, Miller FG, Ethics of Infection Challenges in Primates, Hastings Center Report (2016); Lindeman JN, Bioethics, Sexuality, and Gender Identify, J Bioethical Inquiry (2012).

LIMITS OF EXISTING FRAMEWORK

Open questions for future research

- How can risks to third parties be justified?
- What level of risk and uncertainty is too high in research?
- How should justice be included in a framework?
- Do different issues arise for human challenge trials in endemic regions?
- Can pediatric CHIM be ethical?
- Is self-experimentation a safeguard?

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Lawrence Gostin, JD (Georgetown University)
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Drawing the line: Assessing and analyzing the US Rule on embryo research from ethical, political, and scientific perspectives
Kirstin Matthews, PhD (Rice University)
18 months/$153,637

Click here for project abstract

A new ethical and regulatory approach for the use of human challenge studies with emerging infectious diseases
Seema Shah, JD (Seattle Children's Hospital)
2 years/$199,117

Click here for project abstract.

World Health Organization

Conclusion of Zika virus CHIM consultation

- Identified ethical framework to determine whether Zika virus challenge studies can be ethically justified, and if so, under what conditions
- Concluded a Zika virus human challenge trial could be ethically justified if certain conditions were met and safeguards were in place
- Major concerns: risks to third parties, uncertain social value and alternatives to doing the trial
- Advised that these conditions were not met as of February 2017, but could be in the future

General conclusions for CHIM

- Existing ethical framework for challenge studies offers valuable guidance

- More work is needed to address open questions, determine how challenge studies can be used for emerging infectious diseases and in vulnerable populations or endemic settings settings

https://www.niaid.nih.gov/sites/default/files/EthicsZikaHumanChallengeStudiesReport2017.pdf

3. COMPENSATION FOR RESEARCH-RELATED INJURY

Compensation for research injury

- Endorsed in principle by every bioethics commission that has looked at the issue
- Devil is in the details
- Many institutions provide at least short-term treatment for injury

Resnik et al. *IRB* 2014; Henry LM, Larkin ME, Pike ER, J Law *Biosciences* 2015

4. VULNERABLE POPULATIONS

Vulnerable populations

- Populations chosen for ease and convenience, not scientific reasons
- Many definitions of vulnerability, perhaps most useful approach: Decreased ability to protect one's own interests
- Generally assumed we should exclude people who lack capacity to consent, employees

CIOMS International Ethical Guidelines for Biomedical Research involving Human Subjects (2016)

Pediatric populations

- What about enrolling children?
- Typically don't enroll children before studies have been completed in adults unless:
  - Prospect of direct benefit without good alternatives
  - Pediatric disease
  - Disease manifests differently in children so can't extrapolate from adult data

5. INFORMED CONSENT

Informed consent

- Heightened informed consent process commonly used in CHIM
  - E.g., multiple steps, participants have to take initiative to make second appointment/enroll
  - More time, test-feedback shown to be effective to improve understanding/recall

Flory & Emanuel, JAMA 2004

6. COMPENSATION

Compensation

- Many challenge studies offer high payments→ concerns about coercion or undue inducement
- Coercion: A threat to take away something to which someone was entitled (e.g., your money or your life)
- Undue inducement: an offer is so attractive it blinds subjects to risk or causes them to violate their values

Coercion

- Offering healthcare/payment only if someone participates in research is not a threat, and does not take away something to which the individual was entitled

Undue inducement?

- Yet we all rely on incentives to motivate us
- Studies suggest participants motivated by money spent more time on risks, understood them better
- Other suggest increased willingness to lie/conceal information based on high payments
- No data on health care, but strange to seek health care while seeking excessive risk

Stunkel L, et al. Comprehension and informed consent: assessing the effect of a short consent form. IRB. 2010; Cryder CE et al, Informative inducement: study payment as a signal of risk. Soc Sci Med. 2010.

7. RIGHT TO WITHDRAW

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 leave challenge studies
  - But could withdraw from contributing to research

*Such restrictions not unique

  - E.g., experimental bone marrow transplantation

8. COMMUNITY ENGAGEMENT

Community engagement

- Widely endorsed
- Many different reasons for community consultation
- Sometimes unclear who the relevant community is
- Most important and clear for specific protocol in a particular site

Wendler, Shah, Involving Communities in Deciding What Benefits they Receive in Multinational Research, *J Med Phil* 2015