THE ETHICS OF RESEARCH IN INFECTIOUS DISEASE

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The ethics of research in infectious disease

- Research in infectious disease has produced dramatic advances in the eradication, elimination, or control of infectious disease, but also has been highly controversial.

Notorious experimentation in infectious diseases

- Sir Edward Jenner's use of cowpox to immunize against smallpox (1796).
- Walter Reed's trials of a yellow fever vaccine (1900).
- The Tuskegee syphilis study (1932-1972).
- The Willowbrook study of the transmission of infectious hepatitis (1956-1970).

Questions in the ethics of research in infectious diseases (1/2)

- The extent to which current research is skewed away from research on the prevention and treatment of infectious diseases that threaten the majority of the world's population (the "90/10 divide").

Questions in the ethics of research in infectious diseases (2/2)

- Racism in infectious disease research: AIDS, directly observed therapy for tuberculosis.
- Pharmaceutical companies' protection of their intellectual property, together with their drug pricing policies.
- Dangers of research with pathogens.

Embedded autonomy and the "way-station self"

- The basic contention is that because bioethics' fundamental concepts—among them, autonomy, the harm principle, and responsibility—were rooted in an individualistic picture of actors drawn from liberal theory, bioethics has overlooked or misunderstood our vulnerability to each other as both *victims* and *vectors*, a vulnerability characteristic of communicable disease.

Patient as victim and vector view (PVV)

- An account of the patient—the person—as physically embedded in a web of disease, a "way-station self" who is breeding-ground and launching-pad for some trillions of microorganisms, many of which are benign or crucial to human functioning but some of which are dangerous or lethal, the germs that cause disease.
- The central ethical issues have to do with our efforts to respond to its damage and to try to extricate ourselves from this web of disease.

Third parties in infectious diseases research (1/3)

- Where research involves the possibility of communication of disease, informed consent should not be understood solely as a matter of the consent of the individual subject.
- Others might be infected, put at risk of infection, or left unprotected from these risks.
- These third parties have interests that may be directly affected by the research.

Third parties in infectious diseases research (2/3)

- Although they are not *subjects* in the sense that data is being collected about them, they are indirect *participants* in the research in that the research puts them at risk
- The term *indirect participants* has been cho*sen* to describe these affected third parties, in contrast to *indirect subjects*, a term that implies they are fully subjects, or *indirect objects*, a term that ignores agency.

Third parties in infectious diseases research (3/3)

- Researchers need not inform third parties directly if the risks posed by the research to them are minimal
- When the study involves more than minimal risk and is not commensurate with the experiences of ordinary life, what further contact with indirect participants is required is contingent on whether the indirect participant can readily avoid the risk
  - the risk is readily avoidable: informing indirect participants
  - risk is not readily avoidable by the indirect participant: obtain informed consent from indirect participants

Questions about informed consent

- What constitutes ethical informed consent if a household member at risk is a child, an adult with disabilities, or a patient with dementia?
- Will consent of the direct subject be sufficient?
- Which individuals compose the population of indirect participants?
- What constitutes ethical practice if research poses risks to entire communities?
- What are the parallels between research with infectious agents and other research involving subjects who may be dangerous to others—violent subjects, for example—but not because they are contagious?

Current informed consent policies and contagiousness

- Guidelines for research involving human subjects uniformly fail to address adequately whether research involving the possibility of communicable conditions requires attention to indirect participant information or consent.
- Current guidelines typically first analyze whether the research is permissible based on its scientific merit and risk/benefit ratio, and then establish standards for inclusion of subjects, minimization of risks to subjects, and informed consent.
- The inclusion standards and informed consent protocols consider risks to individual direct subjects.

Historical examples of ignoring contagion—Tuskegee (1/3)

- The Tuskegee syphilis study, in which the natural history of syphilis was studied in some 600 African-American men in the south (399 men already diagnosed with syphilis and 201 men recruited as "controls") by leaving them untreated over a 40-year period—preventing them from receiving treatment even after a simple and highly effective form of treatment, penicillin, had become available.

Historical examples of ignoring contagion—Tuskegee (2/3)

- Critics have viewed this research history as abusive of direct study subjects.
- Noteworthy is that criticism has virtually ignored the issue of informed consent for indirect participants.
- Concerns about indirect participants may have been swamped by the overwhelming nature of the concerns about the treatment of direct study subjects.
- The approach to informed consent that researchers and critics have almost exclusively focused on the autonomy of direct subjects while ignoring potential risks to others who may be directly affected by the research.

Historical examples of ignoring contagion—Tuskegee (3/3)

- The failure to consider indirect subjects pervaded the Tuskegee study and its aftermath
  - the risk that patients might infect others
  - untreated infections may be transmissible by pregnant women to their babies
  - risks to their sexual partners
  - the entire health of a community was jeopardized by leaving a communicable disease untreated

Historical examples of ignoring contagion—Willowbrook (1/2)

- The research used children who were residents of a treatment facility for individuals with developmental disabilities to study the transmission of infectious hepatitis.
- The research was initiated because the infection rate among residents at the facility was high.
- The investigators reasoned that infectious hepatitis was "mild and relatively benign" in children in comparison to adults.
- Its author concluded that it had been justified by the infection rates among patients and employees in comparison to what were judged minimal additional risks to subjects.

Historical examples of ignoring contagion—Willowbrook (2/2)

- The study design isolated children who received the artificial hepatitis infection from exposure to other infectious diseases common in the institution.
- Informed consent was required from the parents of the children involved.
- The extensive criticism of the Willowbrook study design and consent process does not appear to have addressed risks of transmission to the parents or siblings of the children, or staff of the institution, or the need to involve them on their own behalf in the informed consent process.

Historical examples of uncertain attention to contagion: The case of self-experimentation (1/2)

- Perhaps because of the salience of infectious disease in the past, there have been impressive historical examples of researchers who began their experiments with themselves.
- John Hunter, in the late eighteenth century, sought to understand venereal disease by means of self-inoculation with pus from a patient infected with gonorrhea. Hunter apparently died of syphilis—and reportedly conducted his experiment without discussing it with his wife.
- Toward the end of the nineteenth century, Daniel Carreon established—at the cost of his own life—that verruga peruana, a skin disease prevalent in the Andes, and Oroya fever, a potentially deadly blood disease, were caused by the same agent.

Historical examples of uncertain attention to contagion: The case of self-experimentation (2/2)

- Surely in such circumstances consent of the research subject is as informed as it could ever be, but questions still remain about the permissibility of such research.
- Should infectious disease researchers start with themselves as trial subjects and should they consider the risks to others in their decision to undertake such experiments?
- Or, should infectious disease researchers be required both to protect themselves and to ensure that their family and acquaintances give informed consent to the research?

Historical examples of considering contagion: The common cold and polio vaccine (1/2)

- Early research involving transmission of the common cold considered the risks of transmission in the study design.
- Studies performed at the Common Cold Research Unit in Britain during World War II attempted to ascertain whether colds were transmitted via nasal secretions and whether exposure to freezing temperatures was a risk factor.
- Conducted at an isolated research facility, these research designs minimized the risk of external transmission while guarding against contamination of treatment groups.

Historical examples of considering contagion: The common cold and polio vaccine (2/2)

- Researchers developing polio vaccines considered the risk of contracting polio to the person receiving the vaccination.
- With the killed-virus vaccine, IPV, the concerns were that the vaccine was imperfectly killed or would prove ineffective.
- The risk of imperfectly manufactured research material became quickly apparent when vaccine produced by Cutter Laboratories proved to contain live virus that resulted in a number of cases of polio.

Contemporary examples of ignoring contagion

- Trials of a vaccine against herpes simplex and trials of short-course antiretroviral therapy provide examples of contemporary studies where researchers have not included indirect participants in the consent process.
- Investigators have addressed third party risks specifically in studies of xenotransplantation.
- Another example of high profile research where risks of infection and transmission have been raised, but which we do not consider here, is gene therapy, where the mechanism of delivery is a viral vector. Here also the concern apparently has been for direct subjects, not for their direct contacts who might be regarded as indirect participants.

Considering the Risks to Indirect Participants (1/3)

- Participation of direct subjects in the research creates potential risks for their immediate contacts, such as family members or sexual partners, and sometimes for the public at large
- Risks to individual subjects and to society overall have been addressed in public policy requirements, in study design and approval, and in criticism of studies.
- Research practices are considered unethical if they include direct subjects into studies without informing them of the risks they face and thus without providing information relevant to decisions about participation.

Considering the Risks to Indirect Participants (2/3)

- Close contacts of such subjects—sexual partners or family members in particular—may be exposed to risks by the participation of direct subjects.
- Yet these risks to indirect participants have been virtually ignored.
- Indeed, the failure to consider such third party risks extends even to inattention to providing information about risks of infectiousness to study subjects themselves.

Considering the Risks to Indirect Participants (3/3)

- Several changes in current policy in response to these concerns:
  1. Attention to risks to indirect participants in study design.
  2. The process of informed consent with direct subjects.
  3. The requirement in some cases of informed consent on the part of identifiable indirect participants.

Considering indirect participants: How far to cast the net? (1/4)

- Despite the case we have made for considering risks to indirect participants, we also recognize serious issues about the potential range of indirect participants.
- Spreading the range too far—say, to fourth or fifth parties, the contacts of the contacts of the indirect participants—could strangle infectious disease research, which is important to all of us as victims.
- We readily admit that we do not have final answers to this question, although we do think analogies can be developed from efforts at community consent to research.

Considering indirect participants: How far to cast the net? (2/4)

- Another difficulty with our proposals is that some indirect participants may not be able to understand information or to give their informed consent.
- Children and cognitively impaired family members may be both at greater risk of disease transmission and unable to give informed consent.
- The standard way to handle such issues, with which we agree, is to obtain informed consent on their behalf from these third parties' proxies.
- We advise special caution, however, when the proxy, for example a parent, also serves as the proposed direct subject of the research. In that case, the proxy/direct subject may not independently represent the best interests of the indirect participant.

Considering indirect participants: How far to cast the net? (3/4)

- For studies not involving infectiousness, where we know that some community members may be affected by the study but these community members cannot be identified in advance, the model has been community consent.

Considering indirect participants: How far to cast the net? (4/4)

- The ethical problem of indirect participation in research is not an entirely novel concept.
- In the context of genetic information, where participation by some family members can result in the collection of information about identifiable other family members, third party consent has been raised as a possibility when the risks to the third parties are significant.
- In the case of genetic information, the third parties are subjects in the sense that the research involves the collection of information about them, and they have been regarded as secondary subjects of the research.

References

Battin MP, Francis LP, Jacobson JA, Smith CB. *The Patient as Victim and Vector - Ethics and Infectious Disease*. Oxford: Oxford University Press, 2009.