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# 10

# THE ETHICS OF RESEARCH IN INFECTIOUS DISEASE: EXPERIMENTING ON THIS PATIENT, RISKING HARM TO THAT ONE

Research in infectious disease has produced dramatic advances in the eradication, elimination, or control of infectious disease, but also has been highly controversial. Sir Edward Jenner's use of cowpox to immunize against smallpox, Walter Reed's trials of a yellow fever vaccine, the Tuskegee syphilis study, and the Willowbrook study of the transmission of infectious hepatitis are but a few illustrations of experimentation in infectious disease. That these efforts were tolerated at their time—although most now figure among the notorious examples of the exploitation of human subjects—no doubt testifies to the fear in which the infectious diseases at issue were held. It is now canonical in research ethics that most of these studies were deeply problematic despite the knowledge they in some cases yielded. Nonetheless, the ethical principles and the law governing experimentation with human subjects have failed to appreciate the full force of the significance of infectiousness and communicability for research ethics.

Many questions in the ethics of research are raised by infectious disease. Most obvious in today's world—discussed by Solomon Benatar,[1] Peter A. Singer,[2] Paul Farmer,[3] Thomas Pogge,[4] and Michael Selgelid,[5] among others—is 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. Much less research than would be ideal has been devoted to the development of vaccines for diseases such as malaria or to inexpensive modalities for treating common killers of the young, such as infantile diarrhea. Claims of racism in infectious disease research are not limited to the example of Tuskegee, but extend to more contemporary examples of AIDS research and research with directly observed therapy for tuberculosis.[6] Pharmaceutical companies' protection of their intellectual property, together with their drug pricing policies, raise pressing ethical questions.[7]

Also obvious are the dangers of research with pathogens. Laboratories may be difficult to protect, or may be protected imperfectly. Concerns remain that infectious agents stored in poorly guarded laboratories are attractive targets for bioterrorists. Research with pathogens, moreover, may lead to the creation of new infectious agents that are difficult to control—the all-too-realistic stuff of science fiction thrillers. Researchers who want to create XXDR-TB—a super drug-resistant strain of tuberculosis—may be all too able to do so, without any regulation, in the United States or in other countries of the world today.

In this chapter, we give a brief sketch of a range of issues infectious disease raises for the ethics of research, beginning with two aspects of informed consent: the *who* and the *what* of consent. We view our argument for third party and community consent as an example of how concern for the research subject as not only victim but also as vector might require broadening standard accounts of the ethics of research and human subject protection—whether the issue is self-experimentation or experimentation on others.

## Contagion and the *Who* and the *What* of Informed Consent

Our PVV analysis, we think, sheds new light on one core issue in research ethics, the who and what of informed consent, and perhaps broader light on research ethics more generally. Even when research is otherwise justifiable on scientific grounds, 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. If the subject in research involving communicable infectious disease is seen as victim, his informed consent is what is required; but if he is seen as vector, implications for third parties also must be considered. Yet these third party issues are largely ignored by current policies about informed consent, in criticisms of problematic examples in the history of medical research, and by current research practice. If research policies or practices attend to such issues at all, they do so principally through the direct subject—for example, through a consent process that warns the direct subject about the risks of communicability. This focus on the direct subject is inadequate in a significant range of cases of research involving communicable infectious disease.

We begin our argument by explaining how third parties who are at foreseeable and direct risk of contagion when research with human subjects involves a communicable agent are in some respects analogous to direct subjects of the research. 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—or fails to shield them from risk—in the same way direct subjects are put at risk. We have chosen the term *indirect participants* 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. The role of indirect participants as both unwitting victims and autonomous agents with respect to the research is ethically relevant, and failure to consider it is ethically problematic.

Moreover, when the research involves risks that are comparable to the experiences people would otherwise have, and that are only minimal risk, the approach should be to inform the research subject about the risks and to recommend that the research subject inform others about the risks. Researchers need not inform third parties directly if the risks posed by the research to them are minimal. An increased risk of contracting a disease with significant morbidity or mortality would not fall into this category. Finally, 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. If the risk is readily avoidable, for example by abstaining from sexual contact, then informing indirect participants of the risk is sufficient. The indirect participant can then choose whether to take the risk. Such action to inform the indirect participant requires the consent of the direct subject, who is not only potential vector but also potential victim. If the direct subject refuses to permit the indirect participant to be informed, the direct subject should not participate in the research. If the risk is not readily avoidable by the indirect participant, researchers should be required to obtain informed consent from indirect participants— who are potential victims—before direct subjects can ethically participate in the research. An example of research falling into this category would be testing a new live-virus vaccine for a serious disease, where there is a significant possibility of viral shedding that might infect other members of the subject's household.

These claims raise a host of questions about informed consent. For example, 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 recommended analyses of scientific merit and risk/benefit ratio address the research overall rather than the situations of individual subjects. The inclusion standards and informed consent protocols consider risks to individual direct subjects. The requirement of informed consent protects individual direct subjects—but these subjects only—from involuntary participation in research. The *World Medical Association Declaration of Helsinki*, the *United States Federal Regulations Governing Research with Human Subjects*, and the *Guidelines of the Infectious Diseases Society of America* all fit this pattern.

The *World Medical Organization Declaration of Helsinki* specifies that research must meet criteria of scientific and ethical adequacy. The most general requirement specifies caution about risks in research design: "Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected."[8] With respect to inclusion of any human subjects in the research at all, the Declaration requires "careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others."[9]

Addressing the inclusion of individual subjects, the Declaration shifts focus, prohibiting their involvement in research unless the "importance of the objective outweighs the inherent risks and burdens to the subject,"[10] without mention of risks or benefits to others. Informed consent is required from "each potential subject." Required information researchers must supply to subjects includes the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study, and the discomfort it may entail.[11] This list does not include specific mention of risks to others. Instead, the Declaration directs attention only to population risk/benefit analysis in determining the permissibility of the research overall, and to risks to direct subjects in determining the permissibility of their individual inclusion in the research.

The *United States Federal Regulations Governing Research with Human Subjects* describe risks and benefits to be considered in determining whether research is acceptable. The regulations require that "risks to subjects [be] minimized" by "sound research design" and procedures "which do not unnecessarily expose subjects to risk."[12] Research risks must be "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[13]

Under the regulations, Institutional Review Boards (IRBs) must review research with human subjects. As defined by the regulations, "human subject" includes any living human being about whom data are obtained through intervention or interaction or about whom identifiable private information is collected.[14] Taken

literally, this definition would seem to encompass research that involves the researcher him or herself, and not just research involving others. IRB review considers only risks and benefits that may result from the research and not risks and benefits of therapies subjects would receive outside of the research. Possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) are not within IRB responsibility.[15] The regulations require the informed consent process to include "a description of any reasonably foreseeable risks or discomforts to the subject" and "a description of any benefits to the subject or to others that may reasonably be expected from the research."[16] Notably, this list specifically mentions both risks and benefits to direct subjects. With regard to others, including indirect participants, the list mentions benefits but not risks.

In 1993, the Infectious Disease Society of America published guidelines for ethical conduct. The guidelines for ethics in research specified that all research involving human subjects must be subject to IRB review. They charged IRBs to "provide a framework for sound scientific work, while at the same time acting as advocates of the rights of patients, human subjects, and experimental animals and of the public welfare."[17] The guidelines did not explain who might be regarded as experimental subjects or address whether researchers should consider informed consent from indirect participants. The guidelines' silence on these matters might stem from their original purpose, responding to clear abuses of direct subjects in research studies such as the Tuskegee syphilis study.

**Historical Examples of Ignoring Contagion—Tuskegee and Willowbrook**

Some of the most (in)famous examples of research with human subjects have involved infectious diseases. They are well known in the annals of bioethics. We document here, however, that those aspects of these studies that were particularly relevant to infectious disease were not at the forefront of the criticism.

Coincidence alone may not explain why research projects involving infectious disease have been among the more notorious examples of ethically problematic research, and why the principle of informed consent was so often violated. Some researchers may have held the importance of protecting the public health to provide an overriding justification that eclipsed the ethical importance of informed consent in research. Critics have viewed this research history as abusive of direct study subjects.[18] 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. But it may also be indicative of the approach to informed consent that we criticize below 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. 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—fits this paradigm of criticism.[19] The most widely read history of the study, James Jones's *Bad Blood*, describes Nurse Rivers, the nurse who played a long-term role in the study, as going to the homes of study participants and providing general health care to their families. Nurse Rivers was viewed by participants in the study as providing health care to them and to their families; Jones is quite rightly severely critical of this duplicity. Yet Jones's description contains no mention of the ethical issues raised by the possibility of transmission of syphilis or of the possible impact on family members if they contracted the disease.[20] This failure to consider indirect subjects pervaded the Tuskegee study and its aftermath.

The principal compendium of documents on Tuskegee, Susan Reverby's *Tuskegee's Truths*, reflects minimal reference to effects on indirect participants such as sexual partners—even though, at the time the study was initiated, one justification for study of latent syphilis was the risk that patients might infect others. It is now known that latent syphilis is not readily transmissible, although untreated infections may be transmissible by pregnant women to their babies for up to four years.[21] However, it is unclear whether researchers initiated the Tuskegee study with this concern in mind, or whether they worried about the implications of confusion among subjects about whether they were receiving treatment for their disease. The Public Health Service, in deciding to observe the natural history of the disease in those with latent infection, had assumed it was dealing with subjects who would otherwise not be treated. Initial testing indicated lower rates of infection in Macon County, Alabama than had been anticipated at the time the study site was chosen—at 20% instead of 35%. Participants were told they were receiving "treatment" and so understandably might not have anticipated their risks to others. They were not informed of these risks of contagion, nor were they given information about risks to their sexual partners.[22] Moreover, it was clearly known during the early stages of the study, even before the development of penicillin, that treatment of syphilis was possible—although long and arduous, involving arsenicals and other chemicals—and would with one or two treatments greatly reduce the risks of transmission. Indeed, in 1938 the then Surgeon General Thomas Parran referred to treatment of syphilis as in effect "chemical quarantine."[23]

The study was not designed to track or report whether subjects infected others.[24] Transmission of congenital syphilis to offspring was not considered. Jean Heller, the reporter who broke the story about the study, labeled the subjects as the "victims" of the study.[25] The Ad Hoc Study Panel appointed by the U.S.

Department of Health, Education, and Welfare to investigate the study concluded, in 1973, that researchers had wrongfully failed to inform subjects about their being risks to others. They drew no further conclusions about wrongs to third parties.[26] The initial settlement of the class action lawsuit brought on behalf of study victims did not include wives or children—although two years later the settlement was amended to add all wives, widows and offspring of the direct subjects.[27] Neither U.S. Congressional inquiries nor President Bill Clinton's apology on behalf of the nation referred to potential third party indirect victims of disease itself, although the President's apology, like the settlement, extended to wives and children generally.[28] Fairchild and Bayer's recent critique similarly focuses on the direct subject:

> [t]hree critical features that characterize the nature of the consistent research abuses that occurred over the course of forty years. The study involved, first, deceptions regarding the very existence and nature of the inquiry into which individuals were lured. As such, it deprived those seeking care of the right to choose whether or not to serve as research subjects. Second, it entailed an exploitation of social vulnerability to recruit and retain research subjects. Finally, Tuskegee researchers made a willful effort to deprive subjects of access to appropriate and available medical care, which changed over time, as a way of furthering the study's goals.[29]

The third party concerns that were raised in the initial criticisms of Tuskegee focused on the general public health effects of the study, and not on the possibility of harms done to indirect participants. Allan Brandt wrote, for example, "the entire health of a community was jeopardized by leaving a communicable disease untreated."[30] This public health concern, while laudable, is a different concern from the one we raise here. We are concerned that researchers violated the autonomy of indirect participants because they did not consider risks to them, even when these risks were unknown, and did not afford them—in the study design or in subsequent apologies—the choice whether or not to undertake exposure to the study's risks. To be sure, contemporary presentations of Tuskegee reference the possibility that at least 40 wives and 19 children of the men in the study were infected with syphilis,[31] but this is a much later development.

The much-criticized Willowbrook research is a similar example. 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.[32] Reflecting back on the study, 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.[33] The study design isolated children who received the artificial hepatitis infection from exposure to other infectious diseases common in the institution.[34] 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.[35]

**Historical Examples of Uncertain Attention to Contagion: The Case of Self-Experimentation**

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.[36] 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. 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?

Perhaps historical figures such as Hunter were motivated by the well-reasoned belief that their research would not only protect others but also protect themselves and their families. If so, blanket condemnation of self-experimentation might warrant rethinking, because it would reflect a paternalistic judgment that the experimenter should not be able to act on his own informed judgment. Such condemnation of self-experimentation as paternalistic, however, does not extend to cases in which the experimenter puts family or other contacts at risk, as Hunter may have done in his experiments with venereal disease.[37]

Infectious disease researchers may also have believed in the safety of their activities—both for their subjects and for society in general. Jenner did not believe that cowpox was unsafe when he experimented on the son of a local farmer; on the contrary, he thought it would be protective. But the fact remains that he made the judgment about safety *for the boy and for others with whom the boy might come in contact*. For the boy, the issue is whether these are the kinds of risks a researcher may permissibly impose on a child with parental consent—particularly in

circumstances in which the child's best interests may be balanced against the interests of many in the discovery of an inoculant against smallpox. Jenner is widely admired for the experiment that ushered in modern immunization and has saved countless millions of lives, but what if the boy had died? Questions of safety for society include issues about what risks are permissible (what about the possibility that an infectious agent might escape?) and how to assess these risks (by researchers? by institutional review boards? through widespread public discussion—almost a form of democratic informed consent?). They also raise the issue of whether the decision by a researcher to undertake even self-experimentation with infectious agents imposes an impermissible risk of transmission on the community. Are the types of concerns about safety raised by infectious disease concerns that in some cases require a community informed consent? Walter Reed is perhaps the most flagrant example of a researcher who substituted his own judgment for that of others: despite reports of his heroism, he apparently never experimented on himself, replicated experiments that should have been taken more seriously, and permitted his associates to participate in studies that put them at risk of death, in circumstances in which it is arguable that their consent was pressured if not coerced.[38]

Contemporary standards for research ethics make no distinction between self-experimentation and experimentation in which the researchers involve others as human subjects.[39] The U.S. federal regulatory regime contains no discussion of any special issues that may be raised by self-experimentation. Perhaps this is as it should be, guaranteeing protection to researchers and non-researchers alike. However, there remains the risk that researchers may not see self-experimentation as research that really involves human subjects, and thus may fail to bring such research within the purview of IRB review. To the extent that this occurs—and we know of no data about the extent to which this is an actual rather than a merely hypothetical problem—issues of risks to indirect subjects or communities may pass unexamined in studies where the researcher is the sole human subject.

## Historical Examples of Considering Contagion: The Common Cold and Polio Vaccine

Several other historical examples of research placed communicability at the center of concern. Research involving transmission of the common cold and research on the polio vaccine are noteworthy examples.

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. Later studies, addressing the efficiency of manual transmission and issues such as the effect of colds on memory, did not feature the two-week isolation characteristic of the British experiments.[40]

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.[41]

With the live-virus vaccine, OPV, there is viral shedding from the vaccinated person. This has the advantage of increasing population immunity but the disadvantage of risking infection both to the vaccinated patient and to those who come into contact with the vaccinated patient. Discussions of the ethics of using OPV were well aware of these risks. Jonas Salk persistently championed IPV because of its lower third party risk profile. In 1979, arguing for the use of IPV, Salk pointed out that from 1969 until 1977 in the United States there were 24 cases of OPV-associated paralytic polio among vaccine recipients, 47 cases among direct contacts of vaccinees, and 16 among indirect contacts.[42] Advocates of OPV argued that OPV would produce higher levels of population immunity and thus fewer cases of paralytic polio overall than IPV.[43] A 1977 report by the Institute of Medicine Committee for the Study of Poliomyelitis Vaccines concluded that OPV was the preferred method of immunization but that IPV should continue to be offered to people with heightened susceptibility to infection and people who prefer IPV and are prepared to make a commitment to the required full schedule of vaccinations. About informed consent, the report concluded that documents should be "as brief as possible, while conveying sufficient, accurate information on the benefits, risks, and other special characteristics of the vaccines." The report also recommended that the U.S. federal government assume the responsibility to compensate people with vaccine-associated poliomyelitis, including contact cases.[44]

These discussions did not, however, attend to the problems of informed consent for indirect participants at risk of contagion. The fact that many of the subjects were children whose parents were asked to consent on their behalf may complicate this assessment, because the parents would become aware of the risks as they consented to inclusion of their children in the research.[45] Still, we note that there were no indications that parents were asked to consent on behalf of their other children who might be subject to exposure and were not receiving vaccine, or that there were discussions of third party risks in the informed consent process. This assessment might also be complicated by the assumption that the background risk of contracting polio was quite high in any event, especially for children.

The first example of direct attention to the problems of research ethics raised by indirect subjects in polio vaccination was Deber and Goel's 1990 analysis. Deber and Goel pointed to the ethical difference between polio cases that occur to persons who lack immunity, polio cases that involve people who have consented to vaccination, and polio cases resulting from transmission by direct or indirect contact with those who have been vaccinated. Cases in this last category, they contended, involve a kind of involuntary immunization without consent for persons who are susceptible precisely because they have chosen not to be immunized in the first place.[46]

These issues are ongoing in contemporary public health debates about polio eradication.[47] According to a report from WHO, in the past 10 years there have been approximately 200 cases of polio resulting from vaccination in areas of the world with large populations who had not been vaccinated and thus who were at risk for disease—a figure that of course pales by comparison to the number of wild-virus cases of polio annually.[48] Similar controversy may be emerging over the development of a vaccine against avian flu, although the science of flu vaccine is evolving rapidly, as we discuss in Part IV.[49] Concern about risks to immediate contacts also played a role in controversy over recent efforts to immunize first responders against smallpox. The Institute of Medicine has advised caution in extending the immunization program until risks can be evaluated further, including risks to contacts.[50]

**Contemporary Examples of Ignoring Contagion**

Many contemporary examples of research involve contagious conditions. A principal source of contagion for indirect participants occurs when the experiment is testing a method to prevent infection that proves ineffective. In other cases, the research features an intervention that may increase risks of contagion, or the research introduces a new possibility of infection and subsequent contagion. Yet examination of selected examples of current practice evidences little attention to information or consent from anticipated third parties.

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.[51]

GlaxoSmithKline has sponsored several clinical trials of the safety and efficacy of

a vaccine against the herpes simplex virus. The trials enrolled over 400 adult women at risk of contracting herpes, in over 80 study centers on four continents (Africa, Australia, Europe, and North America).[52] The consent form detailed an extended list of risks, including risks of the injection and of blood draws that would be required to test levels of immunity. The consent form explains in detail that the vaccine contains bovine derivatives and has been manufactured to avoid any risk of variant Creutzfeldt-Jacob Disease (vCJD, also called "mad cow disease"). Boldface type cautions participants to avoid pregnancy, as the effects of the vaccine on a fetus are unknown. In an open label study, which offered active vaccine to patients who had received placebo in an earlier trial, patients were informed that 73% of women receiving vaccine in the earlier study had been effectively immunized against herpes simplex. Disclosures reminded participants that the vaccine was still experimental and that they might receive no benefit from study participation. However, the consent form contained no mention of sexual partners or of the risk that if the vaccine proved ineffective and the subjects acquired herpes infection, they might pass the infection on to others.

Participants in this study were at background risk of contracting herpes and transmitting it to their partners, regardless of study participation. Participation in the study offered them a possibility of protection as a result of the vaccination that they would not otherwise have had. Their sexual partners, it might seem, were not at any greater risk from the study than they otherwise would have been, and may even have been at reduced risk, so any discussion of risks to them is arguably unnecessary.

This argument has two related replies. First, research studies are held to higher standards than the background risks that might have occurred regardless of research participation. Risk/benefit ratios must be acceptable and risks to subjects must be minimized if possible. We contend that this minimization of risks should apply not only to direct subjects but also to those who might be immediately affected by their participation and thus are indirect participants in the research. Second, participants in the study may have believed that they were receiving protection, when in fact they were not. Believing they had received adequate protection, they might have been less careful to guard both themselves and their partners against risks of contagion. These concerns, we contend, at a minimum require including in the consent form the reminder that the vaccine might not be effective—and that *if* it is not, participants *as well as* their partners may be at risk of infection.

To take another example, trials of short-course anti-retroviral therapy to reduce the likelihood of transmission of HIV from pregnant women to their fetuses have been highly controversial. Participants in these trials have been HIV-positive women in areas of the world where access to anti-retroviral therapy is limited or non-

existent. Because short-course therapy initially appeared economically feasible whereas optimal therapy did not, the trials were designed to determine whether short course therapy reduced vertical transmission rates.

At least 15 trials have compared vertical transmission rates in patients receiving the short-course therapy against vertical transmission rates in patients receiving placebo.[53] Defenders of the trials argued that the researchers' duty of care to subjects did not extend beyond the best standard of care available in the subjects' circumstances. Critics argued that because there was an alternative to placebo—the standard of care available in the developed world—the studies violated clinical equipoise and were clearly morally wrong, comparable to Tuskegee in observing seriously ill patients for whom treatment was possible.[54]

Bioethicists have raised many serious ethical issues about these trials. Alex John London, for example, has argued that the concept of "equipoise" is ambiguous between a narrow physiological concept and a broader concept of efficacy in social context.[55] Solomon Benatar has argued for sweeping reforms in the understanding of ethics in international research, in the context of international justice in health care.[56] Many discussions have highlighted coercion and exploitation of vulnerable populations.[57] When attention has been turned to informed consent from study subjects, the principal suggestion has been involvement of families or communities in the consent process. This suggestion has rested on several grounds. Family and community support is an important protection against exploitation. The societies in which the studies have taken place frequently are communitarian in structure, and do not see consent as an individualized process.[58] The studies themselves may have effects on the communities in which they take place.

Concerns also surfaced about the risks of short-course anti-retroviral therapy to the women involved. One risk is that if anti-retroviral therapy becomes available, later treatment efforts may prove less efficacious for women who have received the short-course therapy. Another is that the short-course therapy may alter the course of the subjects' disease, generating increased viral load or more resistant viral strains. Either of these risks are direct risks to the study subjects. But given levels of heterosexual transmission of HIV, they are also risks to the subjects' sexual partners.[59] Yet we have found *no* criticisms of the HIV trials that mention the unacknowledged increased risks to partners or to communities as an ethical issue in the studies. Where we did find mention of family members, the focus was not on risks to them, but embedded in familial or communal informed consent models, where the concern was the role of the family or community, or the vulnerability of the subjects not the possibility of spread of resistant disease in the community.[60]

Unlike the studies that are silent regarding third party risks, protocols studying xenotransplantation have undergone extensive scrutiny for the safety of both

individual participants and the public. Perhaps the difference stems from a perception that transplanting tissues or even organs from animals to humans is new and strange, and from fears of species-jumping infections of unknown character. Margaret A. Clark, for example, argues that patients receiving xenotransplants should be required to consent to take precautions against transmission of bodily fluids. She also argues—a view we share—that they and their intimates must receive information about transmission risks. She suggests that population consent should be sought where there are significant public health risks, but does not otherwise raise the possibility of indirect participant consent where direct risks to third parties are apparent.[61]

**Considering the Risks to Indirect Participants**

In both the historical and contemporary examples we have discussed, 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. 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. This gap in policy and practice, we contend, represents a failure to respect the autonomy of these third parties as potential victims that is analogous to the failure to respect the autonomy of the direct subjects. In response to these concerns, we suggest several changes in current policy.

A first change is attention to risks to indirect participants in study design. Risks of third-party transmission should be explicitly considered in the design of studies. This cannot be accomplished by ensuring that the study has a risk/ benefit ratio that is favorable overall. Ethical study design requires not only minimization of risks to subjects, but also minimization of risks to indirect participants. Careful study design may reduce the likelihood of creating indirect participants through strategies such as isolating the direct subject until the likelihood of contagion has passed. Otherwise, people may be subject to risks of the study that might have been avoided in the study design, even though they are not themselves subjects of the research. In some studies involving contagious conditions, however, design features such as these may not be feasible. For example, research with OPV created immunized subjects who continued to shed potentially infectious virus for

extended time periods.[62]

A second change is the process of informed consent with direct subjects. When applicable, the informed consent process should include information about risks of contagion. Issues addressed with direct subjects should include risks of contagion that might result from their participation in the study. Subjects in prevention studies, for example, should be warned that if the method of prevention fails and they become infected, they might pose a risk of contagion to others. In studies that may raise subjects' risks of contagion, such as the trials of short-course anti-retroviral therapy, researchers must inform subjects of this possibility so that they may take it into account in deciding whether to participate in the research.

A third change is the requirement in some cases of informed consent on the part of identifiable indirect participants. Current practice relies on direct subjects to provide contacts with information, if information is to be provided at all, as in the herpes or xenotransplantation research. If the risk to indirect participants is substantial and serious, this may be insufficient. Direct subjects may be reluctant to convey the information. They may have understood the risk imperfectly or may be unable to explain what they have understood. In such circumstances, contacts—the indirect participants—may not receive the information they need to protect themselves should the infection risk eventuate. Protecting the indirect participant requires more than providing information to the direct subject.

At a minimum, indirect participants at significant and serious risk should be provided with the information directly, so that they can understand it and act on it themselves; considering them as potential victims with their own choice to make requires no less. If the risk is unavoidable, consideration should also be given to whether respect for indirect participants requires their independent consent to the direct subject's participation in the study. In short, when risks to indirect participants are potentially as great as risks posed to direct subjects of research, our approach recommends that researchers afford respect for the indirect participant that is similar to that afforded to direct subjects. Contacts or family members of a person participating in infectious disease research must be allowed to understand that the direct subject may be both victim and vector of the disease under study.

We recognize that our approach limits choices open to the direct subject. Direct subjects who do not wish indirect participants to be informed about the risks of the study will not be able to participate in the research. An indirect participant's refusal to grant consent would block participation by the study subject. If the indirect participant refuses consent, when consent is required, the direct subject's participation will also be blocked. Even if self-experimentation were regarded as fully permissible, it might still be blocked if the experimenter/ subject failed to consider the risks he was taking for himself also constituted risks for others.

However, we think that this strikes a defensible balance. Participation in a research study should not be equated with receiving beneficial therapy despite

the standard that encourages subjects to base their decisions about participation on a reasonable assessment of the risks and benefits to them. When subjects participate in research that may directly affect the risks and benefits for others in significant ways but these others are not consulted, the latter are affected by the research without their consent. When the risks are serious and unavoidable, as they might be with transmission of zoonoses from xenotransplants, their informed consent should also be required.

**Considering Indirect Participants: How Far to Cast the Net?**

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. Our goal in this chapter has been to direct attention to this significant ethical issue heretofore virtually ignored. We would suggest, however, that respect for involuntarily involved third parties such as sexual partners or family members requires their involvement in the consent process when they are identifiable and at known, direct, and significant risk.

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.

At some point, concern with transmission to indirect participants might be anticipated to include the community. Suppose we know that risks of rapid transmission of a serious disease such as SARS or avian flu exist. Research on the development of vaccines for these diseases might have an overall favorable risk/benefit ratio, given the apparent seriousness of the diseases. However, in the community in which the vaccine trial takes place, members of the community might be placed at special risk, depending on the design of the study.

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. One example is the trial of installing cardiac defibrillators in community settings such as shopping centers.[63] In this trial, there was little possibility to predict who might use the defibrillators or who might need them. The strategy chosen for consent was to involve the community; nearby workers who might be most likely to be on the scene when an emergency occurred and local governments who arguably might represent the population most likely to be at risk of defibrillator need while shopping. We would suggest further exploration of this possibility in the infectious disease context, if research poses such special risks to communities. Efforts to publicize the study and create an "opt out" possibility, as with the study of the use of the blood substitute polyheme in emergency situations, are logistically difficult in the case of a contagious disease if it is hard to predict who might be at risk of disease transmission from the study.

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.[64] 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. When studies involve diseases that are infectious and contagious, identifiable contacts may not be subjects in the sense that information about them is acquired through the study. Nonetheless, the risks of their indirect participation may be as substantial and serious to them as the risks of collecting their genetic information. Research subjects are potential vectors; indirect subjects are potential victims. Informed consent and the ethics of research must be informed and broadened by this interrelationship.

## Footnotes

An earlier version of this chapter appeared as Leslie P. Francis, Margaret P. Battin, Jeffrey R. Botkin, Jay A. Jacobson, and Charles B. Smith, "Infectious Disease and the Ethics of Research: The Moral Significance of Communicability," in *Ethics in Biomedical Research: International Perspectives*, ed. Matti Häyry, Tuija Takala and Peter Herissone-Kelly (Amsterdam and New York: Rodopi, 2007), 135–150.

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