POLICY FORUM: RESEARCH ETHICS

Managing Risks of Arthropod Vector Research

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On a worldwide basis, arthropod-borne pathogens take an enormous toll in human mortality, morbidity, and loss of productivity. Diseases such as malaria, dengue, filariasis, leishmaniasis, Chagas disease, African sleeping sickness, river blindness, the viral encephalitides, and Lyme disease continue to pose enormous health threats, especially in the developing world. In late 1999, an outbreak of West Nile viral encephalitis in New York City increased public awareness of vector-borne diseases by demonstrating that exotic pathogens can be introduced and transmitted among U.S. populations. Furthermore, diseases of domestic animals impact the future food supply. For many of these diseases, vector control has been and continues to be the only practical means of disease control.

Considerable attention is being focused on alternatives to the traditional approaches to reducing vector populations, such as community-based environmental modifications that reduce vector development or survival, genetic manipulations of vectors or their endosymbionts that render the arthropods incompetent to transmit pathogens or alter their breeding systems, and the use of natural enemies and microbial pathogens for biological control (*1*–*3*). These approaches require an increasingly detailed understanding of the biology, ecology, and physiology of the vectors and the pathogens they transmit. Developing and deploying new control technologies will require a transition from lab to field-based studies.

Field studies in areas where human populations may be naturally exposed to the pathogens these vectors transmit are the only way to examine directly the effects of intervention on vector populations, pathogen transmission dynamics, and, ultimately, human disease. However, such studies must be evaluated and monitored because of the risks they constitute when potentially infected or competent arthropods are brought into contact with humans. As with other fields, there is now an increased public consciousness and focus on the part of funding agencies on these ethical issues.

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Repellent efficacy trials against mosquitoes and black flies.

Until recently, evaluation of vector field studies emphasized scientific merit. After all, there is extensive literature on mosquito release experiments without mention of harm to either humans or the environment (*4*). One often quoted incident, the release of chemically sterilized male *Culex quinquefasciatus* in India during the early 1970s, did produce considerable controversy. Problems associated with that program were not the result of any well-founded public health concerns, but resulted from inadequate public awareness of and participation in the project (*5*).

The experience in India points out the imperative that risks must be discussed with and approved by the people directly affected by or living in the communities where the work will be done. What is urgently needed is a consensus among researchers about the risks of various types of field research and the development by research sponsors of policy regarding experimental design, proposal evaluation, and research monitoring. This will help investigators develop plans that will minimize potential risks and help funding agencies and affected communities to evaluate those plans.

Experimental Design

The design of vector field studies can be remarkably diverse, and the associated risks range from minimal to severe. Examples below are not intended to be comprehensive; rather, they illustrate the spectrum of ethical issues that will have to be addressed during the development of safe research protocols.

Collections of vectors can involve human subjects when questionnaires are administered or when blood in arthropods is analyzed to identify the person(s) upon whom the vectors fed. In those scenarios, risks are minimal; the primary ethical concern is protection of study participants' privacy.

The situation becomes more complex when, as a consequence of the research, people are exposed to bites from arthropods that may become infected naturally or when vectors are purposely released into study communities where they may adversely modify existing patterns of pathogen transmission. For decades, landing collections (in which vectors are captured as they attempt to bite a person) have been a standard practice for assessing the frequency of vector-human contact among arthropod populations that cannot be monitored in less risky ways, as is the case for several anopheline vectors of malaria. The collector sits and waits for the arthropod to land then attempts to capture it before being bitten. When possible, collectors should be provided prophylactic drugs or vaccination.

In vector competence studies, an infected person is identified and asked to participate in research before receiving treatment. He or she then allows laboratory-reared, uninfected mosquitoes to imbibe blood or, alternatively, donates a small amount of blood that is later fed artificially to the vectors. These kinds of experiments involve identifiable individuals and, in general, minimal risk.

Release experiments are of special concern because on the surface they can appear counterintuitive to disease prevention. Recapture of marked specimens has been used for more than half a century as a powerful way to gain information on the role of vectors in determining, for example, the ability of a modified population to survive or the distance of migration. It is often possible to make species and site-specific assessments of the risks to humans by predicting recapture and/or removal rates, potential impact on disease

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transmission, and long-term effects on vector population dynamics. Release-recapture experiments with indigenous insects should be designed so as to have little impact on the absolute number, distribution, or behavior of disease vectors.

Introduction of arthropods that are genetically different from the indigenous population may have an impact on the entomological potential for pathogen transmission (*6*). Examples include the use of genetic markers to study gene flow or the release of genetically modified vectors and/or their endosymbionts. The ultimate justification for these release experiments is to modify—directly or indirectly—the genetic structure of vector populations in ways that reduce or eliminate disease. To define parameters associated with the speed and extent of spread by desired gene(s) under natural circumstances, it will be necessary to conduct release experiments in communities where transmission of vector-borne pathogens does or can occur. All involved parties must consider this type of protocol very carefully.

House surveys for triatomine infestations in Guatemala.

Research Oversight

When an investigator in an academic setting wishes to conduct vector field research in an endemic area, he or she must obtain the approval of a committee at his or her home institution, at the home institution of each of the collaborators, and in the community within which the work will be conducted. The relationships among these committees are poorly defined, and the investigator is required to bring the disparate groups to consensus. This can be a daunting task.

There are two general approaches to administrative oversight of research that involves human risk. Research with hazardous agents invokes biosafety regulations, whereas research on human subjects invokes human subjects regulations. Research sponsors may require either or both of these oversight mechanisms, and investigators should confirm the policies of funding agencies and the institution at which they work early in planning the research. In all cases, necessary precautions to prevent risk must be in place, and review committees in the United States and abroad must be able to review the proposal adequately and to monitor the research.

When the research involves agents that may be hazardous to humans, the oversight involves biosafety regulations. The U.S. Public Health Service publishes a manual, called *Biosafety in Microbiological and Biomedical Laboratories* [BMBL (*7*)], which ascribes levels of risk for different agents and prescribes appropriate steps to mitigate risks. Efforts are currently under way to include in the BMBL a chapter on laboratory containment of medically important arthropods. When protocols for field studies involve an agent listed in the BMBL, the experimental plan is reviewed by an Institutional Biosafety Committee (IBC). Biosafety Committee review provides no opportunity to weigh benefits against risks or to allow more than minimal risk resulting from a research protocol. Biosafety committees are considered to represent the individuals within the affected community, and IBC review does not require individual informed consent.

When field research includes human subjects (*8*), oversight involves Institutional Review Boards (IRBs). These committees compare the risks with any benefits of the research for either the participating subjects or their community. IRB review also includes assessment of the documents provided to research subjects in seeking their consent to participate in the experiments. Each potential subject in a research protocol must be advised of the nature, risks, and benefits of the research, voluntarily give informed consent to participate, be monitored throughout involvement in the project, and be given an opportunity to be informed about the research results.

In many cases, investigators have only limited ability to identify the individual humans who are at risk as a result of the research. In vector release studies, the entire population residing within or traversing an area defined by the range of the vector's dispersal is potentially at risk. When vectors are introduced and not recaptured or killed, future human generations may be affected by a single release. These sorts of studies would appear to make insurmountable the task of both informing and getting consent from all those potentially affected. Whereas an IRB can grant a waiver of the requirement for informed consent if the research poses only minimal risk, what will count as meeting this requirement will be controversial. It is plausible to say that the individuals potentially affected by this research are not truly human subjects for whom oversight by IRBs is necessary (as, for instance, when data are not obtained from or about them). Hence it may be that biosafety oversight is a more appropriate, as well as realistic, model of oversight, but further discussion will be required before this view becomes the consensus.

Care must also be taken so that study participants do not misunderstand the benefits from involvement in the project. A variety of release experiments may prove valuable scientifically and eventually help control disease but have little or no direct benefit to the individual or community. The community within which the research is carried out must be aware of the research, be involved in its conduct to whatever degree is appropriate, and be informed about the research results and their implications once the work is completed.

Conclusions

Vector-borne disease specialists, ethicists, and funding/regulatory agency officials should work in concert to reach consensus on the most appropriate risk-management recommendations for the complex scenarios that constitute vector field research. People who are affected by vector-borne diseases must be included in discussions of the appropriateness of research projects and their justifications. Open debate of the virtues and concerns of vector release experiments will cultivate new approaches and a more rigorous and reasonable system of accountability. Open forums will be an indispensable means of information exchange, consensus building, and, ultimately, policy development.

References and Notes

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8. Code of Federal Regulations (CFR), title 45, part 46, applies to all research involving human subjects. A human subject is defined as a living individual about whom an investigator (whether professional or student) conducting research obtains (i) data through intervention or interaction with the individual, or (ii) identifiable private information.

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