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ETHICAL ISSUES IN FIELD TRIALS OF GENETICALLY MODIFIED DISEASE-RESISTANT MOSQUITOES

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Abstract

Mosquito-borne diseases take a tremendous toll on human populations, especially in developing nations. In the last decade, scientists have developed mosquitoes that have been genetically modified to prevent transmission of mosquito-borne diseases, and field trials have been conducted. Some mosquitoes have been rendered infertile, some have been equipped with a vaccine they transmit to humans, and some have been designed to resist diseases. This article focuses on ethical issues raised by field trials of disease-resistant, genetically modified mosquitoes. Some of these issues include: protecting the public and the environment from harm, balancing benefits and risks, collaborating with the local community, avoiding exploitation, and safeguarding the rights and welfare of research subjects. One of the most difficult problems involves protecting the welfare of community members who will be impacted by the release of mosquitoes but who are not enrolled in the study as research subjects. To address this concern, field trials should take place only when the targeted disease is a significant public health problem in an isolated area, the benefits of the trial for the community are likely to outweigh the risks, community leaders approve of the trial, and there are measures in place to protect the welfare of un-enrolled community members, such as informing the community about the study and offering free treatment to people who contract mosquito-borne diseases. Since the justification of any field trial depends on a careful examination of the scientific and ethical issues, proposed studies should be evaluated on a case-by-case basis.

Keywords

genetically modified mosquitoes; field trials; ethics; public health; environmental impacts; informed consent; malaria

Introduction

Mosquito-borne diseases take a tremendous toll on human populations, especially in developing nations. Each year, over 400 million people contract malaria, and more than a million people die from the disease. Approximately 91% of malaria deaths occur in Africa. Children constitute about 86% of all malaria fatalities. Malaria causes approximately $12 billion in economic costs annually, and results in a 1.3% loss of gross domestic product in Africa.[1] 50-100 million people contract dengue each year, and more than 20,000 die from the disease.[2]

Other mosquito-borne diseases with detrimental effects on human populations include encephalitis, yellow fever, and West Nile disease. Although mosquito-borne diseases have their greatest impact on developing nations, people living in virtually every country in the world face health risks from diseases related to mosquito bites.[3]

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While there are effective treatments for some mosquito-borne illnesses, prevention is by far the preferred method for reducing the impact of disease, because treatments may not be available due to cost or limited health care infrastructure, and diseases can still cause significant suffering and adverse health impacts, even when treated effectively. Some preventative measures include the use of mosquito bed nets, protective clothing, and insect repellants; elimination of breeding grounds for mosquitoes; development and administration of vaccines against mosquito-borne diseases; and spraying of pesticides to reduce mosquito populations. However, these preventative measures are not 100% effective, and some, such as the use of pesticides, can pose risks to human health and the environment. Thus, research on effective methods of preventing mosquito-borne diseases continues to be a top priority for global health.[4]

One proposal for preventing mosquito-borne diseases that has generated considerable interest and controversy is to apply genetic engineering techniques to mosquitoes to control mosquito populations or reduce disease transmission. In the last decade, scientists have developed genetically modified (GM) mosquitoes, and field trials have taken place. In 2009 and 2010, researchers funded by Oxitec, a private company, released male mosquitoes of the species *Aedes aegypti*, which carries dengue, into the wild on an island near Grand Cayman, in the Caribbean. The GM mosquitoes were considered 'infertile' because they have a gene that causes 96% of offspring to die before reaching maturity. The trial resulted in an 80% reduction of the local *Aedes aegypti* population, according to the company.[5] The trial angered some researchers, because they felt that Oxitec had kept its work secret and that more research was needed on the public health and environmental impacts of GM mosquitoes before release into the wild should occur.[6]

Others were concerned about the public backlash of releasing GM mosquitoes into the wild without appropriate community engagement and regulatory oversight.[7] A proposed field trial of Oxitec's GM mosquitoes in Key West, Florida scheduled for January, 2012, was postponed indefinitely by the Florida Keys Mosquito Control District, due to protests from local residents. 100,000 people signed a petition to stop the release of these insects.[8] Although dengue has reemerged in Key West after a 65-year absence, many were concerned about the public health and environmental risks of the proposed trial. For example, some protesters speculated that drastically reducing *Aedes* mosquitoes in the area could lead to a decline in bats, which feed on the mosquitoes.[9] Other communities have taken a different stance toward GM mosquito field trials. In 2012, residents of Juazeiro, Brazil expressed a mixed reaction to Oxitec's GM mosquitoes. Though some welcomed the trial, others did not.[10] One reason why some Brazilians had a more positive attitude toward the trial than the Floridians did is that dengue is a much worse problem in Brazil than it is in Florida.[11] Government agencies and scientists from France, Guatemala, India, Malaysia, Mexico, Panama, Philippines, Singapore, Thailand, the USA, and Vietnam have also been evaluating the release of GM mosquitoes.[12]

Field trials of GM mosquitoes raise a variety of ethical, legal, and social issues, such as assessing and managing public health and environment risks, community consultation, informed consent, and regulatory oversight.[13] In addition, some people have religious or philosophical objections to all forms of genetically engineered life.[14]Reports commissioned by the World Health Organization (WHO) published in 2003[15] and 2012[16] explored many of these issues. In this article, I review these issues and focus on a topic the WHO reports did not adequately address: the ethics of conducting a trial in an area in which many people in the community will be affected by the release of GM mosquitoes but will not be enrolled in the study as human research subjects. This is an important issue to examine because it will usually not be possible to ensure that all members of a community provide informed consent to a field trial of GM mosquitoes. Neighbouring communities may also be affected

by the release of GM mosquitoes. Since field trials of disease-resistant GM mosquitoes may impact many people that do not consent to their release, this leads one to question whether such trials should be conducted at all.

Genetically Modified Mosquitoes

Adult mosquitoes can serve as disease vectors by biting an infected host and transmitting the disease agent when they bite another host. For example, a mosquito can acquire the malaria parasite (one of five types of *Plasmodium*) when it takes a blood meal on a host (such as a human) infected with the parasite. The parasite reproduces in the mosquito's body, and the next time the mosquito bites a host it can transmit the parasite through its saliva. Only mosquito species belonging to the genus *Anopheles* can transmit malaria. Other species of mosquitoes have genotypes that prevent them from serving as *Plasmodium* vectors, though they may have the ability to transmit other disease agents. Some *Anopheles* mosquitoes have natural resistance to *Plasmodium*.[17]

Scientists have pursued three different strategies for genetically engineering mosquitoes to prevent disease: 1) modifying male mosquitoes to produce infertility,[18] 2) modifying mosquitoes to resist disease,[19] and 3) modifying mosquitoes so they vaccinate humans against disease.[20] While the first strategy is potentially safer than the other two, it may not be the best long-term solution for controlling mosquito-borne diseases, because eradication may not occur, and it may not be a desirable outcome in any case, since the targeted species might play a key role in the food chain. Amphibians, bats, birds, fish, insects and other species feed on mosquitoes at various stages of their life cycle. The third strategy also is problematic because receiving a vaccine from a mosquito bite may not be as safe or effective as receiving one from a health care professional. The second strategy is likely to be the most effective way of controlling mosquito-borne illnesses, because it could produce permanent changes in mosquito populations that do not significantly disrupt the ecosystem. Accordingly, this article will focus on field trials involving the release of GM disease-resistant mosquitoes.

To genetically engineer mosquitoes that resist a certain disease, it is necessary to identify genes that can prevent disease transmission. Scientists have explored a variety of ways of engineering mosquitoes to resist disease. Some genetic interventions help the mosquito's immune system to respond to the disease agent (such as a virus or protozoan), while others prevent the agent from reproducing in the mosquito's body. Researchers have developed *Anopheles* mosquitoes that resist rodent and avian malaria and have genetically engineered *Anopheles* mosquitoes that resist human malaria.[21] Recently, researchers succeeded in developing a species of *Anopheles* mosquito that expresses antibodies that confer resistance to the malaria parasite.[22]

For a genetic modification to have a significant impact on a mosquito population, it must increase in frequency and become highly prevalent in the population. Though natural selection can increase the frequency of genotypes in a population, it is not an ideal mechanism for artificially producing disease-resistance, because it takes a long time and disease-resistance genes may not confer any adaptive advantage. A more effective way of increasing the frequency of disease-resistance genes is to exploit gene drive mechanisms, which increase the frequency of genes in a population irrespective of the effects of natural selection or random drift. Gene drive mechanisms increase the odds that a genetic variant will be inherited by altering normal, Mendelian inheritance. Gene-drive mechanisms occur naturally, and can be artificially transferred to target species through genetic engineering. A disease-resistance gene linked to a gene drive mechanism could rapidly increase in frequency in the population.[23]

Research Design Issues

Once a mosquito has been equipped with disease-resistance genes and a gene drive mechanism, investigators can consider designing a field trial to determine whether the genetic modification will have its desired effect. To advance the discussion of the issues explored in this article, I will focus on a hypothetical field trial of malaria-resistant GM *Anopheles* mosquitoes, because the issues raised by such a trial would be similar to those raised by similar trials of disease-resistant mosquitoes. As noted above, scientists have made progress in developing mosquitoes that resist malaria, though field trials have not yet taken place.

One of the most important design issues is selecting appropriate trial sites. [24]Ideally, a trial site should be geographically isolated to minimize environmental contamination and adverse public health impacts (discussed in more depth below).[25] The targeted disease should be endemic in the mosquito population and should pose a major health problem for the community.[26] An ideal location would be an island community where malaria is a serious health problem and there is little risk of contaminating other populations.

Trial outcomes that need to be measured include: 1) effects of the genetic modification on the targeted mosquito population, such as changes in the frequency of the genetic modification over time; 2) effects on the human population, such as changes in the incidence of or disease burden of malaria, and 3) environmental impacts, such as effects on species that feed on the targeted mosquitoes and unintended breeding with related species.[27]

Investigators must also decide how data will be collected from the human population. There are two different ways of collecting this data: 1) collecting data from individuals; 2) collecting aggregate data from public health agencies.[28] Additionally, one may pursue both of these approaches simultaneously, but this approach will not be considered here. Under the first approach, the field trial would be similar to a clinical trial in that human subjects would be enrolled in the study and followed for a period of time. Data would be collected at enrollment and at various times after the intervention. Demographic and health variables, such as blood pressure, pulse, weight, height, age, occupation, etc., could be measured. A medical history could be taken and biological samples could be collected for analysis. Biological samples could be tested for malaria antibodies to determine whether subjects have been infected. The main drawback with the first approach is that it could be difficult to execute and costly, because thousands of individuals might need to be enrolled in the study and followed for many years.[29]

Collecting data from public health agencies would be a cheaper and easier way to measure the effects of the intervention. If the GM mosquitoes have been designed to resist malaria, for example, then data on the incidence of malaria and morbidity and mortality due to the disease could be collected by public health agencies. However, there are some significant problems with the second approach. First, there may not be any local public health agencies in some communities, or, if there are, they may not keep good records on disease incidence, prevalence, and mortality. This is likely to be a problem in communities in developing nations, which may stand to benefit most from research on disease-resistant mosquitoes. Since data collection should be uniform across the different sites, if there are data collection problems with only a few sites, this could compromise the results of the whole study. Second, even if there are no problems with data collection, this approach would not provide much of the important information that would be provided by the first approach, because it would only obtain aggregate public health data and would not obtain biological samples or health and demographic information pertaining to individuals. Because the second approach

has some significant problems with data collection in developing nations that may prevent it from being implemented successfully, this essay will focus on the first approach.

In addition to selecting trial outcomes, investigators must choose an appropriate methodology. The "gold standard" for biomedical research is the randomized controlled trial (RCT). In RCTs, individuals are randomized to receive either the experimental treatment or the control group (e.g. standard treatment or placebo). In public health research, cluster randomized trials are often used to test the effectiveness or interventions. In a cluster randomized trial, the intervention is at the level of a larger group (such as a community or a health care institution) not at the level of the individual.[30] Data collection may be at the individual or population level. For example, a field trial of GM mosquitoes resistant to malaria could include experimental sites in which GM *Anopheles* mosquitoes are released and control sites in which normal mosquitoes of the same species are released.[31]

While randomized cluster trials would be the best way of obtaining evidence on the effectiveness of GM mosquitoes at preventing disease, they can be difficult to implement, due to costs and other factors. For example, dozens of sites may need to be recruited to ensure that the study has adequate statistical power, and it might not be possible to find enough suitable sites for the study and secure the consent of the local community. Also, sites may need to be followed for several years to gather enough data, and communities may not want to be randomized to receive the intervention or the control. Smaller trials involving fewer sites may be the best type of research that can be conducted, given these limitations.[32]

Ethical and Regulatory Issues

Ethical and regulatory issues should be considered at the very earliest stages of the trial, i.e. when it is proposed or funded, as well as at later stages, i.e. prior to implementation. Many of these issues have to do with managing the environmental and public health impacts of the research.[33] The Cartagena Protocol on Biosafety, a part of the Biodiversity Convention, an international agreement signed by 168 countries, requires participating nations to develop laws pertaining to the safe handling and use of genetically modified organisms (GMOs) to protect human health and biodiversity. These biosafety laws should include provisions that address risk assessment and management for GMOs, monitoring and reporting of harms, transport and storage, and public awareness and participation. Countries may authorize government agencies to enforce these laws.[34] For example, in the USA, the Food and Drug Administration and the USA Department of Agriculture have the authority to grant marketing approval for some types of GMOs or GMO products.[35]

The environmental issues raised by the release of GM mosquitoes concern impacts on other species and the ecosystem. GM mosquitoes may disrupt the ecosystem by interbreeding with closely related species to form hybrids. To minimize this risk, release sites should be chosen based on a low risk of interbreeding and interbreeding should be closely monitored. GM mosquitoes may also have impacts on non-target predator species. For example, the mosquitoes might pose a threat to non-target predator species, such as bats or fish, if their genetic modifications produce toxins that are lethal to those species. While this is only a remote possibility, it still must be considered when designing GM mosquitoes that will be released into the wild. As noted earlier, field trials involving the release of infertile GM mosquitoes can pose significant environmental risks, since eliminating a species in a particular area could disrupt the ecosystem if the species plays an important role in the food chain.

In general, selecting a site that is geographically isolated helps to minimize environmental impacts because it limits the effects of the release to a particular area. Environmental

impacts can also be minimized by conducting pilot studies before proceeding to field trials. Pilot studies could include caged field trials in which mosquitoes are physically segregated from the environment. They can interact with the environment but are not free to roam about and breed, so the impact of the trial is minimal.[36] Another type of pilot study would be to conduct small open-release trials before moving to larger ones. The environmental impacts of small trials can be studied and assessed before attempting riskier and larger trials.[37]

The public health issues associated with the release of GM mosquitoes relate to their impact on the human population. Though GM mosquitoes designed to resist disease have the potential to promote public health, they also may pose risks to the human population which must be assessed and managed.[38] People exposed to GM mosquitoes may be placed at risk because the genetic modifications may not function as planned: they may confer no resistance at all or, worse, they may reduce resistance to the target infection. They may also enable the mosquitoes to serve as vectors for a different disease[39] or promote the evolution of pathogens with increased virulence.[40] There may be other risks that are not well-understood at this point. Although laboratory studies to assess the effectiveness of the genetic modifications can help researchers avoid these adverse outcomes, it is impossible to know precisely how GM mosquitoes will interact with disease agents until they are released into the wild. Field trials should not be implemented unless research indicates that overall public health benefits are likely to be greater than public health risks.[41] Geographic isolation can also help to minimize public health risks, since it can limit the effects of the release to participating human populations.

Human Subjects Issues

Since the hypothetical field trial considered in this article would collect data and biological samples from individuals in the community, it would be regarded as research with human subjects. Under the USA Common Rule[42] and other guidance documents,[43] human subjects are individuals about whom information is collected through interactions with investigators or by accessing private data records.[44] Different countries have their own legal rules for research involving human subjects, but some countries have none. Most of the laws enacted by different countries and ethical guidelines adopted by various organizations emphasize the following requirements for research involving human subjects:[45,46,47]

1. The research is scientifically well-designed.
2. The research is expected to produce knowledge that benefits society.
3. The risks to the subjects and others directly impacted by the research are minimized.
4. The risks are reasonable in relation to the benefits to the subjects and the importance of the knowledge produced.
5. Subject selection is fair.
6. Informed consent from the participants or their representatives is obtained and appropriately documented.
7. Confidentiality and privacy are protected.
8. Provisions are in place to protect vulnerable subjects form harm.
9. Provisions in place to avoid exploitation of research subjects or the community in which the research takes place.
10. There is independent review and oversight of the research by an appropriate body, such as an institutional review board (IRB).

11. Where appropriate, there is data and safety monitoring to protect subjects and others.
12. Where appropriate, communities are consulted about the research and have an opportunity to provide their input, approval, or disapproval.

I shall now briefly consider each of these twelve requirements and focus on those that merit additional discussion.

I have already discussed research design issues in the previous section.I will assume that the trial would not take place unless it is well-designed. Concerning benefits, one could argue that the research would produce important social benefits if it helps public health experts develop cost-effective means of preventing mosquitoes from transmitting malaria. Another potential benefit of the research is that it may provide scientists with a better understanding of malaria and how to prevent it. These benefits could accrue to individuals who are prevented from contracting malaria, the communities in which the trials take place, or the larger human population.

With regard to risks, I have already mentioned the potential risks related to receiving bites from malaria-resistant GM mosquitoes, or other mosquitoes that carry a more virulent form of the parasite. To minimize these risks, the health of participants should be monitored on a regular basis and they should receive free treatment for malaria and other health problems related to participating in the study. Offering treatment will not undermine data collection for the study as long as the study is measuring incidence of malaria as a primary outcome, rather than mortality or morbidity due to malaria. Although providing free treatment for malaria and health problems related to participating in the study will increase the costs of the research, one could argue that these expenses are justified in order to minimize risks to participants, promote justice, and avoid exploitation (discussed below).[48] Other risks include the risks of biological sample collection, such as bruising or fainting from a blood draw, as well as the risks of loss of privacy if confidentiality (discussed below) is breached. To minimize the risks of the blood draw, investigators should use trained staff to collect blood.

Concerning the balancing of benefits and risks, one could argue that the benefits of a field trial of GM malaria-resistant mosquitoes will outweigh the risks of the study, if malaria is endemic in the area and poses a major public health concern and the study is well-designed.

Research participants may benefit if the study prevents them from contracting malaria, and the community may benefit from the study if the incidence of malaria decreases as a result of the study. The knowledge produced from the study may also produce benefits for society.

For subject selection to be fair, the population being studied should be appropriate for the scientific design of the study. This requirement can be met for a field trial of malaria-resistant GM mosquitoes if the study is conducted in an area where malaria is a significant public health concern. This requirement would not be met if the targeted disease is not a significant public health problem in a particular area. For example, one could argue that selecting Key West, Florida as a study site for the release of infertile *Aedes* mosquitoes was not appropriate, because dengue is not currently a significant public health problem in Key West.

To meet requirements pertaining to informed consent, subjects (or their representatives if they are unable to consent) should receive relevant information about the study and have the opportunity to decide to participate, free from coercion or undue influence. They should receive information about the purpose of the study, research procedures, benefits and risks, alternatives to participation, confidentiality protections, whom to contact with questions or

concerns, and other relevant information. Consent discussions should take place in a language that they can speak and the consent form should be written in a language the subjects can read and comprehend. The form should not contain complex scientific terms or jargon they do not understand. Subjects should receive a copy of the consent form and they should sign the form. If the subjects are not literate, the research can be explained to them orally, and they can receive a shortened version of the consent form to sign.[49]

One of the consent issues that may arise is that it may be culturally appropriate in some communities to obtain consent from someone else besides a subject who is capable of providing consent. For instance, in some communities it may be the tradition for tribal leaders to provide consent for individuals within the community. In other communities, it may be culturally appropriate for an adult woman's husband or father to provide consent. In situations like these, every effort should be made to respect cultural traditions, provided that the subjects still have the opportunity to decide whether to participate in the study. For example, while tribal leaders may be consulted about the study, the subjects should have the final decision concerning participation. No individuals should be required to participate in the study if they do not give their approval.[50]

Investigators should implement measures to protect confidentiality and privacy, such as restricting access to records to study personnel, developing security mechanisms for electronic records, and using a code to identify individual subjects in research records. Additionally, consent discussions and data and sample collection procedures should take place in a sequestered area to prevent the unwanted disclosure of private information.

Vulnerable subjects are individuals with a compromised ability to consent to participate in research, due to their age, mental or physical health, socioeconomic circumstances, or other factors. In a study taking place in a developing nation, it is likely that many of the subjects will be vulnerable, due to extreme poverty and lack of access to health care.[51] To protect these subjects, measures should be in place to ensure that consent is free from coercion and undue influence. For example, subjects should not feel pressure from family members, political leaders, or others to participate. Since some of the subjects may participate in the study to receive free medical care, investigators should clearly explain the difference between research and therapy during the consent process. They should inform subjects that the main purpose of the study is to generate knowledge and that they may not benefit from participation. If the subjects are children or are mentally disabled, an appropriate representative (such as a parent or guardian) should provide consent.[52]

Exploitation can occur in research when the benefits and risks of participation are not distributed fairly.[53] Individuals or communities may be exploited. Individuals may be exploited if they are harmed in research when there is little expectation that they will benefit, or they do not provide consent. To avoid exploiting individuals, it is important for research to be well-designed and to minimize risks to individuals, including research participants and others. Consent should also be sought, and subjects should receive free medical treatment for injuries resulting from their participation. Exploitation of a community may occur when the community is placed at risk without the expectation of significant benefits. For example, if a clinical trial of a new drug takes place in a community in which people are not likely to have access to the drug after marketing approval, this would be a form of exploitation because the community might not receive a fair share of the benefits of research. To avoid exploitation of the communities where the research takes place, the research should have the prospect of providing important benefits to those communities.[54] To avoid exploitation of communities, field trials of malaria-resistant GM mosquitoes should take place only in areas where malaria is a significant public health concern. Since even well-trained IRB members may not recognize the potential for

exploiting communities, it is important that they receive information about community concerns.

Concerning independent review, most research institutions in developed nations have IRBs or similar bodies, such as Research Ethics Boards or Research Ethics Committees. Some institutions that do not have their own independent review committees may rely on another institution's committee or may contract with a private organization for independent review. Obtaining independent review can be a significant problem in developing nations, since communities may not have an IRB or similar body.[55] To deal with this problem, investigators may seek to obtain review from an appropriate body in close proximity to the community, or they may need to establish an independent review board within the community. If the investigators establish an independent review board within a community, they will need to ensure that members of the board receive appropriate education and training for reviewing and overseeing human subjects research and that they have sufficient resources to perform their tasks.[56]

Data and safety monitoring is important in studies that pose more than minimal risk to the research subjects. The purposes of data and safety monitoring are to evaluate risks to subjects and others in real time and to suggest changes to the study necessary to protect subjects from harm and promote their welfare.[57] Data and safety monitoring can be done by a data and safety monitoring board (DSMB) or by an independent monitor. A field trial of malaria-resistant GM mosquitoes would need some form of data and safety monitoring because it may pose more than minimal risks to research subjects and the community (discussed above). A trial may need to be stopped, for example, if there is evidence that it increases the risk of malaria or other mosquito-borne diseases. A trial could also be stopped if the intervention is proven to be so effective that there is an ethical obligation to offer it to communities in the control group.

Community consultation involves ongoing dialogue and collaboration between investigators and the local community concerning the study.[58] Investigators should obtain approval from political leaders, public health agencies, and other relevant bodies before conducting the study. They should also collaborate with local health clinics, medical professionals, and scientists concerning recruitment, research design, data collection, and other aspects of the study. Ideally, community consultation should begin at the very outset of the study and should continue as long as the study is taking place. Studies should provide meaningful benefits identified by the community, which can help avoid exploitation. In a field trial of malaria-resistant GM mosquitoes, preventing malaria should be a major benefit identified by the community. Practical problems can arise when deciding whom in the community to consult with.[59] For example, it may not be clear who the political leaders are in the community or whether their views represent the opinions of most of the people in the community.[60] Since these sorts of issues arise in any type of community-based research and are not unique to GM mosquito field trials, I will not explore them in-depth here.

I shall now briefly consider each of these twelve requirements and focus on those that merit additional discussion.

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example, while tribal leaders may be consulted about the study, the subjects should have the final decision concerning participation. No individuals should be required to participate in the study if they do not give their approval.[50]

Investigators should implement measures to protect confidentiality and privacy, such as restricting access to records to study personnel, developing security mechanisms for electronic records, and using a code to identify individual subjects in research records. Additionally, consent discussions and data and sample collection procedures should take place in a sequestered area to prevent the unwanted disclosure of private information.

Protecting Individuals Who Are Not Research Subjects

One of the most challenging ethical issues related to field trials of GM mosquitoes is how to protect individuals in the community who are not research subjects. In the hypothetical study of malaria-resistant GM mosquitoes considered in this article, consent would be obtained from members of the community that participate in the study. They would have some protection from the risks of the study because their health would be monitored and they would receive treatment if they develop malaria or some other mosquito-borne disease related to the study. However, there would probably be other individuals in the community who would be placed at risk from research, even though they are not enrolled in the study. While enrolling each individual in the community in the study would be desirable, it will seldom be achievable.[61] First, it may not be possible to identify every individual living in the community who will be impacted by the trial. Even if the local authorities have good records concerning the names and addresses/phone numbers of people living in the community, it may be impossible to contact each person and obtain their consent. Additionally, contact information for each person in the community may be incomplete, because new people may arrive in the community for business, tourism, relocation, or other reasons, and others may change their address/phone number. Second, even if every person in the community can be contacted, some might decide to not participate in the study. Third, there may not be sufficient resources to enroll everyone in the community in the study in any case.

There is little doubt that investigators have an ethical obligation to protect community members who are not human subjects from research-related harm.[62] They have an obligation to protect community members from harms related to the research under the principle of beneficence, articulated in the Belmont Report[63] and other influential guidance documents.[64] Beneficence requires investigators to minimize the risks of their research and maximize benefits. The principle has broad application, and risks are not restricted to risks to subjects.[65] As noted above, protecting community members from harm can help avoid exploitation. Additionally, if the host country follows the Cartegena Protocol, then it should have biosafety laws in place that require individuals and institutions who work with GMOs to protect the public from harm.

Granted that investigators should take steps to protect community members who do not participate in a study from harm, how should they do this? One could argue that the best way to protect these people is to refrain from conducting a field trial in a particular area unless everyone in the community agrees to participate in the study. This option would help to protect all community members from harm and respect their right to make autonomous decisions. The problem with this option, however, is that it will usually not be possible to enroll all members of the community in a trial, for reasons mentioned above. This option would recommend, in effect, that field trials of GM mosquitoes should never be conducted. As I have argued earlier, however, field trials of disease-resistant GM mosquitoes can benefit communities (as a whole) and individual members by helping to prevent disease, and

an important condition for permitting trials to take place is that these benefits are expected to outweigh the risks. Refraining from conducting a field trial of GM mosquitoes because not everyone in the community will participate in the study is a high price to pay for protecting people from risks they do not consent to.

The question of whether to enroll each person affected by a field trial of GM mosquitoes in the study represents a classic conflict between two fundamental values: protecting the rights and welfare of individuals vs. promoting the good of the community. A key question in thinking about such conflicts is deciding whether promoting a type of good for the community is important enough to merit policies that adversely impact the rights or welfare of individuals. Many commentators have held that promoting public health is important enough to justify policies that interfere with the rights or welfare of individuals because public health is vital to the social and economic well-being of all community members.[66] Infectious diseases, such as HIV/AIDS, cholera, and mosquito-borne ones, such as malaria, can threaten the well-being of each member of the community and have devastating impacts on the economy and social institutions. Many public health practices that compromise the rights or welfare of individuals for the common good involve the prevention and control of infectious diseases. Some of these practices include: mandatory vaccinations for school-age children or health workers, required reporting of some types of infectious diseases to public health authorities, isolation and quarantine of individuals with dangerous infectious diseases, and pesticide spraying for mosquito control.[67]

With regard to field trials of GM dengue-resistant mosquitoes, the issue would come down to whether the public health benefits of trial for the community are important enough to justify the imposition of risks on individuals without their consent. If the disease constitutes a major public health concern for the local population, the benefits of the trial for the community as a whole are likely to outweigh the risks, and community leaders have agreed to the trial, then one could argue that the trial can take place without the consent of each person in the community.[68] However, the justification of an actual field trial would hinge on the particular facts of the situation, and each case should be decided on its own merits. For example, if Malaria poses a major health concern in an isolated area where the risks of contaminating other populations by releasing mosquitoes are small, a trial of GM malaria-resistant mosquitoes could proceed, provided that community approves. However if malaria is not a significant public health concern, other communities are likely to be affected, or community leaders have not approved the study, the trial should not be conducted.

If a trial of GM malaria-resistant mosquitoes is conducted in an area where not every community member is enrolled in the study, then investigators should implement measures to minimize risks to the public. These measures would not be a substitute for consent, but they would at least help community members manage their risks. First, investigators should inform the community that the trial is taking place, using newspapers, television, radio, the internet, and other media. They should provide the public with basic information about the study and whom to contact with questions about it. Investigators should also make free malaria treatment available in areas where GM mosquitoes are released and encourage community members to be tested for the disease if they develop symptoms. If the investigators have reasons to believe that GM mosquitoes can increase the risks of other mosquito-borne diseases they may offer testing and treatment for these illnesses as well. Although these safety measures will increase the costs of the study and go far beyond what most funding organizations may be willing to do, they are necessary to protect the community from harm associated with the study and assure community members that they are being treated fairly and will not be unduly burdened by the study. Research sponsors should be willing to cover these costs in order to ensure success of the trial and avoid public

backlash. It is worth noting that these same measures to minimize risks to community members should be implemented even if everyone consents.

It is also possible that communities outside of where the field trial takes place will be impacted by the study if the mosquitoes leave the target area. While geographic isolation of the study site can help to minimize this risk, it is still a potential effect of the study that must be considered and addressed. Neighbouring communities should therefore be informed that the field trial is taking place. They should receive information about whom to contact if they have questions or concerns about the study.

Conclusion

Field trials of disease-resistant GM mosquitoes raise a number of ethical issues and concerns, such as protecting the public and the environment from harm, balancing benefits and risks, collaborating with local the community, avoiding exploitation, and obtaining consent from research subjects. One of the most difficult problems involves protecting the welfare of community members who will be impacted by a trial but who will not be enrolled in the study. To address this concern, field trials should take place only when the targeted disease is a significant public health problem in an area, the benefits of the trial for the community are likely to outweigh the risks, community leaders approve of the trial, the risks of contaminating other populations are small, and there are measures in place to protect un-enrolled community members from harm, such as informing the community about the study and offering free treatment to people who contract mosquito-borne diseases related to the study. Since the justification of any particular field trial depends on a careful examination of the scientific and ethical issues, proposed studies should be evaluated on a case-by-case basis.

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Biography

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