




ETHICS AND VECTOR-BORNE DISEASES



COVER IMAGE:
People waiting in line under a large mango tree at
a yellow fever vaccination site, Yade Bohou, Togo.

Source: WHO / Olivier Asselin



Ethics and vector-borne diseases: WHO guidance

Ethics and vector-borne diseases:**WHO guidance**

ISBN 978-92-4-001273-8 (electronic version)

ISBN 978-92-4-001274-5 (print version)

© World Health Organization 2020

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

Suggested citation. Ethics and vector-borne diseases: WHO guidance. Geneva: World Health Organization; 2020.

Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Contents

ACKNOWLEDGEMENTS	V
1. INTRODUCTION	1
2. BACKGROUND.....	3
2.1 Key facts about vector-borne diseases	4
2.2 Social determinants of vector-borne diseases	4
2.3 Environmental determinants of vector-borne diseases	6
3. RELEVANT ETHICAL ISSUES AND VALUES	8
4. ADDRESSING SOCIAL AND ENVIRONMENTAL DETERMINANTS	10
5. GENERAL ETHICAL CONSIDERATIONS FOR PUBLIC HEALTH INTERVENTIONS....	13
6. VECTOR CONTROL METHODS	17
7. VACCINE CAMPAIGNS AND MASS DRUG ADMINISTRATION.....	25
8. SCREENING AND SURVEILLANCE.....	29
9. RESEARCH.....	35
10. COMMUNITY ENGAGEMENT	44
REFERENCES.....	49

Boxes

BOX 1. A TALE OF TWO CITIES: SOCIAL DETERMINANTS AND VECTOR-BORNE DISEASE IN BROWNSVILLE, TEXAS, UNITED STATES OF AMERICA, AND MATAMOROS, TAMAULIPAS, MEXICO.....	5
BOX 2. DEFORESTATION AND URBANIZATION IN GUANGDONG PROVINCE, CHINA	7
BOX 3. MALARIA ELIMINATION IN THE EASTERN MEDITERRANEAN REGION	22
BOX 4. PUBLIC DISAPPROVAL OF A PUBLIC HEALTH INTERVENTION: AERIAL APPLICATION OF INSECTICIDE TO CONTROL ZIKA VIRUS DISEASE, PUERTO RICO	23
BOX 5. MASS DRUG ADMINISTRATION TARGETING LYMPHATIC FILARIASIS IN ASSAM, INDIA	27
BOX 6. ETHICAL CONTROVERSY SURROUNDING THE USE OF CYD-TDV DENGUE VACCINE	28
BOX 7. BETTER PRACTICES FOR SAFER WATER STORAGE: COMPULSORY VECTOR CONTROL MEASURES AND TARGETED SURVEILLANCE IN INDIA.....	30
BOX 8. THE EYE IN THE SKY: USE OF DRONE TECHNOLOGY FOR DISEASE SURVEILLANCE IN SINGAPORE	31
BOX 9. USE OF HUMAN MOVEMENT DATA TO SHOW SPREAD OF ZIKA VIRUS IN SINGAPORE.....	32
BOX 10. THE WORLD MOSQUITO PROGRAMME: INFORMED CONSENT IN FIELD TRIALS	40
BOX 11. MALARIA HUMAN CHALLENGE STUDY IN NAIROBI, KENYA.....	42
BOX 12. CONFLICTS OVER THE RELEASE OF GENETICALLY MODIFIED MOSQUITOES IN BURKINA FASO	48



Acknowledgements

Urbanization and global health inequities.
A girl in a hammock on a Manila street, Philippines.
Source: WHO / Anna Kari

The development of this guidance document was led by Andreas Reis (Co-Lead of the Health Ethics and Governance Unit in the Department of Research for Health) and Raman Velayudhan (Head of the Veterinary Public Health, Vector Control and Environment Unit in the Department of Neglected Tropical Diseases), in close collaboration with Jan Kolaczinski (Head of the Vector Control and Resistance Unit in the Global Malaria Programme) and Mariam Otmani del Barrio (Scientist, the Special Programme for Research and Training in Tropical Diseases), under the overall guidance of John Reeder (Director, the Special Programme for Research and Training in Tropical Diseases) and Soumya Swaminathan (Chief Scientist).

External experts

Joel Aik, Environmental Health Institute, National Environment Agency, Singapore

Rafael Argilés, Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture, Austria

Bernard Baertschi, University of Geneva, Switzerland

Konstantinos (Kostas) Bourtzis, Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture, Austria

Jérémy Bouyer, Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture, Austria

Christiane Druml, Medical University Vienna, Austria

Vijayaprasad Gopichandran, ESIC Medical College and Post Graduate Institute of Medical Sciences and Research, India

François Hirsch, INSERM, France

Aamir Jafarey, Centre of Biomedical Ethics and Culture, Sindh Institute of Urology and Transplantation, Pakistan

Zeb Jamrozik, Monash University, Australia

Patricia Kingori, Ethox, University of Oxford, Nuffield Department of Population Health, United Kingdom of Great Britain and Northern Ireland

Bocar Kouyaté, Nouna Health Research Centre, Burkina Faso

Carl Coleman (Seton Hall University School of Law, Newark, New Jersey, United States of America) served as the lead writer, and Jerome Singh (University of KwaZulu-Natal, South Africa, and University of Toronto, Canada) contributed to the writing of portions of the report. Overall guidance in drafting the report was provided by Zeb Jamrozik (Monash University, Australia), Florencia Luna (Latin American University of Social Sciences, Argentina), Carla Saenz (PAHO, Washington), and Michael Selgelid (Monash University, Australia).

WHO is grateful to the following individuals who contributed to the development of this guidance:

Peter G. Kremsner, University of Tübingen, Germany

Florencia Luna, National Scientific and Technological Research Council, Latin American University of Social Sciences, Argentina

Cheryl Cox Macpherson, St George's University, Grenada

Lee Ching Ng, National Environment Agency, Singapore

Francine Ntoumi, Congolese Foundation of Medical Research, University Marien Ngouabi, Congo, and University of Tübingen, Germany

Ron Rosenberg, Centers for Disease Control and Prevention, United States of America

Thomas Scott, University of California at Davis, United States of America

Michael Selgelid, Monash University, Australia

Seema Shah, Lurie Children's Hospital of Chicago and Northwestern University, United States of America

Jerome Singh, University of KwaZulu-Natal, South Africa, and University of Toronto, Canada

Hanano Yamada, Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture, Austria

External reviewers

Ronald Bayer, Columbia University Mailman School of Public Health, United States of America

Salome R.A. Bukachi, University of Nairobi, Kenya

Claudia Emerson, Institute on Ethics and Policy for Innovation, McMaster University, Canada

Stephanie James, Foundation for the National Institutes of Health, United States of America

Michael Penkunas, United Nations University International Institute for Global Health, Malaysia

Karen Tountas, Foundation for the National Institutes of Health, Bethesda, Maryland, United States of America

WHO staff

Tasnim Azim, Regional Ethics Focal Point, Regional Office for South-East Asia, New Delhi

Ties Boerma, Director (retired), Health Systems and Innovation, Information, Evidence and Research, Geneva

Lauren Carrington, Veterinary Public Health, Vector Control and Environment unit, Department of Neglected Tropical Diseases, Geneva

Anna Drexler, Technical Officer, Vector and Ecology Management, Geneva

Gaya Gamhewage, Manager, WHO Health Emergencies Programme, Infectious Hazards Management, Experts Networks and Interventions, Geneva

Ki-Hyun Hahm, Technical Officer, WHO Regional Office for the Western Pacific, Division of Health Systems, Manila

Margaret Harris, WHO Health Emergencies Programme, Infectious Hazard Management, Geneva

Patrik Hummel, Consultant, Research, Ethics and Knowledge Management, Global Health Ethics, Geneva

Ronnie Johnson, Scientist, Family, Women's and Children's Health, Reproductive Health and Research, Maternal Perinatal Health, Prevent Unsafe Abortion, Geneva

Vannda Kab, Technical Officer, WHO Country Office, Cambodia

Jan Kolaczinski, Head of Vector Control and Resistance Unit in the Global Malaria Programme, Geneva

Marion Law, Prequalification Unit, Regulation and Prequalification Department, Access to Medicines and Health Products Division, Geneva

Katherine Littler, Co-Lead, Health Ethics and Governance Unit, Geneva

Ahmed Mandil, Coordinator, Research and Innovation, WHO Regional Office for the Eastern Mediterranean, Cairo

Jeannette Martinez, Prequalification Unit, Regulation and Prequalification Department, Access to Medicines and Health Products Division, Geneva

Vasee Moorthy, Coordinator, Health Systems and Innovation, Information, Evidence and Research, Research, Ethics and Knowledge Management, Geneva

Mariam Otmani del Barrio, Technical Officer, HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases, WHO Special Programme for Research and Training in Tropical Diseases, Vectors, Environment and Society, Geneva

Lee-Anne Pascoe, Consultant, Health Ethics and Governance Unit, Geneva

Martha Quinones Pinzon, Technical Officer, HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases, Global Malaria Programme, Entomology and Vector Control, Geneva

Caron Rahn Kim, Medical Officer, Family, Women's and Children's Health, Reproductive Health and Research, Maternal Perinatal Health, Prevent Unsafe Abortion, Geneva

Nigel Rollins, Medical Officer, Family, Women's and Children's Health, Maternal, Newborn, Child and Adolescent Health, Research and Development, Geneva

Carla Saenz, Regional Bioethics Advisor, PAHO, Washington

Abha Saxena, Coordinator (retired), Research, Ethics and Knowledge Management, Global Health Ethics, Geneva

Dominic Schuler, Vector Control Products Assessment, Prequalification Department, Geneva

Soumya Swaminathan, Chief Scientist, Geneva

Rajpal Singh Yadav, Scientist, Veterinary Public Health, Vector Control and Environment Unit, Department of Neglected Tropical Diseases, Geneva

Kirsten Vannice, Scientist, Family, Women's and Children's Health, Immunization, Vaccines and Biologicals, Initiative for Vaccine Research, Geneva

Raman Velayudhan, Head, Veterinary Public Health, Vector Control and Environment unit, Department of Neglected Tropical Diseases, Geneva

Sina Zintzmeyer, Project Management Officer, Polio, Emergencies and Country Collaboration, Enabling Functions, Zika Emergency Response, Geneva

Funding agencies

João Rangel de Almeida, Wellcome Trust, United Kingdom

Susanna Hausmann Muela, Federal Department of Foreign Affairs, Swiss Agency for Development and Cooperation, Switzerland

The project was funded in part by a grant from the Wellcome Trust.



1. Introduction

Beginning with the emergence of human settlements 15 000 years ago, vector-borne diseases have been a major contributor to global morbidity and mortality. In 2017, in recognition of the growing burden and threat of vector-borne diseases to individuals, families and societies, the World Health Organization (WHO) issued a comprehensive Global Vector Control Response Strategy for 2017–2030 (1), which outlines plans to strengthen vector control worldwide through increased capacity, improved surveillance, better coordination, and integrated action across sectors and diseases. Shortly after this strategy was released, the World Health Assembly, in 2017, adopted resolution WHA70.16, which, among other things, called on the organization to provide guidance on the ethical issues associated with vector control implementation (2).

Recognizing the lack of previous attention to the ethical issues raised by the management of vector-borne diseases, WHO organized a scoping meeting in Geneva on 23–24 February 2017 to identify the relevant ethical considerations and lay the groundwork for future guidance. The meeting brought together key stakeholders in vector control, maternal and child health, ecology and climate change, research and vaccine development, infectious disease ethics, and public health communication.

The scoping meeting identified several aspects of vector-borne diseases that raise significant ethical issues. First, many vector-borne diseases are neglected diseases, with a disproportionate impact on the world's poorest populations. This neglect manifests itself in insufficient resources devoted to surveillance and control measures, including inadequate support for research and development of drugs, vaccines, newer vector control approaches, and other potentially beneficial interventions. Vector-borne diseases therefore implicate fundamental issues of global social justice.

Second, unlike other infectious diseases, vector-borne diseases are transmitted between humans via other living beings – the vectors. Because vaccines or drug treatments exist for only a few of the pathogens transmitted by vectors, the primary method for controlling many vector-borne diseases is to control the vectors directly through population-level interventions. The success of these

interventions depends on collective action by many or all community members, often without the possibility of individual consent. Although such actions are intended to benefit the entire community, this does not mean that all individuals within the community will benefit equally or be exposed to equivalent burdens or risks.

Finally, some vector control methods currently being researched involve the genetic modification of mosquitoes and other vectors. These interventions have the potential to produce significant public health benefits, but they may also involve risks or uncertain consequences for human health and the environment. Some genetic vector control interventions, especially gene drives, are likely to be associated with potentially irreversible changes to vector populations that may spread across national borders.

Following publication of a report summarizing the discussions at the scoping meeting (3), WHO convened a larger expert advisory group to contribute to the development of this guidance. The group met in Vienna on 7–9 May 2018 to identify key issues for inclusion in the guidance, and a subgroup met in Washington, DC, on 4–5 February 2019 to begin work on a first draft. The full advisory group met again in Geneva on 23–25 July 2019 to review and refine a working draft, which was then sent out to a diverse group of international technical experts for comment. This document reflects the input of all of these contributors.

The primary audience for this guidance is persons working directly in vector-borne disease prevention and control, including programme managers, researchers and field workers. A brief technical background is provided for the benefit of persons without expertise in vector-borne diseases; readers working in the field may wish to skip the background section and begin with the discussion of ethical issues and values in Chapter 3. The guidance cannot offer universally applicable answers to the complex ethical issues raised, nor can it provide a checklist of issues that are necessarily relevant in all situations. Rather, its goal is to help readers recognize aspects of their work that raise significant ethical challenges and to respond to these challenges in accordance with internationally accepted values and norms.



2. Background

Urbanization and health inequities. Washing and drying clothes next to a creek that is now an open sewer in Yaounde, Cameroon.

Source: WHO / Anna Kari

2.1 Key facts about vector-borne diseases

Vector-borne diseases are human illnesses caused by parasites, viruses and bacteria that are transmitted by a broad range of vectors, including mosquitoes, sandflies, triatomine bugs, blackflies, ticks, tsetse flies, mites and lice. Together, the major vector-borne diseases account for approximately 17% of the global infectious disease burden. More than 700 000 deaths per year are attributable to vector-borne diseases.

Malaria is responsible for the highest global disease burden of all vector-borne diseases, causing approximately 405 000 deaths in 2018, most of them children aged under 5 years. Other major vector-borne diseases include Chagas disease, chikungunya, dengue, leishmaniasis, schistosomiasis, yellow fever and Zika virus disease. Recent major outbreaks of many of these diseases have led to substantial

morbidity and mortality, in some cases overwhelming local health systems. Dengue is the fastest spreading vector-borne disease, with an over 15-fold increase since 2000, and it affects over 129 countries.

The pathogens that cause vector-borne diseases have complex life cycles involving humans, vectors and sometimes intermediate animal hosts. Blood-feeding arthropods, especially mosquitoes, are the chief vectors involved, although some major vector-borne diseases, such as schistosomiasis, are transmitted by other types of vectors. The epidemiology of vector-borne diseases is influenced by whether transmission is primarily human to human (as is the case with malaria and dengue) or only animal to human (as with West Nile fever) (3).

2.2 Social determinants of vector-borne diseases

Some individuals and groups face heightened risks from vector-borne diseases due to the conditions in which they are born, grow, live, work and age, and thus in turn by the forces and systems that shape these conditions. These “social determinants of health” can affect the likelihood of being exposed to vector-borne diseases, of being infected following exposure, and of experiencing negative outcomes once infected (4). An effective global response to vector-borne diseases requires careful attention to these social conditions (1).

Examples of social factors that affect susceptibility and vulnerability to vector-borne diseases are gender, age, socioeconomic status, migration status and membership of an indigenous population. Biological and sociocultural factors interact in different ways across time and location to shape context-specific inequalities that affect health and well-being (5, 6). The intersection of these factors shapes individuals’ vulnerabilities and experience of particular disease conditions, as well as their ability to access health care and treatment (7).

Gender

Gender norms, roles and relations intersect with other axes of inequality, such as age, socioeconomic status, (dis)ability or geographical location, in influencing the risks of vector-borne diseases and individual disease experience. For example, gender-based occupational roles can affect the likelihood that an individual will be exposed to a vector. In certain fishing and farming communities, men often report higher rates of schistosomiasis than women, whereas in communities where women wash utensils and clothes in snail-infected waters they may experience higher infection rates of schistosomiasis than men (8, 9). Similarly, in many malaria-endemic areas, certain activities traditionally assigned to men may increase exposure to malaria vectors, particularly for those working in rural areas or working at night (10). Unequal gender power relations can also influence the use of disease control strategies, for example when household-level decisions about how to allocate a limited supply of bednets are influenced

by gender roles, norms and relationships (10). Furthermore, gender-based factors can affect the outcome of becoming infected, whether because of differential access to medical treatment or because of sociocultural practices associated with household work patterns, which may increase women's likelihood of suffering from malnutrition (11).

Age

Children and elderly people both experience disproportionate burdens from many vector-borne diseases. For example, most malaria mortality occurs in children aged under 5 years (12). While some age-related differences are attributable to biological factors, social factors also play an important role. For example, social norms related to bedtimes may heighten children's risk of exposure to vectors whose peak biting time is in the early evening (3). Similarly, social practices surrounding water storage and waste management may result in increased exposure to mosquitoes in areas where children are likely to play (3). Children, as well as some elderly persons and persons with diminished mental capacity, also face inherent risks due to their dependence on others. In most cases, they will have no access to prevention measures or treatment for vector-borne diseases unless their caretakers provide it.

Socioeconomic status

Socioeconomic status, including educational level, occupation and income, can influence health outcomes in ways that tend to disadvantage or privilege particular segments of the population (13). Work is a major risk factor for exposure to vector-borne diseases; for example, nomadic herders in the African Rift Valley are especially prone to tick-borne diseases such as spotted fever (14). Poverty is also a leading risk factor. One reason is that persons living in poverty are less likely to have access to clean water and sanitation. As a result, households may store water at home in containers, which can become breeding grounds for vectors (particularly *Aedes* mosquitoes). Addressing this problem requires efforts to promote safer methods for collecting and storing water, as well as long-term infrastructure developments that would eliminate the need for families to store water at home.

In addition, persons living in poverty are less likely to have access to preventive measures (such as insecticide-treated nets or indoor residual spraying of insecticides) or treatment for infection, as they depend mostly on publicly provided services. They are also more likely to suffer from other co-morbidities (including malnutrition) that make the consequences of infection more severe.

Box 1 presents a case study of the link between social determinants of health and vector-borne disease.

Box 1. A tale of two cities: social determinants and vector-borne disease in Brownsville, Texas, United States of America, and Matamoros, Tamaulipas, Mexico

Brownsville and Matamoros are sister cities politically separated by the Rio Grande River, which is the international border between the United States and Mexico. In climate and in many commercial and cultural ways the cities are not separate. The population of Brownsville is largely Hispanic, and many families have members living on both sides of the border. About 15 000 people cross the three international bridges linking the two cities every day to work, shop and visit relatives. But the cities differ in their susceptibility to dengue despite the presence of the vector mosquito, *Aedes aegypti*, in both. Matamoros periodically suffers epidemics, while few locally acquired cases are recorded in Brownsville.

A variety of factors increase the risk of dengue infection in Matamoros. While water and sewage facilities are similar in each city, street drainage is worse in Matamoros, sometimes making roads inaccessible and preventing regular garbage collection. Per capita income in Matamoros is substantially lower. Significantly fewer houses are air conditioned or have intact window screens, making them more open to mosquito invasion. Housing and population are denser, increasing the probability of infective mosquitoes finding human hosts. And a higher birth rate in Matamoros more rapidly adds immunologically naïve hosts to the pool of susceptible persons (15–17).

Migration status

In some cases, migration can contribute to the introduction or reintroduction of vector-borne diseases. For example, a recent resurgence of malaria in Greece was associated with increased immigration (18), and outbreaks of leishmaniasis have been linked to migration associated with the Syrian war (19). However, no systematic association has been found between migration and the transmission of vector-borne diseases. Diseases are more likely to enter a country via regular travellers, tourists or health care workers than via migrants or refugees (20). (For further discussion, see the section on travel screening in Chapter 8.)

Nonetheless, even if migration itself does not necessarily contribute to vector-borne disease outbreaks, migrants may have a higher probability of infection or suffering negative outcomes in an area where vector-borne diseases are present. Many of these risks stem from the same factors affecting other disadvantaged communities, such as lack of access to safe or stable housing, clean water, or nutrition and health care. In many cities, migrants form a large proportion of the urban poor, who suffer from a broad range of financial and other disadvantages, including difficulties in finding adequate housing and in accessing social services. In some cases, these risks are exacerbated by legal

restrictions placed on migrants, such as laws in some countries that restrict access to health care for undocumented immigrants (21).

Indigenous peoples and communities

Many vector-borne diseases disproportionately affect indigenous populations. Indigenous communities live mostly in remote rural areas, which typically have high levels of poverty and limited access to medical services. These areas often harbour vectors that do not exist in urban settings, and individuals are more easily exposed to these vectors through activities such as agriculture, fishing and hunting, or by sharing living spaces with animals.

However, the high rate of vector-borne diseases in indigenous communities cannot be explained solely by poverty and its consequences. Language and cultural differences can exacerbate barriers to access to prevention and treatment, as can factors such as physical remoteness to health care facilities and discrimination by members of the majority group. In addition, within indigenous communities, different subgroups may experience differing levels of risk exposure.

2.3 Environmental determinants of vector-borne diseases

The epidemiology of vector-borne diseases is heavily influenced by the environment. In addition to the environment's impact on vectors themselves, human interaction with or within natural environments and ecosystems influences exposure to vectors (22). For example, industrial activities that contribute to pollution, carbon emissions and land degradation, as well as human encroachment on wilderness areas, can increase human exposure to vectors. Similarly, haphazard urbanization can result in dense human

populations without adequate sanitation or access to clean water, conditions that are conducive to the growth of vector populations and increased disease transmission. Other causal factors related to human activities include urban heat islands (built-up areas that are hotter than nearby rural areas) and construction in coastal zones or other fragile ecosystems (23, 24).

Climate change has been associated with adverse health outcomes and is thought to influence the patterns of transmission of vector-borne diseases (25, 26). Changes in temperature, precipitation and humidity can influence the biting, survival and reproductive rates of vectors, as well as their distribution. Higher ambient temperature will often increase the rate of pathogen or vector reproduction. Other effects of climate and weather conditions include the impact of droughts on water storage systems, irrigation practices and land use, while climate-driven population movements may affect

vector ecology and human exposure to infection (27). However, the interactions of climatic and non-climatic factors are complex and poorly understood. More research on the relationship between particular manifestations of climate change and vector-borne diseases is urgently needed, as well as greater attention to the impact of climate-related risks on specific disease control measures.

Box 2 presents an example of the environmental risk factors that may be associated with vector-borne diseases, including deforestation and urbanization.

Box 2. Deforestation and urbanization in Guangdong province, China

In 2014, Guangdong province experienced its worst outbreak of dengue fever since the re-emergence of the disease in China in the late 1970s. There were over 45 000 cases and six deaths reported, with incidence highest in the provincial capital, Guangzhou. The Guangdong outbreak is an example of the role of urbanization, deforestation and population movement in the spread of dengue and the influence of socioeconomic change on outbreaks. The following risk factors contributed to the outbreak.

- The Pearl River delta in Guangdong, where the outbreak was centred, has a hot and humid subtropical climate conducive to *Aedes albopictus* breeding. Average temperatures and rainfall were higher in 2014 than in previous years, which probably contributed to vector survival in the area.
- Guangdong province has experienced rapid urbanization, particularly in the areas where dengue was most prevalent, such as the densely populated cities of Guangzhou and Foshan and nearby cities that experienced clusters, including Zhongshan and Zhuhai.
- Urbanization and economic development entailed land use change and deforestation. Rainwater that was previously absorbed and stored by forests became run-off that collected in stagnant pools, which provided favourable conditions for mosquito breeding.
- Urban villages on the outskirts of cities in the Pearl River delta increased, and urbanization occurred quickly with little planning and sometimes without authorization; limitations in the consequent infrastructure and sanitation create a hospitable environment for mosquitoes.
- Urbanization is compounded by an influx of migrant workers from rural areas to urban centres. This trend has led to migrants living in crowded conditions in Guangdong, resulting in a large and mobile population, some of whom may be particularly susceptible to dengue due to lack of previous exposure.
- The Pearl River delta is a major transport hub, and its well-connected urban centres facilitate the spread of dengue during epidemics.

These dengue risk factors also exist in other countries and regions experiencing rapid development. Deforestation, urbanization and migration present challenges to governments in controlling vector-borne diseases (28–32).



3. Relevant ethical issues and values

Ethics is concerned with identifying appropriate action or policy – that is, action or policy that is consistent with legitimate values (33). In order to engage in ethical analyses, therefore, it is first necessary to identify the values at stake in the context under consideration. While there is no universally agreed-upon list of ethical values that are relevant in all situations, certain values are frequently invoked as particularly important in the context of public health. These values should be understood in light of the overall mission of public health, which is to protect and improve the overall health of people and their communities (34). This focus on the impact of actions and policies on the overall population is the defining characteristic of the discipline that has come to be known as “public health ethics” (35).

First and foremost, public health ethics is concerned with promoting the well-being of individuals and communities. Maximizing well-being requires consideration of the likelihood that a policy will achieve its desired objectives in terms of public health benefits (“effectiveness”) and the costs associated with bringing about a certain amount of benefit (“efficiency”) as compared with the benefits and costs of alternative policy options.

An ethical assessment of public health activities must also be concerned with an action’s potential impact on social justice. Social justice refers to fairness in the distribution of resources, opportunities and outcomes, whether at a broad societal level or within individual units such as households. Public health activities can either promote or hinder social justice. For example, efforts to improve a city’s water and sanitation systems can contribute to social justice by reducing a significant cause of poor health among residents living in poverty. Alternatively, a public information campaign that is not translated into a country’s minority language could exacerbate injustice by leaving members of the minority group uninformed about important health information, such as measures they could take to avoid exposure to disease.

Another key value relevant to an assessment of public health activities is that of respect for persons. Respect for persons requires treating individuals as autonomous, self-governing agents, and avoiding the imposition of undue external constraints. Public health activities can promote respect for persons by removing barriers to individuals’ ability to live healthy,

productive lives. They can also undermine respect for persons, for example when efforts to control disease lead to unjustified restrictions on individuals’ freedom of movement or assembly.

Many other values are frequently invoked in discussions of public health ethics. These include solidarity (acting together for the mutual benefit of a common group), reciprocity (providing something in return for contributions that people have made), accountability (allocating and enforcing responsibility for decisions), and due process (providing notice and an opportunity to be heard to persons who will be affected by a decision). Individual countries, religious groups and other communities may draw on additional values as well.

Most of the issues discussed in this guidance concern situations in which multiple ethical values are relevant. Often, these values point in different directions, giving rise to ethical conflicts or dilemmas. For example, consider a public health agency that is deciding whether to require households to eliminate sources of stagnant water as a means of controlling vectors. A preliminary assessment of the activity suggests that the intervention is likely to be effective and efficient; thus, viewed solely from the perspective of promoting well-being, it would appear that the activity raises no significant ethical concerns. At the same time, requiring households to modify their private living environments, and possibly enforcing that requirement through intrusive government inspections, implicates the ethical value of respect for persons. In addition, when viewed through the lens of social justice, it is relevant that the burdens of the intervention are likely to fall disproportionately on vulnerable members of the community, as poor households are more likely to be dependent on manually collected water supplies that are stored in stagnant water sources. The appropriateness of proceeding with the intervention in these circumstances depends on whether the potential gains in well-being are sufficiently great to outweigh the ethical burdens involved.

Finally, good ethical decision-making requires a careful, inclusive and transparent deliberative process. The importance of inclusive decision-making is one reason that community engagement is emphasized so heavily in this document.



4. Addressing social and environmental determinants

Woman working in a rice field near Luang Namtha, Laos. Climate change affects the geographic range and seasonality of certain infectious diseases.

Source: WHO / Diego Rodriguez

As a matter of social justice, addressing the social and environmental determinants of vector-borne diseases must be a central component of any approach to disease prevention and control. This is particularly relevant in a global context, where climate change affects fundamental social and environmental determinants of health (36). First, as discussed above, factors such as poverty, inequality and environmental degradation directly contribute to the impact of vector-borne diseases by increasing individuals' risk of exposure to and infection by vectors and by exacerbating the consequences of infection for individuals and communities. Attending to these factors is therefore essential to the effectiveness of any public health interventions. Second, ethics is concerned not only with the overall level of health in a society, but also with the way in which good health is distributed among individuals and groups. In light of the value of social justice, the global community has an obligation to ensure that the burdens of vector-borne diseases do not fall disproportionately on the most vulnerable members of society.

How can those involved in planning and control efforts address the disproportionate burden of vector-borne diseases on vulnerable individuals and communities?

The concept of vulnerability has previously been analysed predominantly in terms of discrete groups or subpopulations, defined in terms of factors such as gender, age or membership of a minority group. This view of vulnerability assumed that members of these groups were relatively homogeneous, regardless of context, fostering stereotypes, stigmatization and discrimination (37). In fact, there are multiple factors or layers of vulnerability that interact and may render some individuals within a specific population subgroup more vulnerable than others (38).

In place of the subpopulation approach, an intersectional analysis considers the relationships and interactions among various social stratifiers embedded in processes and systems of power at the individual, institutional and global levels (39, 40). It recognizes that there can be important differences within groups



The implications of water supply, sanitation and hygiene, Mumbai, India.

Source: WHO / Diego Rodriguez

that may be perceived as relatively homogeneous, and that the combination of multiple factors can have synergistic effects (40). By calling attention to the multiple drivers of inequality, an intersectional analysis leads to more targeted and nuanced interventions and policies in complex real-world settings.

Decision-makers should make efforts to become aware of the social factors relevant to the risk of being exposed to, infected with, or suffering harmful consequences from vector-borne diseases, as well as the way that these factors intersect in particular geographical settings. In some cases, these vulnerabilities will only come to light during community engagement processes, which strengthens the case for starting such initiatives at the earliest opportunity. In addition, public health programmes and research agendas should include safeguards and protections to minimize the impact of vulnerabilities and to avoid exacerbating them. This may sometimes require the investment of additional resources. For example, in some cases, it may be necessary to invest in additional staff to reach out to persons with limited mobility or to translate information into the languages of minority groups.

If the balance of benefits and burdens associated with a proposed public health intervention is expected to be substantially worse for vulnerable segments of society, alternative approaches for addressing the problem should be considered. In all cases, efforts should be made to minimize the negative impact of interventions on vulnerable individuals to the greatest extent possible.

How can the international community minimize the environmental impact of vector-borne diseases?

There is an urgent need to address the human actions that contribute to the rise in vector-borne diseases. Before embarking on major construction or development projects, policy-makers should engage in environmental and health impact assessments

that explicitly consider whether the project might increase the vector-borne disease burden. Persons with specific expertise in vector-borne diseases should be involved in such assessments. In addition, governments and other funders should support research into the relationship between vector-borne diseases and factors such as climate, industrialization, urbanization and tourism.

The impact of climate change on vector-borne diseases needs to receive greater attention in global environmental discussions. Despite the fact that low- and middle-income countries have contributed least to the causes of climate change, the increased burden of climate-sensitive vector-borne diseases disproportionately falls on these countries. This is partly because the tropical climates of many developing countries are particularly suitable for certain vectors (27), but also because many low- and middle-income countries in tropical regions have larger segments of the population living in poorer socioeconomic conditions and with lower coverage of health services. In addition, individuals in populations with high levels of poverty are more likely to be infected with vector-borne diseases and, once infected, to suffer negative health outcomes. The inequitable distribution of the burdens of climate-sensitive vector-borne diseases should be taken into account in decisions about the prioritization of prevention and control strategies. As recognized by the United Nations Educational, Scientific and Cultural Organization (UNESCO) Declaration of Ethical Principles in relation to Climate Change, the principle of solidarity implies that wealthy countries have a moral obligation to work with developing countries in responding to climate change by providing “technology development and transfer, support for the synthesis of relevant information and knowledge, capacity-building, and means of financial resources” (41). One way that wealthy countries might fulfil this obligation is to require that health, research, education, policy and development projects explicitly include plans to meet these aims (42).



5. General ethical considerations for public health interventions

In some cases, public health interventions aimed at controlling vector-borne diseases may involve unavoidable intrusions on individual autonomy or conflict with other ethical values. In conducting an ethical analysis of these situations, no single ethical value necessarily takes precedence over all other considerations. Instead, an ethical analysis must include factors such as the anticipated benefits for individual and community well-being, any burdens or risks involved, the burdens and risks of not taking the proposed action, and the distribution of the relevant benefits, burdens and risks among different segments of society. It is also essential to consider whether the intervention could be conducted in a different way to enhance the benefits, reduce the burdens or risks, or make the distribution of benefits, burdens and risks more equitable.

What factors should be taken into account in assessing the risks, burdens and potential benefits of public health interventions?

In conducting an ethical assessment of a proposed public health intervention, a critical question is whether the expected risk–benefit ratio is more favourable than that of available alternatives. Questions to identify relevant factors in making this determination include the following.

Factors regarding benefits

- **What is the expected reduction in disease burden from the intervention in question?** The answer to this question will depend on the existing burden of disease and risk of future disease in the population in question, as well as evidence about the efficacy of the proposed intervention.
- **How sustainable are the benefits?** Interventions that permanently eliminate disease provide greater benefits than those that only temporary control it. In addition, it should be noted that the potential for sustained disease elimination is often limited in the context of vector-borne diseases, due to the potential influence of factors such as climate change and migration. If benefits cannot be sustained in the long term, then

short-term, repeated interventions may be more realistic.

- **How feasible is the intervention?** Relevant considerations include cost, availability of necessary facilities and human resources, and, in the case of vaccines and drugs, ease of administration, transportation and storage.

Factors regarding risks and burdens

- **What are the potential harms to individuals who receive or are subjected to the intervention (or the communities to which they belong), in both the short and long term?** Relevant risks are not limited to the possibility of experiencing physical harm, but also include consequences such as economic harms, loss of privacy or being subjected to stigma. In addition to known risks, consideration should be given to uncertain but plausible consequences based on experience with comparable interventions.
- **Is there a danger that the intervention will contribute to resistance to drugs or insecticides used in control methods?** For example, some mass drug administration programmes may risk promoting resistance, as experience has shown in the history of malaria elimination programmes (43).
- **To what extent would carrying out the intervention interfere with individual autonomy?** Even if the intervention will not be mandated by law, efforts to promote use of the intervention might be perceived as coercive, particularly by disenfranchised individuals and groups.
- **What are the opportunity costs associated with the intervention, in terms of both human and financial resources?** In some situations, resources devoted to an intervention might be more effectively deployed in other interventions that are more likely to have a sustainable benefit. For example, resources devoted to an expensive high-technology intervention might be more productively used to upgrade inadequate water and sanitation systems.



Maasai community partnership in TDR-IDRC research into vector-borne diseases and climate change, Tanzania.

Source: WHO/Andy Craggs

- **Is it likely that the intervention could provoke community opposition?** In some contexts, community opposition may jeopardize individuals' willingness to participate in other important public health initiatives. (Note that it will often be possible to minimize this possibility with an effective community engagement strategy, as discussed further below.)

It is important to recognize that the answers to the above questions depend in part on how the target population for the intervention is defined. In some cases, an intervention targeted to high-risk groups may offer a more favourable balance of benefits and burdens than one that is directed to the entire population. Programmes that are not designed to provide universal coverage of an entire population may, however, raise issues of social justice if members of disadvantaged groups are less likely to receive the benefits or more likely to experience the burdens or harms.

What factors should be considered in determining the degree of voluntariness appropriate for a particular intervention?

Public health interventions can involve a range of limitations on individual autonomy. At one end of the spectrum are interventions such as mass drug administration campaigns in which individuals are

informed of the potential benefits and risks and given an opportunity to decide whether to participate. The opportunity for individual choice can be protected either by requiring explicit consent to participate ("opt in") or by providing notice of the voluntary nature of the activity and an opportunity to object ("opt out").

At the other extreme are actions taken on a community-wide basis without the opportunity for individual objection (for example, aerial crop spraying) and legal requirements imposed on individuals and backed by penalties for non-compliance. For example, some jurisdictions impose fines or other penalties for individuals or entities that fail to intervene against mosquitoes breeding on their property (44–46). Even when vector control measures are not compulsory as a formal matter, efforts to promote compliance may be perceived as coercive.

In general, as a matter of both ethics and human rights law, "public health measures should restrict the freedom of individuals to the least extent possible and/or necessary" (47). Thus, other things being equal, voluntary measures are generally preferable to legal mandates (48). However, more restrictive measures can be ethically appropriate when voluntary efforts are not expected to be equally effective or efficacious under the circumstances.

Given the importance of collective action to controlling vector-borne diseases, limitations on individual

choice can sometimes be justified when there is good reason to believe that less restrictive measures are less likely than alternatives to achieve the desired public health goal (49, 50). The appropriateness of limiting individual autonomy depends on the importance of the intervention to reducing disease risk, given other control mechanisms also available; the extent to which allowing individual choice is likely to interfere with the success of the programme; and the burdens of the disease in question, as well as the burdens of the intervention, to infected individuals and the population overall.

It is also important to consider the potential negative consequences of public health interventions involving limitations on individual autonomy (51).¹ These include erosion of community trust, reduced sense of community solidarity, and a potential reduction in individuals' willingness to cooperate with other public health measures. In some cases, these consequences might outweigh the gains in disease reduction resulting from the use of compulsion.

Can it be ethically appropriate to offer financial remuneration or other incentives to encourage individuals to participate in public health interventions?

Policy-makers may sometimes seek to incentivize participation in public health interventions by providing various kinds of payments or remuneration. In some cases, they may simply offer reimbursement for the actual expenses associated with participating in public health programmes, such as the costs of transportation to a medical facility to participate in a vaccine or mass drug administration campaign. In other cases, they may provide additional sources of remuneration, beyond reimbursement for expenses. There is some evidence that such offers can be an effective means of encouraging participation. For example, some national vaccination programmes have seen substantial increases in uptake after they began to offer food vouchers to participants (52).

For public health interventions that require high levels of participation to be effective, offering remuneration

can be an ethically acceptable way of promoting the common good. Unlike imposing penalties for non-compliance, offering positive incentives does not infringe individual autonomy; thus, it is consistent with the principle that public health measures should rely on the least restrictive means likely to effectively and efficiently achieve the desired public health goal. In addition, providing incentives to individuals who assume burdens to themselves for public health benefits can be justified by the ethical principle of reciprocity, which states that "when individuals accept burdens for the benefit of the community it is appropriate for society to provide something in return" (53).

In determining whether to offer remuneration in exchange for participation in public health interventions, it is essential to take into account the attitudes and values of the relevant community, as determined through a well designed process of community engagement. As the WHO tuberculosis ethics guidance observed, "in some communities, such practices may be seen as inappropriate, or even insulting" (53). Another relevant consideration is the level of evidential support for the safety and efficacy of the intervention. Unproven interventions (such as experimental vaccines) should generally be introduced as part of formal research protocols with prior ethics review; in that context, ethics review committees will assess the protocol to determine what level of remuneration is appropriate (54).

Finally, it is important to consider the degree to which financial incentives might lead individuals to seek to receive a particular intervention that is not appropriate for them in order to receive payment (55). For example, in the case of certain drugs that may be contraindicated for persons who are pregnant or who have particular health conditions, offering incentives might lead individuals to hide relevant risk factors, thereby exposing themselves to harm. Well designed community engagement or social science research may help to characterize the risks of such outcomes and to design appropriate risk minimization strategies.

¹ "The range of options available to government and policy makers can be thought of as a ladder of interventions, with progressive steps from individual freedom and responsibility towards state intervention as one moves up the ladder. In considering which 'rung' is appropriate for a particular public health goal, the benefits to individuals and society should be weighed against the erosion of individual freedom" (51).



6. Vector control methods

A young boy lies under a mosquito net,
Yunnan, China.
Source: WHO / Simon Lim

The term “vector control” refers to methods to reduce or eliminate vector-borne disease burdens by reducing or eliminating vector populations. Vector control includes both positive interventions that actively seek to reduce or eliminate existing populations (such as insecticides) and negative interventions that seek to prevent new vector populations from becoming established (such as source reduction techniques). Core methods of vector control include indoor residual spraying and insecticide-treated nets, which are sometimes supplemented with other interventions such as larviciding of aquatic breeding habitats with chemical larvicides and biolarvicides, and management practices for water storage in homes and buildings (3). Repellents and other personal protection measures are also used by communities to keep vectors at bay.

Most vector control methods have historically targeted mosquitoes, which are responsible for the majority of illness, deaths, disability and economic loss from vector-borne diseases (3). However, an increasing number of vector control methods are being deployed for control of other vector species, which are now recognized to cause a greater burden of disease than had previously been recognized. These methods include indoor residual spraying

for control of sandfly vectors of leishmaniasis and reduviid bugs that transmit Chagas disease (1).

Traditional vector control measures have contributed to a progressive decrease in vector-borne diseases. However, the re-emergence or resurgence of previously controlled vector-borne diseases in some settings precipitated by insecticide resistance and pathogen drug resistance, coupled with the emergence of newly identified pathogens and vectors, has driven the search for complementary and novel interventions to augment existing strategies. These methods offer great promise but also raise a host of complex technical and ethical issues.

Genetic-based methods of vector control have focused on the dissemination of genetic traits designed to reduce a vector’s capacity to reproduce, or to reduce its capacity to spread human disease. These strategies are characterized, respectively, as *population suppression* and *population replacement*.

Population suppression includes strategies to reduce an insect population so that there are fewer insects that will pass on the pathogen (56, 57). Genetic methods for vector population suppression were proposed as a means of vector control as early as 1940 (58). Early proponents of this strategy



TDR-IDRC project teaching communities how to reduce Chagas transmission in Yucatan, Mexico.

Source: WHO – TDR / Isaias Montilla

envisioned releasing sterile male mosquitoes that would fail to produce offspring after mating with wild mosquitoes (59). Research on genetic methods for vector population suppression led to the development of the sterile insect technique, a control strategy that uses radiation to produce genetic mutations or chromosomal breaks to generate sterile male insects (56). Suppression of the target population requires a continuous release of irradiated, sterile males over a prolonged period. In successive generations, as sterile males continue to outnumber wild males and are competitive in mating with fertile females, the population will decline and collapse.

An alternate approach to the sterile insect technique, without the use of irradiation, is the release of males artificially infected with *Wolbachia* into a *Wolbachia*-uninfected population (or a population infected with a different, incompatible *Wolbachia* strain). *Wolbachia* are maternally inherited intracellular, symbiotic bacteria, which are estimated to infect more than 60% of all insect species (60). *Wolbachia* manifests a wide variety of reproductive manipulations that each bias the reproductive output of *Wolbachia*-infected females (thus increasing their frequency in successive generations), relative to those without the bacteria (61). *Wolbachia* were first recognized to manipulate host reproduction as early as 1967 (62). The discovery of cytoplasmic incompatibility arose when males carrying *Wolbachia* mated with uninfected females (or females infected with a different, incompatible *Wolbachia* strain), and all eggs laid by the female from that mating were non-viable, thus establishing that entire *Wolbachia*-free populations (or populations infected with a different strain) could be suppressed. Crosses between infected females and either males infected with the same *Wolbachia* strain or uninfected males were successful; a full complement of eggs hatched, all of which contained *Wolbachia*.

A population suppression strategy using *Wolbachia*, termed the incompatible insect technique, works on the same principle as the traditional sterile insect technique, whereby sustained inundated release of *Wolbachia*-infected males can lead to the crash of a target population. However, in both the traditional sterile insect technique and incompatible insect technique approaches, the large-scale production

of mosquitoes and separation of the sexes prior to field release is intense. Implementation across large geographical regions or in areas with large vector populations is thus unlikely to be sustainable without substantial long-term investment and strong political will (63).

Such challenges have given impetus to the search for more durable vector control strategies. Gene drives are systems that bias the inheritance of a particular DNA sequence (64). In gene drive, a genetic trait spreads to more than half of a species' offspring, boosting the population frequency of the trait over generations above and beyond what is predicted by Mendelian genetics (63). Gene drive systems can be self-sustaining (in which the modification is designed to persist, and even spread, within interbreeding populations of the target vector) or they can be designed so that the effect will be more spatially or temporally limited. Gene drive systems can be used to spread traits that decrease the reproductive potential of a vector population, for example by reducing fertility or biasing towards production of male offspring, both of which would result in longer lasting population suppression.

Population replacement (also termed "population modification" or "population alteration") involves replacing existing wild vector populations with modified versions of those species unable to transmit pathogens. This approach requires a gene drive to spread the anti-pathogen genes through the populations.

While the concept of gene drive in vectors is many decades old (65, 66), and genetically modified organisms have been introduced into the environment for decades (67), recent improvements in site-specific gene editing with clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) – the DNA sequences found within the genomes of organisms such as bacteria – is revolutionizing parasitology and vector research by accelerating the development of synthetic gene drive organisms to quickly spread a genetic modification among the target species (59, 68). Synthetic gene drives significantly increase the chance that a desired genetic trait will spread through a population faster than would normally happen through natural sexual reproduction. Gene

drive organisms intended to spread a desired trait into a population contain two linked sets of genetic modifications (67). The first set includes the genetic modifications that encode the new trait. The second set imparts the ability to “drive” the trait into a wild population with far higher probability than would normally occur under natural circumstances. The combination of these two sets of genetic modifications “drives” through the population of targeted species (67). When drive-inducing genetic modifications are added to an engineered vector, such as a mosquito – once it is released to the environment and mates with a wild mosquito – the offspring will almost always maintain the genetic modification that prevents it from transmitting malaria. Once those offspring mate with wild mosquitoes, they almost always maintain and pass on the desired trait to their progeny, which, in turn, pass on the trait to their progeny, and so forth.

Scientists designing a synthetic gene drive organism measure performance on two grounds: (a) the characteristics of the new trait; and (b) the characteristics of the drive (67). In regard to the characteristics of the new trait, to date, scientists have focused on three general classes of traits or “effectors” to control vectors. *Suppression drives* employ genetic modifications that reduce or eliminate disease vector populations (for example, by modifying mosquitoes so they produce only male offspring). In time, the targeted vector population crashes. *Replacement drives* modify vector populations so that they are no longer disease vectors (for example, by modifying mosquitoes so they are unable to transmit malaria). With this strategy, the number of malaria-causing parasites is reduced, but the number of mosquitoes remains the same. *Reversal drives* include genetic modifications that are designed to disable or reverse the effects of a previously introduced gene drive organism if something goes wrong. In such gene drive systems, the new organisms would be designed to affect only the unwanted modified organism, not the native species.

In regard to the characteristics of the drive, geographical reach and persistence in the environment are crucial factors to consider (67). *Non-localized drives* are designed to spread a trait widely and rapidly from a small number of introduced modified organisms. Non-localized gene drives

might be most appropriate for controlling a disease over a wide geographical area. *Localized drives* are geographically confined in nature, with the goal being to limit the spread of an engineered trait. This might be done in two different ways: a high-threshold drive that can spread only when a large number of modified organisms are introduced, or a self-limiting drive that lasts for only a limited period.

As organisms modified with synthetic gene drives are specifically designed to spread and may persist in the environment for years, with possible irreversible, unintended consequences, such gene drive systems merit special attention for the following reasons (69):

- Synthetic gene drives have the potential to change the gene pool of a population in such a way that certain genetic information prevails within the entire population.
- If this genetic information entails a lethal factor, there is a possibility that other populations beyond the target population could be eradicated.
- Where generations succeed each other rapidly, this can take place within a very short time.
- It is possible that the gene drive will propagate not only in the intended population, but also in unintended populations of the same species. A gene drive may also propagate in a closely related species if it transfers to that species as a result of hybridization and spreads there due to an identical target sequence.

Such factors are crucial to consider in any risk assessment and risk mitigation strategy of a synthetic gene drive construct.

Not all gene drive systems for population replacement involve synthetic gene drives and gene editing. The spread of a microbial genome through a population can occur with manipulation of the host reproductive system. *Wolbachia*, described above (under *population suppression*), manipulates the host reproduction system by shortening lifespan, thereby limiting the potential for completing the pathogen extrinsic incubation period (70), or by increasing resistance to pathogens, as has been demonstrated for dengue virus (71, 72). Unlike the strategy described

above for population suppression, replacement of the wild population with one universally infected with *Wolbachia* would require the release of both infected males and females.

Combined with the ability of *Wolbachia* to drive itself into a population of vectors, the capacity for particular strains to block the development of human pathogenic viruses in *Aedes aegypti* mosquitoes and interrupt transmission has led to population modification strategies exploiting such characteristics (59). Proof-of-principle research has generated evidence that combining multiple strains of *Wolbachia* in a single host (creating a superinfection) can reproduce each of the most desirable traits of individual strains (73, 74). *Wolbachia* has also been investigated for its potential to act as a vector and driver for a synthetic gene construct; however, attempts at modifying the bacteria have not yet been successful (59). Thus, while *Wolbachia*-based approaches have the potential for self-sustaining spread, unlike synthetic gene drives, they do not involve genetic engineering (75).

In what way do vector control methods raise distinct ethical issues?

Vector control methods often achieve greater public health benefits when they are deployed over a wide geographical area. For example, the effectiveness of indoor residual spraying partly depends on achieving mass killing at the community level in order to reduce the average age of the local mosquito population. Because of the importance of broad geographical coverage, decisions about the deployment of vector control methods are typically made on a communitywide basis, without the opportunity for individual-level choice, and are often decided at district or province level.

As discussed above, the importance of promoting the common good can justify public health interventions that involve some limitations on individual autonomy. However, for such interventions to be considered ethical, the limitations on autonomy must be necessary to achieve important public health interests that could not be achieved as effectively and efficiently by less restrictive means, and the expected benefits must exceed the aggregate risks and burdens involved. It is also important to consider

whether the benefits and risks of the interventions will be fairly distributed among all segments of society, giving particular attention to individuals who face vulnerabilities because of factors such as gender, age, or membership of a stigmatized social group. Making these judgements requires transparency in the planning and implementation of vector control measures, as well as a robust process of community engagement throughout the decision-making process, as discussed in more detail in Chapter 10.

What are some of the risks associated with vector control methods?

The expected benefits of vector control methods must be balanced against any reasonably foreseeable harms. One risk of vector control efforts is the toxicity of the interventions themselves. For example, certain insecticides can pose health risks to humans who are exposed to them. They can also pose risks to the safety of the food supply (76).

Another risk is that vectors will become resistant to control measures, potentially leading to control failure and a re-emergence or resurgence of disease. Resistance to insecticides has already been observed, due to both overuse and uses at sublethal doses, although the precise impact of such resistance on the effectiveness of the intervention is not always well understood (3). The use of the same insecticides for agriculture and for public health jeopardizes public health use by increasing the likelihood that vectors will become resistant to them. In addition to other insecticide management measures, countries should consider regulating the use of insecticides in all sectors relying on this intervention, in a similar manner as antibiotics are regulated, in order to reduce the risk of resistance. Other strategies include monitoring the level of insecticide resistance in vectors and deploying resistance management strategies to delay the evolution of insecticide resistance in the target vectors.

Many other risks associated with vector control methods relate to the environment. These include the potential disruption of ecosystems and the threat to biodiversity resulting from the collateral impact of vector control methods on other, beneficial non-target species. In addition to being a concern in their own

right, environmental risks are of additional concern because of the relationship between the environment and human health. For example, biodiversity promotes food security and dietary health and provides important resources for traditional medicine and modern drugs (77). The global community's commitment to preserving biodiversity is reflected in the United Nations Convention on Biological Diversity, which is dedicated to promoting biodiversity and the sustainable use of resources but may not adequately consider benefits to public health within this context (78).

Environmental risks can arise in many types of vector control, but they are particularly pronounced with interventions designed to modify, eliminate or eradicate species. To guard against them, environmental monitoring should be incorporated into all phases of vector control efforts, starting with hazard assessment and human risk assessment

during the research and development phases of new vector control technologies and continuing with health monitoring of operational vector control programmes.

Box 3 presents a case study on efforts to eliminate malaria in the Eastern Mediterranean Region.

What are some of the challenges involved in weighing the risks and potential benefits of vector control measures?

Prospective assessment of the risks and benefits of vector control measures is an inherently difficult process, as it requires making judgements about unpredictable and uncertain future occurrences. However, a variety of tools exist to facilitate a systematic process of risk–benefit assessment grounded in best scientific and ethical practices (84).

Box 3. Malaria elimination in the Eastern Mediterranean Region

The geographical diversity in the Eastern Mediterranean Region determines the endemicity, intensity of transmission and type of malaria. Currently, countries in the region are in different phases of malaria burden reduction and elimination. Six countries are in the burden reduction phase (Afghanistan, Djibouti, Pakistan, Somalia, Sudan and Yemen), where malaria is still a major public health problem. These countries reported more than 5.2 million malaria cases in 2018. The Islamic Republic of Iran and Saudi Arabia have very low, geographically limited malaria transmission and are in the elimination phase. The Islamic Republic of Iran reported zero indigenous cases for the first time in 2018 and 2019. In Saudi Arabia, the number of indigenous malaria cases declined to only 61 in 2018. The malaria control programmes in these countries are self-reliant, have strong political and financial support from national authorities, and are well supported by developed health systems at central and peripheral levels. Certain epidemiological and socioeconomic factors (such as education, equity in resource allocation for marginalized populations, and well developed social and economic infrastructures) also contribute favourably towards the objective of malaria elimination.

The 14 remaining countries and territories in the region are malaria free and in the phase of prevention of re-establishment of local malaria transmission. The risk of malaria reintroduction as a result of importation still exists in these countries. Some of these countries and territories eliminated malaria a long time ago (Bahrain, Jordan, Kuwait, Lebanon, Libya, occupied Palestinian territory, including east Jerusalem, Qatar and Tunisia), and others in the more recent past. Two countries, Morocco (2010) and the United Arab Emirates (2007), have achieved certification of elimination, and four other countries (Egypt, Iraq, Oman and Syrian Arab Republic) for more than three years have reported no indigenous cases. Egypt and Oman have expressed interest in certification of malaria-free status that will be supported by WHO.

The main challenge for this group of countries is to prevent re-establishment of local malaria transmission in the presence of continual population movement from malaria-endemic countries. This will involve maintaining awareness of malaria risk and maintaining the skills of health staff at governmental and private facilities to diagnose and promptly treat the disease.

Since 2000, the geographical distribution of malaria in the region has been shrinking. However, ongoing political instability, civil crises and conflicts in several areas of the region represent a great challenge to sustaining the gains achieved, including scaling up interventions and moving towards elimination in the six high-burden countries. Malaria elimination is the core of the regional vision, and all Member States are committed to this target. Malaria elimination is the right of at-risk populations and an ethical responsibility of governments and health systems. Reaching malaria elimination status in each area is one more step towards greater equity in health, and one more step towards the goal of malaria eradication (79–83).

Those responsible for making decisions about the use of vector control methods for which the risk–benefit ratio is unclear should familiarize themselves with these tools and incorporate them in their decision-making. In addition, it is essential to view risk–benefit assessment as an ongoing process. Thus, in addition to identifying and evaluating potential harms before an intervention is implemented, continuous monitoring should occur during and after the intervention, and processes should be created to mitigate any harms that occur (35).

One of the challenges in assessing vector control methods is the fact that those who benefit from these interventions will not always be the ones who bear the brunt of the harm. For example, controlling disease in the present may come at the expense of long-term environmental degradation, the harm of which will primarily be experienced by future generations. It is important to remember that the needs of existing and future persons are both important goals; neither one necessarily trumps the other in all situations. Instead, decision-makers should seek to quantify the risks – that is, the magnitude and likelihood of both current

and long-term harms associated with using, or not using, particular vector control methods – without assuming that either present or future concerns are inherently of greater importance.

In addition, decision-makers should guard against the common assumption that familiar interventions (such as insecticides) are necessarily safer, while newer ones (such as the release of genetically modified mosquitoes) are necessarily riskier. In fact, the risks and benefits of technologies are not always correlated with whether they are new. Likewise, decision-makers should avoid making judgements based on the characterization of an intervention as “natural” or “non-natural”, an artificial construct that has no bearing on the intervention’s potential harms or benefits. Finally, it is important to remember that, when faced with unmet health needs or a public health crisis, both action and inaction are choices with ethical consequences. The harms avoided by foregoing the use of a risky new technology must therefore be weighed against the likely harms if the technology is not used (Box 4).

Box 4. Public disapproval of a public health intervention: aerial application of insecticide to control Zika virus disease, Puerto Rico

Because vector control is often effective only when applied to large areas, public acceptance is critical.

The first case of Zika virus infection in Puerto Rico, a Caribbean island territory of the United States, was confirmed on 31 December 2015. By that time, it was known that women infected by the virus during pregnancy could give birth to severely disabled babies. Because there was no vaccine, the only public health intervention available to the 3 million inhabitants was vector control. The vector mosquito, *Aedes aegypti*, was found everywhere on the island, and previous attempts to prevent dengue epidemics using source reduction and truck-mounted insecticide foggers had never been very effective. Because of the urgency, United States authorities proposed aerial application of the insecticide Naled, an organophosphate insecticide that had often been used successfully to control mosquitoes on the United States mainland. Naled had been shown to have a low toxicity to humans and a potency half-life of only about 30 minutes. Initially, Puerto Rican authorities, including the governor and secretaries of health and agriculture, agreed, and a supply of Naled was shipped to the island.

The Puerto Rican public, however, were caught unaware by the arrival of the Naled shipment. There was a general opinion, amplified by the press, that the proposed aerial spraying posed a risk greater than Zika virus and that the populace had been inadequately consulted and prepared. The Puerto Rico College of Physicians and Surgeons was among local organizations concerned about the spraying. Many provincial authorities and mayors, who had not been part of the decision-making, were also sceptical. The seed of mistrust grew rapidly. Some activists believed the strategy was an experiment of a new, untried method on the population, even though aerial spraying of Naled had been successfully and uneventfully used to quell a dengue epidemic in the capital, San Juan, in 1987. Beekeepers and environmentalists questioned the effect of Naled on the environment. In response to large demonstrations and critical press, authorities withdrew their support, and no aerial spraying or application of Naled was done.

The degree to which early use of aerial spraying would have reduced Zika incidence in Puerto Rico is unknown. By mid-2017, there were over 40 000 cases of Zika infection in Puerto Rico, including 3703 among pregnant women, and at least 38 cases of apparent Zika-associated birth defects (85, 86).

Who should be involved in the assessment of the risks and potential benefits of vector control methods?

Vector control measures should be periodically evaluated. These assessments should involve national public health authorities and regulators as well as scientists, ethicists, other experts and community representatives.

Novel vector control measures should be subject to formal environmental and health risk–benefit assessments (87). In many cases, international organizations such as WHO will assess the quality, safety and efficacy of particular interventions as part of their registration or authorization process. However, countries still need to engage in discussions regarding the use of these types of products, taking into account their specific national circumstances (for example, prior experience, laws, values, safety and impact on the environment), and reflect on these findings in their own assessments. In addition, country authorities play the leading role in monitoring the use of vector control interventions and any adverse effects on end users. National-level risk–benefit assessments should be conducted according to each country’s regulatory procedures, if such procedures exist. The international community should assist low- and middle-income countries in building capacity to design, implement and maintain adequate regulatory systems.

Scientists with specific expertise in vector control need to be involved in all levels of risk–benefit assessment. However, other specialties are important as well, including environmentalists, social scientists, economists and physicians. The involvement of diverse types of expertise can help ensure that no one group overemphasizes potential benefits while minimizing risks, or vice versa.

Because the weighing of risks and benefits has an inherent ethical aspect, persons with ethics expertise can also play an important role in the process. By helping to articulate relevant underlying values such as respect for persons or privacy, such experts can help identify potential costs or benefits that might not otherwise be considered. In addition, a focus on values can guide decisions about the type of actions

that should be taken in light of the potential costs and benefits at stake.

Finally, community engagement is an essential component of an ethically acceptable process of risk–benefit assessment. As discussed further below, community engagement is a critical means for sharing accurate information, understanding local perceptions, identifying concerns and misconceptions, ensuring that public health interventions are aligned with community values, and avoiding unjust burdens on vulnerable individuals and groups. Community engagement is also a necessary part of mobilizing communities to take an active role in vector control efforts, particularly those that will require collective action to be successful, for example, controlling mosquito breeding sites such as sources of stagnant water (25). In order to facilitate effective community engagement, communication and transparency by the decision-making bodies are essential.

Is there an ethical obligation to provide access to vector control technologies?

The Sustainable Development Goals (SDGs) call on all countries to achieve universal access to “quality essential health-care services” and “safe, effective, quality, and affordable essential medicines and vaccines” by 2030 (88). Similarly, the United Nations has set a target date of 2030 for achieving the goal of universal health coverage (89). Given the importance of vector control to human health, access to locally relevant vector control methods should be added to this list. Likewise, the human right to health, as enshrined in numerous international human rights treaties (90–96), should be interpreted to include a right to access to basic vector control tools such as insecticide-treated nets and insecticides.

Recognizing a right of universal access to vector control methods does not mean that all countries must provide immediate access to all methods regardless of feasibility or cost. Rather, countries should strive for “progressive realization” of the right to universal access, taking into account other critical demands for available resources (97). For example, as an initial measure, countries could commit to providing access to vector control measures to target populations at a high risk of exposure.



7. Vaccine campaigns and mass drug administration

To date, vaccines have played an important role in controlling some vector-borne diseases. At present, the only vaccines proven to have high levels of safety and efficacy against a vector-borne disease are for yellow fever and Japanese encephalitis virus (98). More research on vaccines and other methods of preventing vector-borne diseases is urgently needed (3).

Mass drug administration has been demonstrated to be effective in controlling some vector-borne helminthic parasites, such as bancroftian filariasis. Mass drug administration seeks to provide treatment to all or most members of an at-risk population. It may include individuals who are infected but asymptomatic, as well as uninfected individuals. WHO-promoted mass administration of ivermectin has eliminated lymphatic filariasis, the cause of elephantiasis and onchocerciasis (river blindness) in much of Africa (99).

Mass drug administration is similar to vaccination in that they both offer potential benefits that extend beyond the individual receiving the intervention. Vaccines do this by making vaccinated individuals immune so that they cannot become infected and transmit the infection to others, ultimately contributing to herd immunity (100). Although mass drug administration does not confer immunity, it can help lower disease transmission by reducing the number of persons harbouring the disease, thereby shrinking the human reservoir from which vectors become infected (101).

Is it ethically acceptable to implement mass drug administration programmes when some or all recipients will not receive direct benefits?

In addition to the expected public health benefits, vaccines and mass drug administration often provide direct benefits to at least some of the individuals receiving the intervention, whether through enhanced protection against future disease or treatment of an existing infection. On the other hand, other individuals might not receive any direct benefits from drugs administered on a population-wide basis. This would be the case for individuals who receive an

antiparasitic drug, despite the fact that they do not currently harbour any parasitic infections.

Researchers are currently exploring the possibility of administering ivermectin on a large scale in communities with a high prevalence of malaria in order to render individuals' blood lethal to mosquitoes (102). In this scenario, the drug would neither be treating an existing condition nor conferring enhanced protection on an individual; instead, its intent would be to render the individuals receiving it poisonous to mosquitoes. While it is likely that some individuals would benefit directly because the drug kills other parasites those individuals happen to be harbouring, the intention of the policy is to kill mosquitoes. Many individuals receiving the drug would receive no direct benefits, but all those who are at risk of mosquito-borne diseases would receive indirect benefits.

In general, the absence of potential direct benefits to all recipients does not, in itself, render a mass drug administration programme ethically unacceptable, as long as the overall benefits to the community (in terms of the reduction in disease burden) are reasonably expected to exceed the risks and burdens involved. Before introducing such a programme, however, decision-makers should consider whether equivalent public health benefits could be achieved without exposing some individuals to risks for which there are no offsetting direct benefits. They should also consider whether the balance of risks, burdens and benefits of the programme are likely to be less favourable for vulnerable individuals or communities (Box 5).

Must individuals be asked for their informed consent before participating in a vaccine campaign or mass drug administration programme?

Like vector control methods, vaccine campaigns and mass drug administration can be justified by the importance of promoting the common good, even if some persons may face risks or burdens that are not outweighed by direct individual benefits. The difference is that, unlike most vector control methods, vaccines and drugs are administered on an individual basis, which makes it possible to offer individuals the opportunity to decide whether to participate. This

Box 5. Mass drug administration targeting lymphatic filariasis in Assam, India

Efforts to eliminate lymphatic filariasis in India have made significant progress through mass drug administration. However, a closer look at the situation in the state of Assam demonstrates that, if methods used to determine eligibility for mass drug administration do not account for high-risk groups within the population, the intervention will fail to eliminate the disease and neglect those most in need.

To stop the spread of lymphatic filariasis, mass drug administration of preventive chemotherapy is used to target areas in India where the disease is endemic. Districts are classed as eligible for mass drug administration when the reported microfilaria rate is higher than 1%, as determined through sampling. In Assam, where lymphatic filariasis is endemic, 96.39% of cases occur in tea garden workers, and their microfilaria rate is much higher than the rest of the population, whether urban or rural, which is less than 1% when tea garden workers are excluded. Despite being a high-risk group, whether tea garden workers are eligible for the intervention depends on the microfilaria rate in their district of residence. Therefore, they will not benefit from mass drug administration in districts where the number of tea garden workers is not high enough to raise the district population microfilaria rate above 1%, which frequently occurs in Assam because tea garden workers are spread across the state rather than being clustered in certain areas.

This example highlights that population-level thresholds (for the use of mass drug administration) might not capture the presence of subpopulations with higher prevalence of infection. In such contexts, public health agencies should compare the expected benefits, risks and burdens of whole-population mass drug administration with more focused interventions in such subpopulations (99, 103).

can be done either through a full process of informed consent or by providing individuals with access to information about benefits and risks and an opportunity for those who do not want to participate to opt out.

In some cases, the importance of achieving universal or near-universal coverage may justify requiring individuals to participate in vaccine campaigns or mass drug administration programmes, with an exception only for those with known medical contraindications that would put them at excessive risk. As with the use of vector control measures, overriding individual autonomy is appropriate only when necessary to achieve important public health interests that could not be achieved equally effectively and efficiently by less restrictive means, and when the expected benefits exceed the risks and burdens involved. Compulsory measures should generally not be introduced without taking into account the community's attitudes and values, which requires a robust process of community engagement.

As discussed above, it is important to consider the potential negative consequences of mandatory measures, which in some cases might outweigh the gains in disease reduction resulting from the use of compulsion. In addition, even if a mandatory programme is warranted, the appropriate level of coercion depends on the circumstances. In most

cases, it will be sufficient to impose strong incentives for compliance, such as repeated requests, public censure or fines. Forcibly administering a vaccine or drug over a person's objections is rarely, if ever, feasible or justifiable, and could contribute to a significant erosion in community trust in public health authorities (53).

Box 6 presents a case study on issues arising from the use of CYD-TDV dengue vaccine.

Is it appropriate to track individuals during vaccine campaigns or mass drug administration programmes to ensure that optimum doses are taken?

Some vaccines or drugs are most effective when administered in multiple doses over a period of time. In some situations, even individuals who receive fewer than the recommended doses may receive some degree of benefit, but public health benefits are often increased significantly when a high proportion of individuals complete a full course of treatment or vaccination. In order to increase public health benefits and avoid wasting limited resources, it is ethically appropriate to keep track of individuals who have not completed a full course of vaccines or drugs and to follow up with such cases. Individuals should be informed when they receive their initial doses that they may be contacted if they do not return for

Box 6. Ethical controversy surrounding the use of CYD-TDV dengue vaccine

Standard vaccination programmes generally confer direct benefits to vaccinated individuals as well as large public health benefits, with only small risk to individuals who are vaccinated. Dengue disease is caused by four closely related viruses, and severe dengue disease usually only occurs when individuals are infected for the second time. The CYD-TDV dengue vaccine became controversial because it provides benefits for seropositive individuals (those who have previously been infected with dengue) but increases risk for seronegative individuals (who have never been infected). The suspected explanation for the worse outcomes of vaccinating those who are seronegative is that inoculation with dengue vaccine behaves like an asymptomatic first dengue infection, “priming” those vaccinated for a second infection.

Therefore, unless pre-vaccination screening is used to exclude seronegative individuals, overall public health gains derived from dengue vaccination involve exposing seronegative individuals to greater risk. This issue is further complicated because people may not know whether they are seropositive or seronegative. No rapid diagnostic tool is available; existing methods of pre-vaccination screening may be too logistically difficult or expensive to be feasible in some places; and screening – even if feasible – may result in false positives, causing a small number of seronegative individuals to be vaccinated by mistake.

The use of the CYD-TDV vaccine thus raises several ethical dilemmas. First, in populations with high prevalence rates, modelling suggests that mass vaccination (without screening) may benefit those who are seropositive and have overall population-level benefits – but this would entail harm to some of those who are seronegative. This creates an ethical dilemma as to whether it is acceptable to maximize overall welfare while knowingly exposing some people to risk.

Second, if seronegative individuals could be identified and excluded, any harm caused to them by vaccination would be preventable, so failure to screen would lead to preventable harm to seronegative individuals. If screening is not technically feasible in the meantime, however, some may argue that the failure to vaccinate would lead to preventable harm to those who are seropositive (and would have benefited from vaccination).

Third, as the purpose and value of vaccines is the prevention of disease, the public may not tolerate a measure that increases the risk of severe illness to some people, particularly when vaccination programmes target children, who are often considered to be an especially vulnerable group (and are more likely to be seronegative). Finally, peculiarities of the dengue vaccine, such as variable risk–benefit ratios and the need for pre-vaccination screening, increase communication challenges, which may erode public trust in and acceptance of other vaccination programmes. In 2017, when further evidence clarified the risk of severe dengue among vaccinated seronegative individuals, the vaccine was already privately available in several countries, and public immunization programmes were under way in parts of both Brazil and the Philippines where dengue is endemic. In the wake of this controversy, public trust in immunization has been damaged in those countries, leading to a rise in vaccine refusal (104, 105).

follow-up appointments and, when feasible, should be given a choice about their preferred method of communication (106). In addition, tracking and follow-up systems should be conducted in a manner that safeguards individuals’ privacy to the maximum extent possible. For example, those who visit individuals at home or in the community should avoid wearing clothing or driving in vehicles that readily identify them as public health workers (53). Finally, the entity responsible for managing the system should minimize risks to privacy, for example by using pseudonyms in records and establishing clear rules for accessing individually identifiable information (107).

What obligations do governments and donors have to ensure the quality of vaccines and drugs used in vaccine campaigns and mass drug administration programmes?

Government officials have an obligation to promote the health and well-being of their citizens. As a result, those responsible for vaccine campaigns or mass drug administration programmes, as well as any donors who support these efforts, should have reasonable confidence in the quality of the vaccines and drugs that will be used. This requires careful procurement practices to avoid the inadvertent use of counterfeit or substandard products, as well as oversight of all aspects of the storage, transportation and distribution process. The international community should assist countries in building capacity to create strong health infrastructures capable of supporting these efforts.



8. Screening and surveillance

Use of fish in water storage containers for larval control to prevent dengue outbreaks, Cambodia.
Source: WHO / Stephanie Hollyman

WHO defines public health surveillance as “the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice” (108). As recognized in the *WHO Guidelines on ethical issues in public health surveillance*, countries have an ethical duty to engage in these activities because, “without public health surveillance systems, population health cannot be protected and inequalities cannot be adequately addressed” (35). In addition, once surveillance data have been collected, countries “have the moral duty to use the data actively to promote better health outcomes” (35). This duty includes the obligation to share surveillance data with relevant public health officials and others involved in disease prevention and control efforts, in a manner consistent with ethical and legal principles regarding the protection of individual confidentiality.

Surveillance of both vectors and vector-borne diseases is important because many individuals infected with vector-borne disease pathogens are asymptomatic or have symptoms that are clinically too mild to be reported. Thus, the early identification of disease outbreaks requires the ongoing collection, analysis and interpretation of data about infection

prevalence, vector movement and environmental risk factors. For this reason, vector surveillance is one of the four foundations of the World Health Assembly-approved Global Vector Control Response Strategy for 2017–2030 (1, 2).

Screening is defined as “the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population” (109). Screening is sometimes employed as a part of surveillance, for example when a population is tested for a vector-borne disease as part of an outbreak response effort. Screening can also be used for non-surveillance purposes. For example, a community health clinic might offer screening for vector-borne diseases to at-risk individuals in order to promote early access to care.

Under what circumstances is the surveillance of private living spaces to identify vector sources ethically acceptable?

The surveillance of private living spaces to identify vector sources is an important component of vector control programmes. For example, the traditional

Box 7. Better practices for safer water storage: compulsory vector control measures and targeted surveillance in India

In 2017, the south Indian state of Tamil Nadu suffered a major dengue outbreak during which there were 23 294 infections and 65 deaths. Compulsory entomological surveillance and antilarval measures, both of which involved public health workers entering private households, successfully reduced incidence of the disease. However, the top-down, invasive and punitive nature of these interventions also raised ethical concerns.

First, entomological surveillance frequently targeted areas close to state borders, where people are often poor and disadvantaged by lack of access to many public services and facilities available in more affluent areas. While surveillance data benefited all residents of Tamil Nadu, repeated entry into people’s homes in the targeted areas disproportionately burdened an already vulnerable group, raising questions of social justice, equity and reciprocity.

Second, as *Aedes* mosquitoes breed in container water, the government sought to prevent larval breeding by eliminating domestic sources of stagnant water through door-to-door inspections of households and removal of any unsafe water. However, this measure caused considerable resentment because inspections often took place without residents being forewarned. Public health officials were authorized to break into any homes they found locked and issue legal notices to penalize non-compliant households with fines or imprisonment. Water is scarce in the drier regions of Tamil Nadu, so emptying water containers angered the public. Removal of domestic water sources also disproportionately burdened women, who walk long distances to collect water for their families, which was then wasted. Moreover, this left women, who were predominantly homebound, without access to water, unlike men who had alternative sources of water outside the home, such as at their workplaces.

Whenever feasible, policy-makers should consider relying on less burdensome, more respectful measures to prevent mosquitoes from breeding, such as encouraging the public to keep larvae-eating fish in water containers, to empty and clean water containers once a week, or to add safe larvicides to water not used for drinking (113).

method of surveillance for *Aedes aegypti* involves periodic household inspections for larvae-bearing containers (110), which was found in a study to be associated with reduced odds of mosquito larval habitat reports (111). In addition to house-to-house inspections, drones or satellite imagery are sometimes used to identify stagnant sources of water. This process can generate high-resolution imagery of individuals' homes (112).

In general, before public health workers inspect private living spaces for potential vector sources, they should seek the consent of the property owner or occupant. If the owner or occupant is absent or unwilling to allow the inspection, a judicial warrant or similar type of authorization should be obtained, except in an emergency situation. Such authorization should be granted only if there is a genuine public health

need for the inspection that outweighs the burdens on the owner or occupant. The ethical obligation to obtain consent or an external authorization does not depend on whether the inspection involves a physical intrusion to the property; for example, it applies equally to aerial inspections by drones. Countries should assess their laws and policies related to surveillance of private living spaces to ensure that they conform to these ethical principles (Box 7 and Box 8).

Individually identifiable surveillance data should not be shared with law enforcement agencies without express legal authorization, which should be granted only in compelling circumstances. Inappropriate sharing of surveillance data with law enforcement threatens the public's trust in public health surveillance, thereby creating a disincentive for individuals to seek health care or to report information honestly (35).

Box 8. The eye in the sky: use of drone technology for disease surveillance in Singapore

Drones allow their users to collect data from the skies. An area in which drone technology use has experienced growth is the control of arboviral diseases such as dengue, Zika virus, chikungunya and yellow fever. These diseases are conveyed to humans by mosquitoes. One of the most important objectives in control efforts is the elimination of arbovirus-carrying mosquitoes that breed in standing water.

The National Environment Agency is responsible for the control of arboviral disease transmission in Singapore. It adopts a multipronged strategy that integrates national disease and entomological surveillance, prevention and control, legislative measures, community advocacy and research. Public health inspectors from the National Environment Agency carry out routine and outbreak-related inspections of public and private premises to identify and eliminate mosquito larval habitats. A major challenge is the identification of standing water in structures and containers beyond the visual acuity of the inspectors. Since 2015, the National Environment Agency has incorporated drone technology into its inspection regime to facilitate inspections of hard-to-reach areas. Because of its potential widespread impact on the community, the use of drones is undertaken with high regard for public safety and ethical concerns.

In Singapore, only public health inspectors who are licensed by the Civil Aviation Authority of Singapore are allowed to pilot drones for regulatory inspection work. Individuals must pass an examination before the licence is granted. The use of drones requires two licensed pilots, with one taking the controls and the other acting as a safety officer. The most common use of drones is the surveillance and larvicidal treatment of areas for standing water that cannot be reached without a ladder – this is usually on rooftops but may also include other building structures.

Before a drone is used for inspection, authorization must be granted by the Civil Aviation Authority of Singapore. At the site of deployment, permission is obtained from the owner or occupier of the premises before the drone can take flight. If permission is denied or the owner or occupier is absent, the drone cannot be deployed. To minimize the infringement of privacy, the most direct path to the target area is taken, carefully avoiding windows if possible. To avoid issues of data confidentiality, the video footage is streamed directly onto a screen visible to the drone pilot and is not stored. Once the target area is within sight, a still shot of the potential mosquito breeding habitat is taken and shown immediately to the owner or occupier of the premises for reference before it is deleted.

The use of drone technology in the implementation of measures aimed at reducing vector-borne diseases will continue to grow and gradually replace the use of human resources to varying degrees. Vector control policy-makers and practitioners that rely on this technology must remain accountable in order to build community trust in its safe and ethical use.

Under what circumstances is it ethically acceptable to use human movement data as part of vector control surveillance programmes?

Monitoring human movement, for example through global positioning system (GPS) tracking on cellular phones, may provide useful information about the geographical distribution of vector-borne diseases and can help predict gaps in the coverage of control measures for outbreaks (3, 114). However, such monitoring should be approached with caution, particularly when applied to vulnerable populations such as refugees or traditional pastoralists. Engagement with communities, as discussed further below, is critical to developing surveillance and response efforts that are sensitive and non-stigmatizing to individuals, communities and cultures. Moreover, the results of surveillance activities should be shared with the relevant community, except in exceptional circumstances when doing so might cause significant harm (35).

At a minimum, individuals and communities should be informed if GPS data on phones or devices will be used for public health surveillance, and any identifiable information collected should be appropriately secured (Box 9) (35).

Under what circumstances is it ethically acceptable to disseminate surveillance maps indicating the location of vectors?

Surveillance maps with information about the location of vectors, or of individuals affected with vector-borne diseases, can benefit the public by letting individuals know if they are living in or entering a high-risk area. Providing such information can be a useful tool in a comprehensive vector control programme. To protect personal privacy, information in surveillance maps should be aggregated and de-identified to the maximum extent possible; for example, one option is to delete the last several digits of GPS coordinates from data that are presented on publicly available maps. However, it should be recognized that even aggregated and de-identified information can be stigmatizing to residents and affect property values. Before disseminating surveillance maps, it is important to consider whether the potential benefits to the public outweigh these risks.

Ensuring the accuracy of surveillance maps is also an important ethical consideration. In some cases, maps may be based on faulty assumptions; for example, it can be misleading to track the locations of individuals based on mobile phone usage in settings where mobile phones are routinely shared.

Box 9. Use of human movement data to show spread of Zika virus in Singapore

During the 2015–2016 Zika virus epidemic, Singapore reported 460 cases. Of these, 64.8% occurred in a cluster in the Aljunied Crescent area at the beginning of Singapore's outbreak in 2016. Retrospective analysis of anonymized human movement data from call data records found that local transmission of Zika virus was higher in places where people had moved from the Aljunied Crescent. This supports the view that human location data from mobile phone use can be utilized to mimic population movement during an outbreak and identify areas at risk of transmission, thereby providing a powerful tool to control the spread of infection.

Through the use of call data records, researchers were able to categorize mobile phone users into residents, visitors and construction workers within the Aljunied Crescent cluster area and compare the movements of these three groups with case study data provided by the Ministry of Health. Human movement data indicated that visitors and residents in the Aljunied Crescent area were probably responsible for transmission of Zika virus to other areas. Early in the outbreak, cases were particularly high among construction workers in the cluster, supporting their inclusion as a group in the study. This study finding also emphasized the need to address the vulnerability of construction workers, who, due to the transient nature of their stay, may reside in living conditions that increase their risk of disease acquisition.

The use of human movement data such as call data records can result in ethical and data privacy concerns. To minimize these concerns, individual-level data should be de-identified and aggregated prior to analysis whenever it is feasible to do so (114–118).



Meteorological, socio-economic, environmental and socio-sanitary factors and the transmission of malaria and schistosomiasis in Korhogo, Côte d'Ivoire.

Source: WHO / TDR / Andy Craggs

Disseminating unreliable surveillance maps is ethically problematic because it leaves individuals with an inaccurate understanding of their risk of exposure and contributes to overall distrust in the public health system.

What ethical issues are raised by population screening for vector-borne diseases?

As noted above, vector-borne disease screening can be conducted either as part of public health surveillance or to provide health information to a specific population. When screening is conducted for surveillance purposes, such as mass blood screening conducted during an outbreak response, the purpose is primarily to generate information about the prevalence of a disease. However, when screening reveals a vector-borne disease that could benefit from medical intervention, individuals who test positive have the right to be informed of the results. When possible, such individuals should be provided with access to further diagnosis and treatment; at a minimum, they should be given information about the health care options that are available to them.

Before screening, individuals should be told whether they can expect to receive the results of any tests performed, and about the possibility and significance of false positives or false negatives.

Unauthorized disclosure of individually identifiable screening results exposes persons to risks of stigmatization and discrimination. Thus, information generated through screening should be used only for the benefit of the individual or for legitimate public health purposes. The confidentiality of such information should be safeguarded, as for any other medical information.

The manner of population screening for vector-borne diseases depends on a variety of context-specific factors, including population density, access to transportation, and availability of needed personnel and equipment. Depending on the epidemiological situation, house-to-house screening can be an appropriate option. House-to-house screening should be conducted in a manner that is respectful of individuals' privacy to the maximum extent possible. For example, screening teams should avoid knocking on doors when residents are likely to be sleeping.

Individuals who refuse to participate in surveillance should be informed of any negative consequences (for example, fines or other penalties), but they should not be subject to harassment.

Under what circumstances can travel screening for vector-borne diseases be ethically justifiable?

In most situations, travel screening is not an effective means of preventing the spread of vector-borne diseases. In addition to the logistical burdens involved, a large number of infections are likely to be missed by non-invasive screening as a result of incubation periods, asymptomatic or minimally symptomatic infections, and the fact that not all persons who cross borders do so at official points of entry. However, travel screening could potentially be justified when a particular route has been identified as a likely source of introducing a particular pathogen to an infection-free area (119). When travel screening is used, individuals should be selected for screening based on medically justifiable factors, and the screening process should be conducted in conformity with the International Health Regulations (2005) and applicable national laws (120). Screening should never be carried out as a subterfuge for denying entry to migrants or other populations (53).

How should blood or organ donation programmes make decisions about screening for vector-borne diseases in high-prevalence settings?

Vector-borne diseases, like other infectious diseases, can be transmitted to individuals who receive blood, blood components, tissues or organs from infected donors. This creates risks for individual recipients and public health.

Blood banks have inconsistent practices and policies regarding screening donors for vector-borne diseases (121). Ideally, in settings where a vector-borne disease is present, individuals should not be accepted as blood donors if they are infected with a transmissible pathogen. At a minimum, prospective donors should not be accepted if they manifest symptoms of the disease or fall into high-risk groups as determined through questioning. In addition,

all blood should ideally undergo screening for the prevailing endemic infectious agents (for example, malaria), as well as pathogen inactivation if such methods are available (122–129).

The problem is that, in some settings with a very high prevalence of vector-borne diseases, following this process would result in excluding the vast majority of donor blood, resulting in an insufficient supply for patients in need of transfusion. Depending on available resources, it may be possible to mitigate this problem by using more sophisticated tests that can directly detect the presence or absence of the infectious agent. However, these tests might not be available in low-resource settings; moreover, even when they are available, the supply of uninfected blood may still be insufficient to meet the demand.

In these situations, blood transfusion programmes should weigh the risk of disease transmission resulting from accepting potentially infected blood against the risks associated with having an insufficient supply of blood available for transfusions. In making this assessment, they should take into account factors such as the severity of the disease in question for transfusion recipients, the availability and efficacy of diagnostic methods and treatments for recipients who become infected, and the likelihood that recipients are already infected or will become infected with the disease by means other than transfusion. It is also necessary to consider whether a policy of accepting potentially infected blood might decrease community trust in the health system generally or the blood donation system in particular, potentially deterring individuals from becoming donors or agreeing to receive transfusions when needed.

Blood transfusion programmes and health care providers should also seek to avoid unnecessary blood transfusions by implementing evidence-based patient blood management programmes. Doing this is important in all settings, but it is particularly necessary in situations where the safety of the donor blood supply cannot be ensured.

Finally, as with all screening programmes, asymptomatic blood donors who are identified as carriers of a treatable vector-borne disease as a result of questioning or serologic testing should be informed of this fact and offered access to treatment.



9. Research

Community members in Salto, Uruguay, engaged in the management of a research programme on mosquito breeding and dengue transmission.
Source: WHO / Sebastian Oliei

There is an urgent need for more research on vector-borne diseases. In addition to basic scientific research, priority research areas include vaccines, vector control and other preventive measures, surveillance techniques, the use of data to predict disease outbreaks and disease severity, social science research on the role of human behaviour in disease transmission and prevention, and strategies for designing effective community engagement and educational campaigns.

Research should not be considered a stand-alone enterprise, but instead should be integrated into all aspects of public health practice and health service delivery. For example, implementation research should be done before, during and after public health initiatives such as mass drug administration, distribution of insecticide-treated nets, or indoor residual spraying programmes (130). Research efforts should be tailored to the needs of particular countries and settings.

What factors should researchers and research sponsors consider in designing and conducting collaborative international research?

Collaborative international research should be conducted in a manner that ultimately improves local research capacity in low- and middle-income countries. To this end, when research projects come from abroad, local investigators should be involved as collaborators as early on in the process as possible. In addition, an ongoing process of community engagement is essential to ensure that studies respond to questions of local public health importance. In trials of new technologies, this process should include efforts to determine whether those technologies, if successfully developed, would be deemed acceptable in light of local attitudes and values.

Collaborative international research should be designed so that the populations in which it is carried out stand to benefit from the results. Thus, research

should lead to technology transfer, whenever applicable, for the benefit of the local community, along with access to any necessary ancillary resources, such as diagnostic tools. If capacity to implement new technology is lacking, the sponsors, researchers, institutions and governments involved should specify the capacity-building efforts that will be undertaken, as well as any additional resources that will need to be provided in order to make the technology available throughout the community on an equitable basis.

What sources of ethical guidance are relevant to vector-borne disease research?

Human studies on vector-borne diseases should adhere to relevant international standards on research involving human participants. Those standards have been articulated in numerous international documents, including guidelines from WHO, the Council for International Organizations of Medical Sciences (CIOMS), and the World Medical Association (54, 131–133).² In addition to ethical guidelines on research involving human participants, various organizations have issued guidance on ethical issues for research with animals, including CIOMS, the Nuffield Council on Bioethics, and the Norwegian National Committees for Research Ethics (134–136). Guidance also exists for research integrity issues, including standards for data practices and management and publication practices (137). Finally, several organizations have issued specific guidance on ethical issues related to research on genetic modification of vectors, including WHO (on behalf of the Special Programme for Research and Training in Tropical Diseases), the United States National Academies of Sciences, Engineering, and Medicine, and a coalition of public and private sector organizations that are sponsors or supporters of gene drive research (138–140). Those responsible for designing, conducting or reviewing research on vector-borne diseases should familiarize themselves with these resources.

² Additional guidance on ethical issues in research can be found in documents related to research on specific diseases. See for example UNAIDS/WHO guidance document on *Ethical considerations in biomedical HIV prevention trials* (133).

Does guidance on informed consent and community engagement in global research ethics documents apply to genetically modified vector research?

The World Medical Association Declaration of Helsinki and the CIOMS International Ethical Guidelines for Health-Related Research Involving Humans both provide guidance on informed consent and community engagement. However, it is not clear whether either is applicable to research focused on gene drive constructs aimed at reducing or altering vector populations (141). The Declaration of Helsinki characterizes itself as “addressed primarily to physicians” and restricted to “medical research”. The 2016 iteration of the CIOMS International Ethical Guidelines does not restrict its guidance primarily to physicians or biomedical research but describes its current scope as “confined to the classic activities that fall under health-related research with humans, such as observational research, clinical trials, biobanking and epidemiological studies”. Neither of these guidance documents is thus apt for genetically modified vector field research, which is multidisciplinary in nature and involves a different testing and development pathway to clinical trials and “classic” human research activities (141). Similarly, the testing of area-wide vector control methods does not conform to the clinical trial model of soliciting individual informed consent (142). Accordingly, additional guidance related to genetically modified vector research would be useful (142, 143).

Can it ever be ethically acceptable to conduct research on vector-borne diseases without obtaining individual informed consent?

International guidelines on research ethics provide that, in most cases, human beings should not be involved as participants in research without their individual informed consent. The process of informed consent includes giving prospective research participants information about the potential benefits and risks of and alternatives to research participation, and ensuring that they are in a position to make a voluntary decision. It is also important to confirm that participants actually understand the information that they have been given.

In some cases, it can be ethically acceptable to conduct research without obtaining individual informed consent. For example, most ethics guidelines recognize that individual informed consent is not necessary when it would be impracticable to obtain due to the nature of the research design, provided the study involves no more than minimal risks and other safeguards are included to protect participants’ rights and welfare (54). One example of such a situation is certain types of cluster randomized trials, in which groups of participants are randomly assigned to receive different interventions (54). This kind of design might be used in some types of vector-borne disease research, such as a study comparing different protocols for outdoor insecticide spraying in different urban settings. In studies such as this, a research ethics committee could waive the requirement of individual informed consent if it determines that the risks to participants are minimal and other relevant protections are in place, including an appropriate process of community engagement (141).

To what extent does the notion of individual informed consent apply to gene drive field trials?

An individual qualifies as a research participant and should normally give informed consent as a condition of their participation if:

- they are directly intervened upon by an investigator;
- they are deliberately intervened upon via manipulation of their environment by an investigator;
- they interact with an investigator for the purpose of collecting data;
- an investigator obtains identifiable private information about the individual for the purpose of collecting data (144).

Based on these criteria, caged field trials or open releases of modified vectors in the context of a research trial would not satisfy the requirements of the first two criteria, since no individual is intervened upon directly or deliberately, even if they live in close proximity to the cages or release sites (138).

This is because release trials typically involve male mosquitoes, which do not bite humans. Accordingly, simply living in the vicinity of a genetically modified mosquito release is not sufficient grounds to require informed consent from any individual for an open release of mosquitoes (138, 142).

Even when gene drive research does involve direct interventions on individuals, written informed consent will not always be required. For example, it may be unnecessary to obtain written consent to access homes for the placement of vector traps or collecting vectors in the context of genetically modified vector trials, as people often allow visitors into their homes without a formal consent process; only the oral agreement or authorization of the inhabitant is usually required in everyday life (145).

On some occasions, written informed consent may be necessary, but not at an individual level. For example, in some studies, vector placement in, or collection from, households may be linked to GPS data, which would be required for spatial analysis of the spread and species composition of vectors after release. When GPS data are highly precise, they will tie the associated vector data to specific households. Since it is the *household* that is identified, and not an *individual*, the consent of the head of the household or their designate is more appropriate than a requirement for all members of the household to provide informed consent. Such reasoning may be problematic, however, if only one individual lives in a household. In such instances, the sole occupant of the household may be indirectly identifiable at an individual level.

However, the notion of household consent may be problematic because of the implicit power dynamics within a household (146). For example, consent on behalf of the household is often given or refused by the male head of the household, which may reflect a patriarchal bias. Household consent may also not be appropriate when more than one mentally competent and autonomous adult or family shares a household and no single adult person is deemed to be a representative of the household. In such instances, one adult may give household consent on behalf of other mentally competent adults in that household who hold different views on the provision of consent. Reliance on household consent may also

be problematic if a child is the head of the household. In such a situation, a child may not have the legal right to give consent on behalf of other children or mentally incompetent adults in that household (147).

Why is community and stakeholder engagement important in gene drive field research and how should engagement processes unfold?

Researchers have an ethical obligation to advance trustworthy gene drive science, and community engagement is an essential part of achieving this goal. Engagement should never be regarded as simply a series of minimum actions or steps to be taken to facilitate the conduct of gene drive science (141). Instead, the establishment of trust between researchers and sponsors on the one hand, and stakeholders, the public and communities on the other hand, is morally important in its own right (141). Engagement is also a means of empowering community members to play an active role in the research process, which can generate important insights into the way in which the research is designed and conducted.

There may be many individuals living within a trial site who are not, in a traditional sense, subjects of the research at hand, but who nonetheless may be affected by the conduct of research. Community engagement addresses ethical obligations to these people, including undertaking procedures that would be expected to identify them, advising them that they may have interests at stake, finding out what concerns they may have, responding to those concerns, and reaching some form of agreement about whether the trial should proceed.

It is important to reflect on who should drive or steer community engagement processes and why building trust in proposed gene drive field sites is an important goal worth pursuing (148). In light of the complicated matters concerning community engagement and ethics that are inextricably linked with gene drive technology, and because researchers and sponsors may be conflicted in driving the engagement process, an ethics advisory group comprising experts external to the project is an important mechanism to supplement the input from

community advisory boards or other community engagement activities (149).

Trial authorization by the hosting community and, potentially, peripheral communities that may be affected may also be necessary (148). Because the nature of community authorization will vary in different contexts, it is essential to investigate what the community itself considers to constitute a valid authorization. Therefore, identification of key stakeholders and community representatives is vital, and early and ongoing engagement with these parties is essential (148).

Community engagement does not imply advocacy, and it should not be conflated with or mistaken for public relations or marketing (149). Researchers should have a plan for interacting with those who do not agree with the conduct of research on gene drive vectors in their community. Trustworthiness of the information shared – including the potential risks and benefits of gene drives relative to alternative control options, and who develops and assesses the risks for gene drive applications – is crucial to informing public perception of gene drive science (75).

What factors should be considered in risk management of gene drive research?

Gene drive applications offer the promise of major reductions in disease burden (150). However, gene drive research has faced social resistance based on the concern that engineered vectors could spread beyond intended boundaries to communities or areas where the idea is not welcomed. While some methods for retrieving synthetic gene drives are being developed (151, 152), more attention needs to be paid to the challenges that might arise if released gene drives need to be recalled. Other concerns centre around the absence of a firm international regulatory framework, and the potential evolution of resistance in mosquito populations that will stop the gene from spreading.

Unforeseen negative consequences of a genetically modified vector release are risks that cannot be managed with the solicitation of informed consent alone. Risk assessment should be grounded in the protection goals established by the countries that would host the testing or use the technology (149). Such assessment should cover not only

environmental and health risks, but also social and economic risks (153, 154). Given that the risks that the research team identifies as most significant may not align with those of greatest concern to the lay public, investigators and funders must plan for how public input on perceived risks can be solicited and integrated with the proposed study. Site selection must consider issues such as necessary entomological conditions and adequate access to local, technical and regulatory expertise, as well as appropriate isolation. Small-scale release sites should ideally not be located in close proximity to national borders (149). Confinement strategies, safeguards, and appropriate governance for use are also critically important components of gene drive research (64). Beyond potential risk, researchers working on gene drives must also broadly assess the technology's potential impacts, including societal impacts, public perception and acceptance, ecological and health impacts, and biosafety and biosecurity issues, as well as how regulation and other forms of governance might manage the risks and promote the benefits (64). Each setting will require a bespoke risk assessment and mitigation plan.

An external risk assessment, conducted by qualified individuals with no vested interest in the success of the product, is essential for building community, stakeholder and public confidence. The results of the risk assessment should be made publicly available in the interests of transparency, and to facilitate trust-building between the research team and the community. Funders should be prepared to support the costs for risk assessment and environmental monitoring as integral parts of the overall research plan.

Risk assessment must be re-examined and updated before moving forward along the testing pathway to take into account any changes in human or environmental exposure, additional data, and any further public concerns. Such risk assessment should occur independent of, and not supersede, the risk assessments of the proposal performed by regulators. Genetically modified vector studies should also develop a risk mitigation plan. After a decision to implement genetically modified vectors has been taken, there will be a need for ongoing surveillance, monitoring and evaluation.

Researchers, funders and government authorities should work together to reach an understanding on potential liability and remediation measures before trial commencement (149).

Box 10 presents an example of how the World Mosquito Programme deals with the matter of informed consent in field trials.

Box 10. The World Mosquito Programme: informed consent in field trials

Wolbachia-based open field trials offer an example of how the introduction of an experimental intervention in a field trial context may or may not necessitate the solicitation of individual informed consent. The World Mosquito Programme (previously the Eliminate Dengue Programme), an international research programme focusing on open field releases of *Wolbachia*-infected mosquitoes, has developed bespoke approaches to the solicitation of informed consent in their open field trials in Australia, Indonesia and Viet Nam (141, 155–160).

In Australia and Viet Nam, World Mosquito Programme investigators deemed the solicitation of informed consent from at least one member of a household a prerequisite for the release of *Wolbachia*-infected mosquitoes on that household's property (141). In Indonesia, *Wolbachia*-infected insects were released in public areas near households without the consent of nearby households, or on a household's property with the consent of a household member (141).

The World Mosquito Programme has developed a public acceptance model of engagement to cultivate community support for its research activities (161). Such a model has been scaled for a citywide deployment of gene drive mosquitoes and could be used cross-culturally for future deployments in other settings, with appropriate local adaptation. The public acceptance model is premised on the following “public participation principles”.

- **Respectfulness:** caring for and heeding the interests and concerns of others.
- **Inclusiveness:** making an effort to include everyone within its scope.
- **Transparency:** being clear, open, and not hiding anything.
- **Responsiveness:** showing that requests or concerns have been heard and trying hard to accommodate them.
- **Honesty:** telling the truth, not trying to deceive or allowing untruths to prevail.

Each principle is linked to one or more “measures of success”.

The public acceptance model consists of four key components:

- **Raising awareness.** This is achieved by providing information to residents and key stakeholders about the programme. These activities included face-to-face meetings, media events, stalls at community markets, community presentations utilizing existing community networks such as community associations, information kiosks in public spaces, traditional and electronic mail-outs of information letters and deployment coverage updates, a public billboard and newspaper advertising, a school outreach programme and a social media incentive programme.
- **Quantitative surveys.** These surveys measured community awareness and acceptance. Each telephone survey was undertaken at roughly six-month intervals.
- **Issues management system.** The system allowed community members to easily contact the programme with questions or concerns and have them addressed by programme staff typically within 24 hours of receipt. This also allowed residents to opt out of direct participation if they had concerns.
- **Community reference group.** The group consisted of respected community members from key stakeholder groups and included representation from the local city council, provincial health officials, the local indigenous community, the defence force, local businesses, community development and environmental groups, the tourism sector and the education sector. The reference group's primary function was to independently review the World Mosquito Programme's activities to ensure that it had carried out engagement in accordance with its commitments and stated public participation principles. The reference group was also kept regularly updated on the latest results of the programme.

While the World Mosquito Programme's approach provides a helpful template for the conduct of other gene drive field trials, investigators of genetically modified vector trials should devise their own bespoke community and stakeholder engagement processes, and consider conducting preceding social science research, to gauge perspectives of the host community on the technology (75, 141). Published guidance on stakeholder engagement practices specific to area-wide vector control methods may be helpful in developing such engagement strategies (139, 141, 148, 149, 157).

Under what conditions are human challenge studies with vector-borne pathogens ethically acceptable?

Human challenge studies – that is, studies in which healthy people are intentionally infected with a pathogen or other microorganism – have a long history in the study of vector-borne diseases. At first glance, the idea of deliberately causing infections might seem ethically problematic. However, a general consensus exists that these studies can be ethically acceptable if the risks are limited and justified by the potential scientific benefits, and the participants are in a position to provide voluntary, informed consent (3).

Challenge studies are particularly useful in developing vaccines, as they enable multiple vaccine candidates to be first tested with a small number of participants in a controlled clinical environment. Then, those that show sufficient promise can be tested in large-scale field trials in endemic areas. By making it possible to subject a larger number of candidates to preliminary testing, this process potentially increases the efficiency of vaccine development, thus enabling public benefits to be achieved sooner than might otherwise be possible. In addition, it substantially reduces the total number of persons exposed to risk, because field trials are conducted only after a candidate has already shown promise in smaller studies (162). There can thus be strong ethical reasons in favour of conducting challenge studies, including in endemic settings.

In most cases, challenge studies are similar to early stage drug toxicity studies in that they expose healthy individuals to risks without any possibility of direct medical benefit. However, in some cases, participation in challenge studies might have direct benefits for healthy persons in countries where the disease in question is endemic. This would be the case if “(i) controlled infection leads to protective immunity against endemic diseases that otherwise would have put them at risk and/or (ii) [a human challenge study] involves infection with a locally prevalent pathogen which participants might otherwise have been infected with later; but controlled infection (yielding immunity) leads to less severe illness than would otherwise be expected (in light of the controlled timing of infection,

early diagnosis, monitoring, and care provided during the study)” (163).

Challenge studies should be performed with particularly stringent informed consent processes. Since these studies are complex and may involve significant risks, participant understanding should be tested during the consent process – this is standard practice in contemporary challenge study research (164). In addition to ensuring that the risks of such studies are minimized and reasonable in relation to the anticipated scientific benefits, research ethics committees should consider whether to define a locally acceptable upper limit to the total level of risks to which participants are exposed. As in all studies involving a potential risk of harm, mechanisms should be in place for compensating any participants who suffer injuries and ensuring that they receive appropriate medical care.

Research ethics committees should carefully review any financial incentives offered to study participants. At a minimum, such payments should be adequate to compensate participants for their time and out-of-pocket expenses, such as transportation costs. Since challenge studies sometimes require large time commitments (for example, inpatient stays), they are frequently associated with relatively high levels of payment that are nonetheless widely viewed as ethically appropriate (164). Some ethics committees might decide to prohibit additional incentive payments because of concerns about undue inducement. Others might reasonably decide to allow such payments in order to incentivize participation and dispel the “therapeutic misconception” – participants’ mistaken belief that research studies are primarily designed to provide a therapeutic benefit to them (165, 166).³ In determining the appropriateness of providing incentive payments, researchers and ethics committees should consider the attitudes and values of the population from which participants will be drawn; doing this requires a carefully designed process of community engagement.

Because challenge studies involve deliberately causing infections, they pose risks not only to the participants but also, in some cases, to third parties. It is therefore important to ensure that they are conducted under circumstances in which risks to third parties can be adequately contained. In some cases, this will require

3 For an argument that “there are no moral limits on the amount of risk or money participants should be allowed to accept to take part in clinical trials”, including challenge studies, see Anomaly and Savulescu (166).

conducting such studies in inpatient settings. When third-party risks are significant, appropriate infection control measures should be implemented as part of the research protocol. Where appropriate, research ethics committees should consider requiring researchers to seek approval from local public health authorities, and inform, and possibly obtain the consent of, identifiable third parties known to be at heightened risk from the study (for example, family members of participants).

It can be important to conduct human challenge studies in settings in which the disease of interest is endemic in order to evaluate how the immune response differs among individuals previously exposed to the pathogen and, particularly, how vaccines and other interventions work in the populations most at risk. In addition, appropriately designed studies conducted in endemic settings may pose below-average risk to participants, as some individuals may already have immunity to the pathogen based on previous infection or genetic factors. However, conducting human challenge studies in endemic regions also raises special ethical

challenges. For example, third-party risks may be higher where challenge studies are conducted without inpatient isolation in areas with vectors capable of transmitting the pathogen being studied (167). Many persons in these settings also suffer from additional sources of vulnerability, such as poverty or membership of stigmatized groups. Moreover, in some regions, there may be high levels of distrust in research, particularly when it is undertaken by foreign entities. Engagement with local communities in the design and implementation of challenge studies is therefore particularly important.

In light of the importance of challenge studies to the development of vector-borne disease vaccines, countries should ensure that their laws and regulations do not explicitly or implicitly make it impossible to conduct them (for example, through broad criminal prohibitions against infecting individuals with infectious diseases).

Box 11 presents a case study of a malaria human challenge study in Nairobi, Kenya.

Box 11. Malaria human challenge study in Nairobi, Kenya

Conducting malaria challenge studies in endemic countries helps ensure that data generated are applicable to similar populations that will ultimately receive malaria interventions, which may not be the case if the genetic traits of research participants or their previous exposure to malaria differ substantially from those of the population where the interventions will be used. The Hodgson et al. 2014 study (168) in Nairobi involving falciparum malaria was the first human challenge study performed in Kenya and was based on years of similar trials done at the Walter Reed Army Institute of Research in Washington, DC (169). To inform the conduct of future studies, the authors outlined lessons learned from the study.

First, investigators implemented measures to minimize risks to participants. Extensive screening was used to exclude potential participants with conditions that would result in unacceptable risks related to malaria infection. However, the study also included measures to avoid unfairly excluding groups from participating in the study. In addition, inpatient monitoring was used to prevent participants from experiencing delays in accessing medical care due to Nairobi's traffic conditions. Risks were further reduced by the short length of the challenge infection and universal treatment of participants either once diagnosed or when the study finished. Investigators also highlighted the necessity of support from institutions experienced in conducting malaria challenge studies to ensure participant safety.

Second, risks to the community were also minimized because it was an inpatient study and Nairobi itself lacks mosquito vectors of malaria.

Third, care was taken to ensure adequate informed consent. Investigators emphasized the need for thorough information sessions, and prospective participants were stringently tested for understanding before enrolment was permitted. Researchers initially aimed to recruit medical students but ultimately enrolled a wider range of participants.

Fourth, investigators reported the payment amount given to participants and how this was calculated relative to local wages to fairly compensate for time and burdens without constituting undue inducement. Payments attracted some negative attention in the media, to which the institution responded by further clarifying the decision-making process.

Fifth, the study was registered with the Pan African Clinical Trials Registry and approved by local and international ethics committees. The authors reported the stages and time taken for ethics committee review and regulatory approval.

Finally, investigators emphasized the importance of early, multidisciplinary engagement with key stakeholders and of incorporating the views of the local community (164, 168–170).

What safeguards should be employed in studies involving the use of human landing catches?

Human landing catches involve the participation of individuals who act as “baits” for mosquitoes. This method has been used in the past as a standard method for estimating infection rates and human biting rates (3). Many of those who serve as bait in human landing catches come from low-status, marginalized populations, and they may therefore assume these roles in order to obtain food, shelter or similar benefits (171, 172).

Individuals who serve as human landing catches should be specifically trained for this activity; generally in good health; clearly informed of the risks they are assuming; and given vaccines, chemoprophylaxis or treatment as appropriate (173). In addition, they should be ensured compensation for any injuries they suffer as a result of being a landing catch. Policy-makers should consider limiting how frequently individuals can serve as human landing catches (174).

Many ethics review boards no longer allow such collections, regardless of conditions. There are a variety of methods, such as Shannon traps, that allow the quantifiable capture of mosquitoes attracted to an individual while protecting the person from being bitten (175). Studies relying on quantifying direct human–mosquito contact should try to use an indirect trapping method instead of human landing catches.

What role can research play in reducing the pregnancy-related risks of vector-borne diseases?

Many vector-borne diseases pose unique risks during pregnancy. For example, malaria is more likely to be severe or fatal in patients who are pregnant, and it can also cause morbidity and mortality by exacerbating anaemia (176). Similarly, dengue during pregnancy can lead to low birth weight and miscarriage (177), and Zika virus can cause microcephaly and other serious birth defects, including neurological changes that disrupt and damage normal processes of early childhood development (178). It is therefore crucial that governments and other funders support research on the impact of vector-borne diseases during pregnancy, as well as the safety and efficacy of drugs in persons who are pregnant.

Historically, persons who were pregnant – or even non-pregnant persons who were capable of becoming pregnant – were excluded from most types of research on new drugs and other medical interventions on the theory that they were inherently vulnerable and in need of protection (3). It is now recognized that this approach was misguided, as pregnancy is not itself a source of vulnerability (179). In addition, excluding pregnant persons from research is counterproductive because, if research during pregnancy is not conducted, medical treatments will still be given to persons who are pregnant, but in uncontrolled situations and without an evidentiary basis. To avoid this concern, researchers should ensure that all inclusion and exclusion criteria, including pregnancy, have a valid scientific justification based on a study-specific analysis of the benefits and risks involved.

What type of governance frameworks should be involved in overseeing vector-borne disease research?

It is essential to have a governance framework in place to ensure that ethical standards in research are followed. While many countries have created governance frameworks for research with human participants, these frameworks are often not supported by sufficient resources to be effective. Moreover, few countries have well developed frameworks for evaluating the health and environmental implications of research not involving human participants, such as studies on the release of genetically modified organisms. National, commercial, and other types of research funding bodies can fulfil their benefit-sharing responsibilities by partnering with host countries to strengthen their capacity for such governance (42).

The appropriate type of governance framework will vary depending on a country’s overall regulatory framework, as well as the types and amount of research conducted in the country. In some cases, the appropriate locus of oversight may be institutionally based committees, while in other settings it may be preferable to rely on regional or national-level oversight. Oversight responsibilities might also be divided among multiple entities within a country; for example, one entity might have responsibility for issues of research ethics while another has responsibility for biosafety considerations (138).



10. Community engagement

TDR-IDRC research with Maasai communities to improve resilience to African trypanosomiasis in Tanzania.

Source: WHO / Andy Craggs

The value of involving a diverse range of individuals and institutions in the conduct of public health activities is increasingly recognized as a best practice in global public health (180). This process is referred to by different terms, including “participation”, “engagement”, “consultation” and “involvement”, with the relevant groups variously described as the “public”, “community” or “stakeholders”. This section uses the term “community engagement” following WHO’s recognition that “people and the communities in which they are born, raised, live, work and play, are at the heart of delivering people-centred and integrated health services” (181).

Broadly speaking, community engagement is “a process of developing relationships that enable stakeholders to work together to address health-related issues and promote well-being to achieve positive health impact and outcomes” (180). Premised on the idea that people should be at the centre of any effort to improve health conditions (182), it has become a critical component of all public health activities, including surveillance (35), prevention, treatment and research (54).

No single approach to community engagement is appropriate in all situations. Rather, the process will vary in size, scope and location depending on the nature of the issue, the goals of the interaction, the individuals and groups involved, and other contextual factors. Often, the challenge is determining how genuine community engagement can take place in ways that are both timely and sensitive to context.

Why is community engagement essential to the control of vector-borne diseases?

Community engagement has been recognized as a fundamental element in developing effective approaches to combating vector-borne diseases (183). It enhances the effectiveness of vector control efforts by facilitating the contextualization and adaptation of health services and interventions in a manner that takes into account the attitudes, practices and values of affected individuals and groups (25, 184).⁴ In addition, community engagement can play an important role in promoting trust,

community ownership and participation, ultimately contributing to the sustainability of interventions and initiatives. Finally, community engagement has an inherent ethical value, as it demonstrates respect for communities and their individual members.

Community engagement is particularly important in the context of vector-borne diseases, because the risks and benefits of many control measures affect large segments of the population. Moreover, many of these measures require broad levels of public participation. For example, an intervention intended to control vectors by eliminating sources of stagnant water will not be successful unless all households in a community are motivated to participate.

For these reasons, it is essential that any significant public health intervention related to vector-borne diseases include a community engagement strategy. These strategies should identify the specific issues and decision points about which engagement will be sought, as well as the types of activities that will be used and the relevant communities that will be involved. In addition, community engagement strategies should include mechanisms to ensure that information generated through engagement activities will be communicated to regulators and others involved in implementing decisions.

What kind of activities does community engagement involve?

Community engagement includes a spectrum of activities, including the following:

- reaching out to and informing the community of policy directions of the government;
- consulting the community as part of a process to develop government policy or to build community awareness and understanding;
- involving the community to ensure that their issues and concerns are understood and considered as part of the decision-making process;

⁴ For example: “Using appropriate technology means paying attention to the ways in which communities use and perceive existing vector control strategies, as well as thinking about end-user preferences and concerns” (25).

- collaborating with the community by developing partnerships to formulate opinions and provide recommendations;
- shared leadership and empowering the community to make decisions and to implement and manage change (185).

The first level – providing information – is essential in all situations. The key is to provide accurate information that is simple enough for the general public to easily grasp. The manner in which information is provided need not be resource intensive. For example, messages can be disseminated inexpensively through text messages, radio programmes, social media, or pre-existing community resources such as community health volunteers. The type of method used should take into account existing practices for information sharing. However, providing relevant information in a way that community members can understand is simply a minimum baseline; it is not sufficient to satisfy the obligation to conduct community engagement.

An important consideration in determining the intensity of community engagement efforts is the amount of time remaining before a decision needs to be made or implemented. In emergency situations, it may be impractical to engage in lengthy deliberative processes, but expedited methods for involving the community, such as phone consultations with established community leaders, will usually be possible. In general, community engagement activities should be conducted at the earliest possible opportunity, both to avoid time pressures and to ensure that the community's input is obtained before critical decisions are made.

Because vector-borne diseases have long-lasting effects on communities, it is likely that issues requiring community engagement will arise more than once. Mechanisms for community engagement should therefore be designed with an eye towards long-term sustainability, taking advantage of pre-existing community health structures. In some situations, it may be appropriate to set up ongoing community advisory groups.

Who counts as the “community” for purposes of community engagement activities?

The relevant community for engagement activities should be determined in light of who is most likely to be affected by the issue under discussion. For example, for an intervention designed to eliminate sources of stagnant water, the target community might be limited to households that store water at home in containers, as opposed to all households located in the area. Community engagement strategies would therefore be aimed at direct dialogue with members of those households in order to identify methods for collecting and storing water that will be accepted and sustainable over time. By contrast, an intervention involving the aerial spraying of insecticides would affect a larger group of people and require different engagement methods. As the size of the relevant community increases, ensuring the inclusion of diverse and representative perspectives may require the involvement of pre-existing groups, such as governmental institutions, community advisory boards, trade unions, and religious or cultural associations.

Defining the relevant community for issues related to vector-borne diseases is complicated because vectors are not confined to discrete geographical areas. This means that a collaborative effort is required for their control, which can involve multiple communities, sometimes across different countries. The views and perspectives of these groups can be shaped by different agendas and resources, which can create tensions in community engagement efforts, especially where mistrust and historical concerns about outside communities exist.

It is important to recognize that the most vocal members of a community are not necessarily representative of the majority perspective. In addition, local norms, roles and relations can also affect the composition and representativeness of community groups, which can result in the marginalization of vulnerable individuals. Such circumstances can produce partial or biased accounts of how interventions ought to be conducted, with insufficient attention to the attitudes and values of those without social power or status. Those designing community engagement activities should be aware of how local power structures may lead to the silencing of

particular voices, such as those of women, young people, certain ethnic groups or elderly people. When feasible, multiple meetings with differently configured groups can help bring more voices into the discussion.

What are some additional challenges involved in conducting community engagement activities related to vector-borne diseases?

As discussed above, community members will not necessarily experience equivalent levels of benefits or risks from vector control interventions (3). This can be a challenge for community engagement, especially when the potential beneficiaries of interventions have more power or status in the community than those who might be harmed. Taking seriously the burdens and risks of interventions means understanding and considering why certain groups might be resistant to interventions and considering the best approach to involve them.

Those responsible for designing and implementing community engagement activities should think carefully about the appropriate role of State and non-State actors. There is growing concern about community engagement strategies that bypass governments and seek to engage only with individuals and households within countries (186). This approach can leave governments unaware of what communities within their jurisdiction have agreed to, potentially enabling powerful external bodies to push outcomes that might not be in the population's best interests. On the other hand, in some cases, direct engagement with local communities can be an important safeguard when conducting interventions in countries with undemocratic governments.

One of the greatest challenges in all health-related community engagement activities is the difficulty of communicating complex medical and scientific information. This challenge is particularly pronounced in the area of vector-borne diseases, given the highly technical nature of much of the relevant information, as well as the fact that more information is often emerging from ongoing research and there may not always be full consensus among experts as to how to apply the relevant data to the particular problem at hand. Those organizing and running community engagement activities should seek to communicate clearly and understandably, without oversimplifying or ignoring important nuances or areas of disagreement. They should also be aware of how their own gaps in knowledge and personal or professional biases might undermine the objectivity of information they are conveying. The media can be helpful in counterbalancing inaccurate messages, but uninformed or sensationalistic media coverage can also fuel misinformation. Thus, media training should be seen as an essential element of an effective community engagement strategy.

Given the complexities of designing and conducting effective community engagement activities, social scientists and experts in community engagement need to be part of vector control activities. Their expertise can be crucial to understanding community power dynamics, values, beliefs, attitudes, practices, misconceptions and fears. They can also be instrumental in incorporating this information into the design of effective risk communication strategies.

Box 12 presents a case study on conflicts arising from the release of genetically modified mosquitoes in Burkina Faso.

Box 12. Conflicts over the release of genetically modified mosquitoes in Burkina Faso

In July 2019, with approval from national authorities, Target Malaria released 10 000 genetically modified, but infertile, male mosquitoes in the village of Bana in Burkina Faso. Target Malaria's ultimate goal is to reduce transmission in sub-Saharan Africa by using innovative technologies to specifically target *Anopheles gambiae* and related mosquito species that are major vectors of malaria in the area.

The scientific rationale for the study was that, because malaria is endemic in Bana, a successful release of gene drive mosquitoes targeting malaria could potentially have ongoing public health benefits for the community. There is no vaccine protective against malaria, and controlling the mosquito vectors using pesticides is usually not practicable, so a self-sustaining technology that would eliminate the vector is attractive.

The release in Bana was an initial step in collecting data to inform future research, especially about mosquito survival and dispersal, but it was not intended to have an immediate public health impact in controlling malaria. Male mosquitoes do not feed on blood and, because they were infertile, they could not pass any genes into the wild population. Nevertheless, the study attracted strong opposition from some civil society organizations from around Africa, who argued that it would expose the community to unknown risk of harm without public health benefit and demonstrated against national authorization of the release.

Research conducted in developing countries raises concerns for the vulnerability of participants. Research funded by foreign entities, such as Target Malaria's work, is especially susceptible to accusations of exploitation for this reason. The debate sparked by Burkina Faso's approval of the release of genetically modified mosquitoes in Bana reflects the interests of broader society in the use of novel technologies for which the risks to people and the environment are unclear (138, 187–189).

References

1. Global vector control response 2017–2030. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/bitstream/handle/10665/259205/9789241512978-eng.pdf>, accessed 3 July 2020).
2. Resolution WHA70.16. Global vector control response: an integrated approach for the control of vector-borne diseases. In: Seventieth World Health Assembly, Geneva, 22–31 May 2017. Geneva: World Health Organization; 2017 (http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R16-en.pdf?ua=1, accessed 3 July 2020).
3. Ethical issues associated with vector-borne diseases: report of a WHO scoping meeting, Geneva, 23–24 February 2017. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/bitstream/handle/10665/259687/WHO-HTM-NTD-VEM-2017.07-eng.pdf>, accessed 3 July 2020).
4. Social determinants of health. Geneva: World Health Organization (https://www.who.int/social_determinants/en/, accessed 3 July 2020).
5. Larson E, George A, Morgan R, Poteat T. 10 best resources on intersectionality with an emphasis on low- and middle-income countries. *Health Policy and Planning*. 2016;31(8):964–9. doi:10.1093/heapol/czw020.
6. Manandhar M, Hawkes S, Buse K, Nosrati E, Magaraet V. Gender, health and the 2030 Agenda for Sustainable Development. *Bulletin of the World Health Organization*. 2018;96(9):644–53.
7. Theobald S, MacPherson EE, Dean L, Jacobson J, Ducker C, Gyapong M et al. 20 years of gender mainstreaming in health: lessons and reflections for the neglected tropical diseases community. *BMJ Global Health* 2017;2:e000512. doi:10.1136/bmjgh-2017-000512.
8. Allotey P, Gyapong M. The gender agenda in the control of tropical diseases: a review of current evidence. Geneva: World Health Organization; 2005.
9. The gender dimensions of neglected tropical diseases. Access and Delivery Partnership; 2019 (http://adphealth.org/upload/resource/2523_AD_P_Discussion_Paper_NTDs_211119_web.pdf, accessed 3 July 2020).
10. Garley AE, Ivanovich E, Eckert E, Negroustoueva S, Ye Y. Gender differences in the use of insecticide-treated nets after a universal free distribution campaign in Kano state, Nigeria: post-campaign survey results. *Malaria Journal*. 2013;12(1):119. doi:10.1186/1475-2875-12-119.
11. Elder L, Ransom E. Nutrition of women and adolescent girls: why it matters. Washington (DC): Population Reference Bureau; 2003 (<https://www.prb.org/nutritionofwomenandadolescentgirlswhyitmatters/>, accessed 3 July 2020).
12. Malaria: key facts. Geneva: World Health Organization; 2020 (<https://www.who.int/news-room/fact-sheets/detail/malaria>, accessed 3 July 2020).

13. Fitzpatrick T, Rosella LC, Calzavara A, Petch J, Pinto AD, Manson H et al. Looking beyond income and education: socioeconomic status gradients among future high-cost users of health care. *American Journal of Preventive Medicine*. 2015;49(2):161–71.
14. Richards AL, Jiang J, Omulo S, Dare R, Abdirahman K et al. Human infection with *Rickettsia felis*, Kenya. *Emerging Infectious Diseases*. 2010;16(7):1081–86.
15. Reiter P, Lathrop S, Bunning M, Biggerstaff B, Singer D, Tiwari T et al. Texas lifestyle limits transmission of dengue virus. *Emerging Infectious Diseases*. 2003;9(1):86–9.
16. Ramos MM, Mohammed H, Zielinski-Gutierrez W, Hayden MH, Robles López JL, Fournieret M et al. Epidemic dengue and dengue hemorrhagic fever at the Texas-Mexico border: results of a household-based seroepidemiologic survey, December 2005. *American Journal of Tropical Medicine and Hygiene*. 2008;78(3):364–9.
17. Brunkard JM, Robles López JL, Ramirez J, Cifuentes E, Rothenberg SJ, Hunsperger EA et al. Dengue fever seroprevalence and risk factors, Texas-Mexico border, 2004. *Emerging Infectious Diseases*. 2007;13(10):1477–83.
18. Epidemiological report on malaria in Greece, 2019, up to 15/05/2019. Athens: National Public Health Organization; 2019 (https://eody.gov.gr/wp-content/uploads/2019/05/MALARIA_REPORT_15_5_-2019_ENG.pdf, accessed 3 July 2020).
19. Alawieh A, Musharrafieh U, Jaber A, Berry A, Ghosn N, Bizri AR. Revisiting leishmaniasis in the time of war: the Syrian conflict and the Lebanese outbreak. *International Journal of Infectious Diseases*. 2014;29:115–9.
20. Migration and health: key issues. Copenhagen: WHO Regional Office for Europe (<http://www.euro.who.int/en/health-topics/health-determinants/migration-and-health/migrant-health-in-the-european-region/migration-and-health-key-issues>, accessed 3 July 2020).
21. Ghent A. Overcoming migrants' barriers to health. *Bulletin of the World Health Organization*. 2008;86(8):583–4.
22. Myers SS, Gaffikin L, Golden CD, Ostfeld RS, Redford KH, Ricketts TH et al. Human health impacts of ecosystem alteration. *Proceedings of the National Academy of Sciences*. 2013;110(47):18753–60. doi:10.1073/pnas.1218656110.
23. LaDeau SL, Allan BF, Leishnam PT, Levy MZ. The ecological foundations of transmission potential and vector-borne disease in urban landscapes. *Functional Ecology*. 2015;29:889–901. doi:10.1111/1365-2435.12487.
24. Grijalva MJ, Terán D, Dangles O. Dynamics of sylvatic Chagas disease vectors in coastal Ecuador is driven by changes in land cover. *PLoS Neglected Tropical Diseases*. 2014;8:e2960.
25. Bardosh KL, Ryan SJ, Ebi K, Welburn S, Singer B. Addressing vulnerability, building resilience: community-based adaptation to vector-borne diseases in the context of global change. *Infectious Diseases of Poverty*. 2017;6(1):166. doi:10.1186/s40249-017-0375-2.
26. Patz JA, Frumkin H, Holloway T, Vimont DJ, Haines A. Climate change: challenges and opportunities for global health. *Journal of the American Medical Association*. 2014;312(15):1565–80.

27. Campbell-Lendrum D, Manga L, Bagayoko M, Sommerfeld J. Climate change and vector-borne diseases: what are the implications for public health research and policy? *Philosophical Transactions of the Royal Society of London B: Biological Sciences*. 2015;370(1665):20130552.
28. World Health Organization and Secretariat of the Convention on Biological Diversity. *Connecting global priorities: biodiversity and human health – a state of knowledge review*. Geneva: World Health Organization; 2015.
29. Globalization and infectious diseases: a review of the linkages. Geneva: World Health Organization; 2004 (https://www.who.int/tdr/publications/documents/seb_topic3.pdf, accessed 3 July 2020).
30. Xiao J, He J, Deng A, Lin H, Song T, Peng Z et al. Characterizing a large outbreak of dengue fever in Guangdong province, China. *Infectious Diseases of Poverty*. 2016;5:44. doi:10.1186/s40249-016-0131-z.
31. Ren H, Wu W, Li T, Yang Z. Urban villages as transfer stations for dengue fever epidemic: a case study in the Guangzhou, China. *PLoS Neglected Tropical Diseases*. 2019;13(4):e0007350. doi:10.1371/journal.pntd.0007350.
32. Zheng X, Zhang D, Li Y, Yang C, Wu Y, Liang X et al. Incompatible and sterile insect techniques combined eliminate mosquitoes. *Nature*. 2019;572:56–61.
33. Global health ethics: key issues. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/bitstream/handle/10665/164576/9789240694033_eng.pdf, accessed 3 July 2020).
34. What is public health? CDC Foundation (<https://www.cdcfoundation.org/what-public-health>, accessed 3 July 2020).
35. WHO guidelines on ethical issues in public health surveillance. Geneva: World Health Organization; 2017.
36. Climate change and health: key facts. Geneva: World Health Organization, 2018 (<https://www.who.int/news-room/fact-sheets/detail/climate-change-and-health>, accessed 3 July 2020).
37. Luna F. Identifying and evaluating layers of vulnerability: a way forward. *Developing World Bioethics*. 2019;19:86–95. doi:10.1111/dewb.12206.
38. Luna F. Elucidating the concept of vulnerability: layers not labels. *International Journal of Feminist Approaches to Bioethics*. 2009;2(1):121–39.
39. Hankivsky O. *Intersectionality 101*. Vancouver, British Columbia: Institute for Intersectionality Research and Policy; 2014.
40. Kapilashrami A, Hankivsky O. Intersectionality and why it matters to global health. *Lancet*. 2018;391:2589–91.
41. Declaration of Ethical Principles in relation to Climate Change. Paris: United Nations Educational, Scientific and Cultural Organization; 2017 (<https://unesdoc.unesco.org/ark:/48223/pf0000260129>, accessed 3 July 2020).
42. Macpherson CC. Research ethics guidelines and moral obligations to developing countries: capacity-building and benefits. *Bioethics*. 2019;33:399–405. doi:10.1111/bioe.12577.

43. Zuber JA, Takala-Harrison S. Multidrug-resistant malaria and the impact of mass drug administration. *Infectious Drug Resistance*. 2018;11:299–306.
44. Viennet E, Ritchie SA, Williams CR, Faddy HM, Harley D. Public health responses to and challenges for the control of dengue transmission in high-income countries: four case studies. *PLoS Neglected Tropical Diseases*. 2016;10(9):e0004943.
45. Teng AK, Singh S. Epidemiology and new initiatives in the prevention and control of dengue in Malaysia. *Dengue Bulletin*. 2001;25:7–12.
46. Boo CS. Legislation for control of dengue in Singapore. *Dengue Bulletin*. 2001;25:69–73.
47. Byskov MF. Qualitative and quantitative interpretations of the least restrictive means. *Bioethics*. 2019;33(4):511–21.
48. Childress JF, Faden RR, Gaare RD, Gostin LO, Kahn J, Bonnie RJ et al. Public health ethics: mapping the terrain. *Journal of Law, Medicine and Ethics*. 2002;30(2):170–8.
49. Guidance for managing ethical issues in infectious disease outbreaks. Geneva: World Health Organization; 2016.
50. Selgelid M. A moderate pluralist approach to public health policy and ethics. *Public Health Ethics*. 2009;2(2):195–205.
51. Public health: ethical issues. London: Nuffield Council on Bioethics; 2007 (<http://nuffieldbioethics.org/wp-content/uploads/2014/07/Public-health-ethical-issues.pdf>, accessed 3 July 2020).
52. Achat H, McIntyre P, Burgess M. Health care incentives in immunization. *Australian and New Zealand Journal of Public Health*. 1999;23(3):285–8.
53. Ethics guidance for the implementation of the end TB strategy. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/bitstream/handle/10665/254820/9789241512114-eng.pdf>, accessed 3 July 2020).
54. International Ethical Guidelines for Health-related Research Involving Humans. Geneva: Council for International Organizations of Medical Sciences and World Health Organization; 2016 (<https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf> accessed 3 July 2020).
55. Bentley J, Thacker P. The influence of risk and monetary payment on the research participation decision making process. *Journal of Medical Ethics*. 2004;30:293–8.
56. Knipling E. Possibilities of insect control or eradication through the use of sexually sterile males. *Journal of Economic Entomology*. 1955;48:459–69.
57. RTS,S Clinical Trials Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. *PLoS Medicine*. 2014;11(7):e1001685.
58. Serebrovskii AS. On the possibility of a new method for the control of insect pests. *Zoologicheskii Zhurnal*. 1940;19:618–30.
59. Macias VM, Ohm JR, Rasgon JL. Gene drive for mosquito control: where did it come from and where are we headed? *International Journal of Environmental Research and Public Health*. 2017;14(9):1006.

60. Hilgenboecker K, Hammerstein P, Schlattmann P, Telschow A, Werren JH. How many species are infected with *Wolbachia*? A statistical analysis of current data. *FEMS Microbiology Letters*. 2008;281:215–20.
61. Werren JH, Baldo L, Clark ME. *Wolbachia*: master manipulators of invertebrate biology. *Nature Reviews Microbiology*. 2008;6:741–51.
62. Laven H. Eradication of *Culex pipiens fatigans* through cytoplasmic incompatibility. *Nature*. 1967;216:383–4.
63. Hammond AM, Galizi R. Gene drives to fight malaria: current state and future directions. *Pathogens and Global Health*. 2017;111(8):412–23. doi:10.1080/20477724.2018.1438880.
64. Gene drive research: why it matters. Royal Society; 2018 (<https://royalsociety.org/~media/policy/Publications/2018/08-11-18-gene-drive-statement.pdf>, accessed 4 July 2020).
65. Craig GB Jr, Hickey WA, Vandehey RC. An inherited male-producing factor in *Aedes aegypti*. *Science*. 1960;132(3443):1887–9.
66. Frieß JL, von Gleich A, Giese B. Gene drives as a new quality in GMO releases: a comparative technology characterization. *PeerJ*. 2019;7:e6793. doi:10.7717/peerj.6793.
67. Friedman RM, Marshall JM, Akbari OS. Gene drives: new and improved. *Issues in Science and Technology*. 2020;XXXVI:2.
68. Bryant JM, Baumgarten S, Glover L, Hutchinson S, Rachidi N. CRISPR in parasitology: not exactly cut and dried! *Trends in Parasitology*. 2019;35(6):409–22.
69. Gene drives: ethical considerations on the use of gene drives in the environment. Swiss Confederation: Federal Ethics Committee on Non-Human Biotechnology; 2019 (https://www.ekah.admin.ch/inhalte/ekah-dateien/dokumentation/publikationen/EKAH_Bericht_Gene_Drives_EN_V2.pdf, accessed 4 July 2020).
70. McMeniman CJ, Lane RV, Cass BN, Fong AW, Sidhu M, Wang YF et al. Stable introduction of a life-shortening *Wolbachia* infection into the mosquito *Aedes aegypti*. *Science*. 2009;323:141–4.
71. Moreira LA, Iturbe-Ormaetxe I, Jeffrey JA, Lu G, Pyke AT, Hedges LM et al. A *Wolbachia* symbiont in *Aedes aegypti* limits infection with dengue, chikungunya, and plasmodium. *Cell*. 2009;139:1268–78.
72. Dutra HL, Rocha MN, Dias FB, Mansur SB, Caragata EP, Moreira LA. *Wolbachia* blocks currently circulating Zika virus isolates in Brazilian *Aedes aegypti* mosquitoes. *Cell Host Microbe*. 2016;19(6):771–4.
73. Fu Y, Gavotte L, Mercer DR, Dobson SL. Artificial triple *Wolbachia* infection in *Aedes albopictus* yields a new pattern of unidirectional cytoplasmic incompatibility. *Applied and Environmental Microbiology*. 2010;76(17):5887–91.
74. Leftwich PT, Edgington MP, Harvey-Samuel T, Carabajal Paladino LZ, Norman VC, Alphey L. Recent advances in threshold-dependent gene drives for mosquitoes. *Biochemical Society Transactions*. 2018;46(5):1203–12. doi:10.1042/BST20180076.
75. Jones MS, Delborne JA, Elsensohn J, Mitchell PD, Brown ZS. Does the U.S. public support using gene drives in agriculture? And what do they want to know? *Science Advances*. 2019;5(9):eaau8462. doi:10.1126/sciadv.aau8462.

76. Pesticide residues in food: key facts. Geneva: World Health Organization; 2018 (<https://www.who.int/en/news-room/fact-sheets/detail/pesticide-residues-in-food>, accessed 14 July 2020).
77. Climate change and human health: biodiversity. Geneva: World Health Organization (<https://www.who.int/globalchange/ecosystems/biodiversity/en/>, accessed 14 July 2020).
78. Convention on Biological Diversity. Rio de Janeiro: United Nations; 1992 (<https://www.cbd.int/doc/legal/cbd-en.pdf>, accessed 14 July 2020).
79. World malaria report 2019. Geneva: World Health Organization; 2019 (<https://www.who.int/publications-detail/world-malaria-report-2019>, accessed 14 July 2020).
80. Regional Malaria Action Plan 2016–2020: towards a malaria-free region. Cairo: World Health Organization Regional Office for the Eastern Mediterranean; 2017 (http://applications.emro.who.int/docs/EMROPUB_2017_EN_19546.pdf?ua=1, accessed 14 July 2020).
81. Progress towards malaria elimination in the Kingdom of Saudi Arabia: a success story. Ministry of Health of Saudi Arabia and World Health Organization Regional Office for the Eastern Mediterranean; 2019 (<https://www.moh.gov.sa/Ministry/MediaCenter/Publications/Documents/Malaria.pdf>, accessed 14 July 2020).
82. Malaria in Morocco: relentless efforts towards the goal of elimination. Ministry of Health of Morocco and World Health Organization Regional Office for the Eastern Mediterranean; 2007 (<http://applications.emro.who.int/dsaf/dsa777.pdf>, accessed 14 July 2020).
83. Schapira A, Zaim M, Raeisi A, Ranjbar M, Kolifarhood G, Nikpour F et al. History of the successful struggle against malaria in the Islamic Republic of Iran: from the earliest records to imminent elimination. Ministry of Health and Medical Education of the Islamic Republic of Iran; 2018 (https://endmalaria.org/sites/default/files/Iran%20Story%20new%2026_Sep_2018_GF.pdf, accessed 14 July 2020).
84. National Research Council. Science and decisions: advancing risk assessment. Washington (DC): National Academies Press; 2009.
85. Zika virus: 2016 case counts in the US. United States Centers for Disease Control and Prevention; 2016 (<https://www.cdc.gov/zika/reporting/2016-case-counts.html>, accessed 14 July 2020).
86. Zika virus: 2017 case counts in the US. United States Centers for Disease Control and Prevention; 2017 (<https://www.cdc.gov/zika/reporting/2017-case-counts.html>, accessed 14 July 2020).
87. World Health Organization and International Atomic Energy Agency. Framework for health and environmental risk assessment. In: Guidance framework for testing the sterile insect technique as a vector control tool against Aedes-borne diseases. Geneva: World Health Organization; 2020: Chapter 2 (<https://www.iaea.org/sites/default/files/aedes-who-iaea-2020.pdf>, accessed 14 July 2020).
88. The Sustainable Development Goals. United Nations Department of Economic and Social Affairs (<https://sdgs.un.org/goals>, accessed 14 July 2020).

89. Resolution 74/2: Political declaration of the high-level meeting on universal health coverage. Resolution adopted by the General Assembly on 10 October 2019. In: United Nations General Assembly, 74th session (<https://undocs.org/en/A/RES/74/2>, accessed 14 July 2020).
90. Universal Declaration of Human Rights. United Nations General Assembly resolution 217(III)A, Article 25, 1948 (<https://www.un.org/en/universal-declaration-human-rights/>, accessed 14 July 2020).
91. International Covenant on Economic, Social and Cultural Rights. United Nations General Assembly resolution 2200(XXI)A, Article 12, 1967 (https://treaties.un.org/doc/Treaties/1976/01/19760103%2009-57%20PM/Ch_IV_03.pdf, accessed 14 July 2020).
92. Convention on the Elimination of All Forms of Discrimination against Women. United Nations General Assembly resolution 34/180, Article 12, 1979 (<https://www.un.org/womenwatch/daw/cedaw/>, accessed 14 July 2020).
93. United Nations Convention on the Rights of the Child. General Assembly resolution 44/25, Article 24, 1989 (<https://www.ohchr.org/en/professionalinterest/pages/crc.aspx>, accessed 14 July 2020).
94. International Convention on the Elimination of All Forms of Racial Discrimination. General Assembly resolution 2106(XX), Article 5, 1965 (<https://www.ohchr.org/EN/ProfessionalInterest/Pages/CERD.aspx>, accessed 14 July 2020).
95. African Charter on Human and Peoples' Rights, Article 16, 1981 (<https://www.achpr.org/legalinstruments/detail?id=49>, accessed 14 July 2020).
96. Additional Protocol to the American Convention on Human Rights in the Area of Economic, Social and Cultural Rights, Article 10, 1988 (<https://www.oas.org/juridico/english/treaties/a-52.html>, accessed 14 July 2020).
97. Human rights and health: key facts. Geneva: World Health Organization; 2017 (<https://www.who.int/news-room/fact-sheets/detail/human-rights-and-health>, accessed 14 July 2020).
98. Immunization, vaccines and biologicals: yellow fever. Geneva: World Health Organization; 2018 (https://www.who.int/immunization/diseases/yellow_fever/en/, accessed 14 July 2020).
99. Lymphatic filariasis: key facts. Geneva: World Health Organization; 2020 (<https://www.who.int/en/news-room/fact-sheets/detail/lymphatic-filariasis>, accessed 14 July 2020).
100. Andre FE, Booy R, Bock HL, Clemens J, Datta SK, John TJ et al. Vaccination greatly reduces disease, disability, death and inequity worldwide. *Bulletin of the World Health Organization*. 2008;86(2):140–6.
101. Webster JP, Molyneux DH, Hotez PJ, Fenwick A. The contribution of mass drug administration to global health: past, present and future. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*. 2014;369(1645):20130434. doi:10.1098/rstb.2013.0434.
102. de Souza DK, Larbi I, Boakye DA, Okebe J. Ivermectin treatment in humans for reducing malaria transmission. *Cochrane Database of Systematic Reviews*. 2018;2018(9):CD013117. doi:10.1002/14651858.CD013117.

103. Khan AM. Lymphatic filariasis elimination programme in Assam, India, needs change in mass drug administration strategy to target the focus of infection. *Indian Journal of Medical Research*. 2018;147:7–10. doi:10.4103/ijmr.IJMR_1843_16.
104. Wilder-Smith A, Hombach J, Ferguson N, Selgelid M, O'Brien K, Vannice K et al. Deliberations of the Strategic Advisory Group of Experts on Immunization on the use of CYD-TDV dengue vaccine. *Lancet Infectious Diseases*. 2019;19(1):e31–e38. doi:10.1016/S1473-3099(18)30494-8.
105. Dengue vaccine: WHO position paper – September 2018. World Health Organization: *Weekly Epidemiological Record*. 2018;36(93):457–76.
106. Ohkado A, Sugiyama T, Murakami K, Ishikawa N, Borgdorff M, van Cleeff M et al. Informed patient consent for defaulter tracing: should we obtain it? *International Journal of Tuberculosis and Lung Disease*. 2009;13(5):551–5.
107. Electronic immunization registry: practical considerations for planning, development, implementation, and evaluation. Pan American Health Organization; 2017 (https://iris.paho.org/bitstream/handle/10665.2/34865/9789275119532_eng.pdf?sequence=5&%20=y, accessed 14 July 2020).
108. Surveillance. Geneva: World Health Organization (<https://www.who.int/emergencies/surveillance>, accessed 14 July 2020).
109. Cancer: screening. Geneva: World Health Organization (<https://www.who.int/cancer/prevention/diagnosis-screening/screening/en/>, accessed 14 July 2020).
110. Codeço CT, Lima AWS, Araújo SC, Lima JBP, Maciel-de-Freitas R, Honório NA et al. Surveillance of *Aedes aegypti*: comparison of house index with four alternative traps. *PLoS Neglected Tropical Diseases*. 2015;9:2 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4323346/>, accessed 14 July 2020).
111. Aik J, Neo ZW, Rajarethinam J, Chio K, Lam WM, Ng L-C. The effectiveness of inspections on reported mosquito larval habitats in households: a case-control study. *PLOS Neglected Tropical Diseases*. 2019;13(6):e0007492. doi:10.1371/journal.pntd.0007492.
112. Hardy A, Makame M, Cross D, Majambere S, Msellem M. Using low-cost drones to map malaria vector habitats. *Parasite Vectors*. 2017;10:29. doi:10.1186/s13071-017-1973.
113. Gopichandran V. Ethics of preventive strategies against vector borne diseases: a case study of dengue prevention from Tamil Nadu. Conference paper. In: Joint 14th World Congress of Bioethics and 7th National Bioethics Conference, 5–7 December 2018, Bengaluru, India.
114. Rajarethinam J, Ong J, Lim S-H, Tay Y-H, Bounliphone W, Chong C-S et al. Using human movement data to identify potential areas of Zika transmission: case study of the largest Zika cluster in Singapore. *International Journal of Environmental Research and Public Health*. 2019;16(5):808. doi:10.3390/ijerph16050808.
115. de Montjoye Y, Hidalgo CA, Verleysen M, Blondel VD. Unique in the crowd: the privacy bounds of human mobility. *Scientific Reports*. 2013;3:1376. doi:10.1038/srep01376.
116. Heng J. 41 cases of locally transmitted Zika confirmed in Aljunied Crescent cluster, 34 fully recovered. *The Straits Times*, 28 August 2016 (<https://www.straitstimes.com/singapore/health/41-cases-of-locally-transmitted-zika-confirmed-in-aljunied-crescent-cluster-34>, accessed 14 July 2020).

117. Raymond N. Safeguards for human studies can't cope with big data. *Nature*. 2019;568:277. doi:10.1038/d41586-019-01164-z.
118. Oliver N, Matic A, Frias-Martinez E. Mobile network data for public health: opportunities and challenges. *Frontiers in Public Health*. 2015;3:189. doi:10.3389/fpubh.2015.00189.
119. Tatem AJ, Huang Z, Das A, Qi Q, Roth J, Qiu Y. Air travel and vector-borne disease movement. *Parasitology*. 2012;139(14):1816–30.
120. International Health Regulations (2005): third edition. Geneva: World Health Organization; 2016 (https://www.google.co.uk/?gfe_rd=cr&ei=OLYaVZ8j1KrzB-KwgKAG, accessed 15 July 2020).
121. Jamrozik E, de la Fuente-Núñez V, Reis A, Ringwald P, Selgelid MJ. Ethical aspects of malaria control and research. *Malaria Journal*. 2015;14:518. doi:10.1186/s12936-015-1042-3.
122. Maintaining a safe and adequate blood supply during Zika virus outbreaks: interim guidance. Geneva: World Health Organization; 2016 (https://www.who.int/csr/resources/publications/zika/Safe-blood_supply18Feb2016.pdf, accessed 15 July 2020).
123. Protecting the blood supply during infectious disease outbreaks: guidance for national blood services. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/bitstream/handle/10665/311443/9789241515214-eng.pdf>, accessed 15 July 2020).
124. Position paper on use of convalescent plasma, serum or immune globulin concentrates as an element in response to an emerging virus. Geneva: World Health Organization Blood Regulators Network; 2017 (https://www.who.int/bloodproducts/brn/2017_BRN_PositionPaper_ConvalescentPlasma.pdf?ua=1, accessed 15 July 2020).
125. Considerations of the WHO Blood Regulators Network (BRN): potential for use of convalescent plasma in management of Ebola. Geneva: World Health Organization; 2014 (https://www.who.int/bloodproducts/brn/potential_use_convalescent_plasma_in_management_of_ebola-brn_considerations.pdf?ua=1, accessed 15 July 2020).
126. Position statement on collection of blood for transfusion in the setting of a vaccination campaign against yellow fever. Geneva: World Health Organization Blood Regulators Network; 2017 (https://www.who.int/bloodproducts/brn/2017_BRN_PostitionPaper_YFV.pdf?ua=1, accessed 15 July 2020).
127. Position paper on use of convalescent plasma or serum as an element in filovirus outbreak response. Geneva: World Health Organization Blood Regulators Network; 2014 (https://www.who.int/bloodproducts/brn/BRN_PositionPaperConvPlasmaFiloviruses_FINALWEB14August2014.pdf?ua=1, accessed 15 July 2020).
128. Position paper on collection and use of convalescent plasma or serum as an element in MiddleEastrespiratorysyndromecoronavirusresponse. Geneva: World Health Organization Blood Regulators Network; 2014 (https://www.who.int/bloodproducts/brn/BRN_PositionPaperConvPlasmaMERSCoV_March2014.pdf?ua=1, accessed 15 July 2020).
129. Donor selection in case of pandemic situations. Geneva: World Health Organization Blood Regulators Network; 2007 (<https://www.who.int/bloodproducts/brn/DonorSelectionincaseofPandemicSituations.pdf?ua=1>, accessed 15 July 2020).

130. Peters DH, Tran NT, Adam T. Implementation research in health: a practical guide. Geneva: Alliance for Health Policy and Systems Research, World Health Organization; 2013 (https://apps.who.int/iris/bitstream/handle/10665/91758/9789241506212_eng.pdf, accessed 15 July 2020).
131. Standards and operational guidance for ethics review of health-related research with human participants. Geneva: World Health Organization; 2011.
132. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequently amended at other General Assemblies. *JAMA*. 2013;310(20):2191–4.
133. Ethical considerations in biomedical HIV prevention trials. UNAIDS/WHO guidance document. Geneva: Joint United Nations Programme on HIV/AIDS and World Health Organization; 2012 (http://www.unaids.org/sites/default/files/media_asset/jc1399_ethical_considerations_en_0.pdf, accessed 15 July 2020).
134. International Guiding Principles for Biomedical Research Involving Animals. Council for International Organizations of Medical Sciences and International Council for Laboratory Animal Science (https://olaw.nih.gov/sites/default/files/Guiding_Principles_2012.pdf, accessed 15 July 2020).
135. The ethics of research involving animals. London: Nuffield Council on Bioethics; 2005.
136. Ethical guidelines for the use of animals in research. Oslo: Norwegian National Committee for Research Ethics in Science and Technology; 2018.
137. The European Code of Conduct for Research Integrity, revised edition. Berlin: ALLEA – All European Academies; 2017 (<https://www.allea.org/wp-content/uploads/2017/05/ALLEA-European-Code-of-Conduct-for-Research-Integrity-2017.pdf>, accessed 15 July 2020).
138. World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases. Guidance framework for testing of genetically modified mosquitoes. Geneva: World Health Organization; 2014 (https://www.who.int/tdr/publications/year/2014/Guidance_framework_mosquitoes.pdf, accessed 15 July 2020).
139. National Academies of Sciences, Engineering, and Medicine. Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values. Washington (DC): National Academies Press; 2016.
140. Emerson C, James S, Littler K, Randazzo F. Principles for gene drive research. *Science*. 2017;358(6367):1135–6. doi:10.1126/science.aap9026.
141. Singh JA. Informed consent and community engagement in open field research: lessons for gene drive science. *BMC Medical Ethics*. 2019;20:54 (<https://bmcmmedethics.biomedcentral.com/articles/10.1186/s12910-019-0389-3>, accessed 15 July 2020).
142. Kolopack PA, Lavery JV. Informed consent in field trials of gene-drive mosquitoes. *Gates Open Research*. 2017;1:14. doi:10.12688/gatesopenres.12771.1.

143. World Health Organization and International Atomic Energy Agency. Ethics and community/ stakeholder engagement. In: Guidance framework for testing the sterile insect technique as a vector control tool against Aedes-borne diseases. Geneva: World Health Organization; 2020: Chapter 7 (<https://www.iaea.org/sites/default/files/aedes-who-iaea-2020.pdf>, accessed 15 July 2020).
144. McRae AD, Weijer C, Binik A, White A, Grimshaw JM, Boruch R et al. Who is the research subject in cluster randomized trials in health research? *Trials*. 2011;12:183. doi:10.1186/1745-6215-12-183.
145. Annas GJ. Reviewer report: informed consent in field trials of gene-drive mosquitoes. *Gates Open Research*. Open letter, 3 January 2018 (<https://gatesopenresearch.org/articles/1-14/v1#referee-response-26148>, accessed 15 July 2020).
146. Wiles R, Crow G, Heath S, Charles V. Research ethics and regulation in the UK: the case of informed consent. Paper presented at the 1st International Congress of Qualitative Inquiry, University of Illinois at Urbana-Champaign. May 2005 (<http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.602.7274&rep=rep1&type=pdf>, accessed 15 July 2020).
147. Guidance on ethical considerations in planning and reviewing research studies on sexual and reproductive health in adolescents. Geneva: World Health Organization; 2018 (<https://www.who.int/reproductivehealth/publications/adolescence/ethical-considerations-srh-research-in-adolescents/en/>, accessed 15 July 2020).
148. Thizy D, Emerson C, Gibbs J, Hartley S, Kapiriri L, Lavery J et al. Guidance on stakeholder engagement practices to inform the development of area-wide vector control methods. *PLoS Neglected Tropical Diseases*. 2019;13(4):e0007286. doi:10.1371/journal.pntd.0007286.
149. James S, Collins FH, Eckhoff PA, Emerson CH, Godfray CJ, Gottlieb M et al. Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa: recommendations of a scientific working group. *American Journal of Tropical Medicine and Hygiene*. 2018;98(Suppl. 6):1–49. doi:10.4269/ajtmh.18-0083.
150. Ferguson NM. Challenges and opportunities in controlling mosquito-borne infections. *Nature*. 2018;559:490–7.
151. Noble C, Min J, Olejarz J, Buchthal J, Chavez A, Smidler AL et al. Daisy-chain gene drives for the alteration of local populations. *Proceedings of the National Academy of Sciences*. 2019;116(17):8275–82. doi:10.1073/pnas.1716358116.
152. Marshall JM, Akbari OS. Can CRISPR-based gene drive be confined in the wild? A question for molecular and population biology. *ACS Chemical Biology*. 2018;13(2):424–30. doi:10.1021/acscchembio.7b00923.
153. Vanclay F. International principles for social impact assessment. *Impact Assessment and Project Appraisal*. 2003;21(1):5–11.
154. Murray JV, Jansen CC, De Barro P. Risk associated with the release of Wolbachia-infected *Aedes aegypti* mosquitoes into the environment in an effort to control dengue. *Frontiers in Public Health*. 2016;4:43.

155. Popovicil J, Moreiral LA, Poinsignonl A, Iturbe-Ormaetxe I, McNaughton D, O'Neill SL. Assessing key safety concerns of a Wolbachia-based strategy to control dengue transmission by *Aedes* mosquitoes. *Memórias do Instituto Oswaldo Cruz*. 2010;105(8):957–64. doi:10.1590/s0074-02762010000800002.
156. Hoffmann AA, Montgomery BL, Popovici J, Iturbe-Ormaetxe I, Johnson PH, Muzzi F et al. Successful establishment of Wolbachia in *Aedes* populations to suppress dengue transmission. *Nature*. 2011;476:454–7.
157. Kolopack PA, Parsons JA, Lavery JV. What makes community engagement effective? Lessons from the Eliminate Dengue Program in Queensland Australia. *PLoS Neglected Tropical Diseases*. 2015;9(4):e0003713. doi:10.1371/journal.pntd.0003713.
158. O'Neill S. How a tiny bacterium called Wolbachia could defeat dengue: scientists are immunizing mosquitoes against disease with the help of a common microbe. *Scientific American*, 1 June 2015 (<https://www.scientificamerican.com/article/how-a-tiny-bacterium-called-wolbachia-could-defeat-dengue/>, accessed 15 July 2020).
159. Frequently asked questions about dengue fever. *Jakarta Post*, 4 October 2016 (<https://www.thejakartapost.com/life/2016/10/04/frequently-asked-questions-about-dengue-fever.html>, accessed 15 July 2020).
160. McNaughton D, Duong TTH. Designing a community engagement framework for a new dengue control method: a case study from central Vietnam. *PLoS Neglected Tropical Diseases*. 2014;8(5):e2794. doi:10.1371/journal.pntd.0002794.
161. O'Neill SL, Ryan PA, Turley AP, Wilson G, Retzki K, Iturbe-Ormaetxe I et al. Scaled deployment of Wolbachia to protect the community from dengue and other *Aedes* transmitted arboviruses. *Gates Open Research*. 2019;2:36. doi:10.12688/gatesopenres.12844.3.
162. Bamberg B, Selgelid M, Weijer C, Savulescu J, Pollard AJ. Ethical criteria for human challenge studies in infectious diseases. *Public Health Ethics*. 2016;9(1):92–103.
163. Selgelid M, Jamrozik E. Ethical challenges posed by human infection challenge studies in endemic settings. *Indian Journal of Medical Ethics*. 2018;III(4):274–8.
164. Jamrozik E, Selgelid MJ. Human challenge studies in endemic settings: ethical and regulatory issues. *SpringerBriefs in Ethics*; 2020 (<https://www.springer.com/gp/book/9783030414795>, accessed 15 July 2020).
165. Appelbaum PS, Lidz CW. The therapeutic misconception. In: Emanuel EJ, Grady CC, Crouch RA, Lie RK, Miller FG, Wendler DD, editors. *The Oxford textbook of clinical research ethics*. Oxford: Oxford University Press; 2008.
166. Anomaly J, Savulescu J. Compensation for cures: why we should pay a premium for participation in “challenge studies”. *Bioethics*. 2019;33:792–7.
167. Jamrozik E, Selgelid MJ. Ethical issues surrounding controlled human infection challenge studies in endemic low-and middle-income countries. *Bioethics*. 2020;00:1-12.
168. Hodgson SH, Juma E, Salim A, Magiri C, Kimani D, Njenga D et al. Evaluating controlled human malaria infection in Kenyan adults with varying degrees of prior exposure to *Plasmodium falciparum* using sporozoites administered by intramuscular injection. *Frontiers in Microbiology*. 2014;5:686. doi:10.3389/fmicb.2014.00686.

169. Spring M, Polhemus M, Ockenhouse C. Controlled human malaria infection. *Journal of Infectious Diseases*. 2014;209(Suppl. 2):S40–5.
170. Hodgson SH, Juma E, Salim A, Magiri C, Njenga D, Molyneux S et al. Lessons learnt from the first controlled human malaria infection study conducted in Nairobi, Kenya. *Malaria Journal*. 2015;14:182. doi:10.1186/s12936-015-0671-x.
171. Kilama WL. Health research ethics in malaria vector trials in Africa. *Malaria Journal*. 2010;9:S3.
172. Andrade-Narvaez F, Canto-Lara SB, Garcia-Miss MDR. Leishmaniasis entomological field studies: ethical issues. *Developing World Bioethics*. 2009;9(3):157–60.
173. Achee NL, Youngblood L, Bangs MJ, Lavery JV, James S. Considerations for the use of human participants in vector biology research: a tool for investigators and regulators. *Vector Borne and Zoonotic Diseases*. 2015;15(2):89–102.
174. Ndebele P, Musesengwa R. Ethical dilemmas in malaria vector research in Africa: making the difficult choice between mosquito, science and humans. *Malawi Medical Journal*. 2012;24:65–8.
175. Pereira Lima JB, Rosa-Freitas MG, Melo Rodovalho CM, Santos F, Lourenço-de-Oliveira R. Is there an efficient trap or collection method for sampling *Anopheles darlingi* and other malaria vectors that can describe the essential parameters affecting transmission dynamics as effectively as human landing catches? -A Review. *Memórias do Instituto Oswaldo Cruz*. 2014;109(5):685-705.
176. Malaria in pregnant women. Geneva: World Health Organization; 2017 (https://www.who.int/malaria/areas/high_risk_groups/pregnancy/en/, accessed 15 July 2020).
177. Friedman EE, Dallah F, Harville EW, Myers L, Buekens P, Breart G et al. Symptomatic dengue infection during pregnancy and infant outcomes: a retrospective cohort study. *PLoS Neglected Tropical Diseases*. 2014;8(10):e3226. doi:10.1371/journal.pntd.0003226.
178. Zika virus: key facts. Geneva: World Health Organization; 2018 (<https://www.who.int/news-room/fact-sheets/detail/zika-virus>, accessed 15 July 2020).
179. Heyrana K, Byers HM, Stratton P. Increasing the participation of pregnant women in clinical trials. *JAMA*. 2018;320(20):2077–8. doi:10.1001/jama.2018.17716.
180. WHO community engagement framework for quality, people-centred and resilient health services. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/bitstream/handle/10665/259280/WHO-HIS-SDS-2017.15-eng.pdf>, accessed 15 July 2020).
181. Community engagement for quality, integrated, people-centred and resilient health services. Geneva: World Health Organization (<https://www.who.int/servicedeliverysafety/areas/qhc/community-engagement/en/>, accessed 15 July 2020).
182. Framework on integrated, people-centered health services: report by the Secretariat. In: Sixty-ninth World Health Assembly. Geneva: World Health Organization; 2016 (http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_39-en.pdf, accessed 15 July 2020).

183. Otmani del Barrio M. Social dimensions factored into mosquito-borne diseases, their prevention and control: from a global perspective to the Zika case in Latin America. In: Claeys C, editor. *Mosquitoes management: between environmental and health issues*. Bern: Peter Lang B; 2019 (<https://www.peterlang.com/view/9782807602434/chapter02.xhtml>, accessed 15 July 2020).
184. Selgelid MJ. Gain-of-function research: ethical analysis. *Science and Engineering Ethics*. 2016;22(4):923–64.
185. *Community engagement: module B5*. Geneva: World Health Organization (<https://www.who.int/risk-communication/training/Module-B5.pdf>, accessed 15 July 2020).
186. Kothari U, Cooke B. The case for participation as tyranny. In: Kothari U, Cooke B, editors. *Participation: the new tyranny?* London: Zed Books; 2001.
187. Diabate A. Target Malaria proceeded with a small-scale release of genetically modified sterile male mosquitoes in Bana, a village in Burkina Faso. *Target Malaria*, 1 July 2019 (<https://targetmalaria.org/target-malaria-proceeded-with-a-small-scale-release-of-genetically-modified-sterile-male-mosquitoes-in-bana-a-village-in-burkina-faso/>, accessed 15 July 2020).
188. Resnik DB. Ethical issues in field trials of genetically modified disease-resistant mosquitoes. *Developing World Bioethics*. 2014;14(1):37–46.
189. Beisel U, Ganle JK. The release of genetically engineered mosquitoes in Burkina Faso: bioeconomy of science, public engagement and trust in medicine. *African Studies Review*. 2019;62(3):164–73.



Vector-borne diseases (VBDs) are a major contributor to global morbidity and mortality and have a disproportionate impact on the world's poorest populations. However, despite the growing burden and threat of VBDs to individuals, families and societies, the significant ethical issues raised by VBDs have received only limited attention. Recognizing this gap, WHO developed this guidance to help programs and staff working in VBD prevention and control identify and respond to the core ethical issues at stake.

The guidance was developed by an international group of experts in vector control, infectious disease ethics, maternal and child health, ecology and climate change, research and vaccine development, and public health communication. It examines a broad range of ethical considerations related to VBD prevention and control, including the social and environmental determinants of health; vector control methods, including emerging technologies; screening, surveillance and research; vaccine campaigns and mass drug administration. Grounded in a multidisciplinary framework, the guidance emphasizes the critical role of community engagement in designing and implementing an appropriate, sustainable public health response.

**Health Ethics and Governance Unit
Research for Health Department
Division of the Chief Scientist**

**Veterinary Public Health, Vector Control and Environment Unit
Department of Neglected Tropical Diseases (NTD)
Division of Communicable and Noncommunicable Diseases**

World Health Organization
Avenue Appia 20
1121 Geneva 27
Switzerland

