

ETHICAL ISSUES ASSOCIATED WITH VECTOR-BORNE DISEASES

REPORT OF A WHO SCOPING MEETING
GENEVA, 23–24 FEBRUARY 2017



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Executive summary

Vector-borne diseases (VBDs) are associated with heavy burdens, particularly in poor and vulnerable communities. Their transmission by vectors provides opportunities for specific public health interventions and gives rise to unique ethical issues. Despite their growing importance, ethical issues associated with VBDs have not previously been explored comprehensively.

Many VBDs are prototypical examples of “neglected diseases”. This is ethically problematic because, when research and control activities are not proportional to disease burden, the consequences include avoidable harm (particularly for the poor) and failure to predict and prepare for epidemics (as was observed during the recent outbreaks of Zika virus infection and yellow fever).

More generally, the burden of VBDs is inequitably distributed among the poor, and pregnant women and children are often at highest risk. Such vulnerability in terms of the social determinants of VBDs is compounded by environmental factors. When the influence of climate change increases VBD burden among the worst-off groups of humankind, existing global injustice is exacerbated.

Appropriate policy-making often requires explicit consideration of not only scientific but also ethical matters. Yet, the ethical issues that arise in VBD control and research have not previously received the analysis necessary to further improve public health programmes, and WHO Member States lack specific guidance in this area.

On 23–24 February 2017, WHO held a scoping meeting to identify the ethical issues associated with VBDs. At the meeting, over 25 international and WHO experts discussed salient ethical issues and the main features of a future guidance document. They mapped the ethical issues associated with VBDs, highlighting in particular: environmental and social determinants of health, the ethics of vector control (including new technologies), relevant aspects of ethics in surveillance and research, and the ethics of mass public health interventions.

These main topics will form the basis of a project to identify and analyse ethical issues associated with VBDs more comprehensively, with the eventual aim of providing relevant WHO guidelines within the next two years.

1. Introduction

Vector-borne diseases (VBDs) are important causes of global morbidity and mortality. More than half the global population is at risk, yet the burden of VBDs falls disproportionately on the poorest and the most vulnerable individuals and populations (1). Thus, poverty is closely linked to the incidence of VBDs, and the cycle of poverty and disease is self-perpetuating (2,3). As many of the social determinants of poor health are clustered in populations with high burdens of VBDs, improving public health interventions for these neglected diseases can promote global health justice (2). Like other health problems of the poor, many VBDs were neglected for decades, with insufficient funding for surveillance, research and control, as exemplified in the recent outbreaks of Zika virus infection and yellow fever, with significant health consequences. Such emergencies highlight the urgent need to fill these gaps and implement global health policies aimed at more equitable distribution of resources and health benefits.

Vectors are sensitive to environmental factors. Climate change is already increasing the burden of some VBDs, with a greater impact on the most vulnerable, thus exacerbating social injustices (4–7). Recent advances in science have, meanwhile, led to new vector control technologies, including genetically modified mosquitoes. Climate change and novel technologies thus provide additional, new reasons to ethically evaluate current and future VBD policies. Important priorities should include ensuring that inequities in disease burdens are not exacerbated, that risks are mitigated where possible, and that public health decisions (potentially affecting large populations) are based upon good governance and careful risk–benefit assessment.

Of the VBDs, malaria is responsible for the largest global disease burden. At the turn of the twenty-first century, only 2% of infants at risk for malaria in sub-Saharan Africa slept under a long-lasting insecticidal net. (versus 68% in 2015), while the disease caused over 1 million deaths in the WHO African Region annually (8). Increased funding and control of malaria since 2000 have been part of an ethical reframing of global health priorities. Improved, intensified control has averted an estimated 600 million deaths from malaria alone (8). However, many challenges remain for this disease and for other even more neglected VBDs.

The unique defining feature of VBDs is their transmission by vectors. Thus, their epidemiology is influenced by factors that affect the vectors as well as by host factors. This provides opportunities for disease control that

are not available for other infectious diseases, and also raises ethical issues that specifically concern vector control and are therefore unique to VBDs. These unique issues include the ethics of coercive or mandated vector control, the use of insecticides (and growing vector resistance to insecticides), and research on and/or deployment of new vector control technologies. Other important, under-examined ethical issues that are not unique to VBDs, but loom large in the context, include justice implications of environmental and social determinants of health; screening and vaccination; approaches to asymptomatic infection, mass drug administration and antimicrobial resistance; and research ethics issues such as human challenge studies and the need for research on pregnant women and children. Recent outbreaks have shown that it is time to focus greater ethical attention on all these issues.

Given the wide array of issues and the lack of previous attention to the ethical issues associated with various aspects of VBDs, the WHO Global Health Ethics unit organized a scoping meeting in Geneva on 23–24 February 2017 to map the largely unexplored terrain of relevant ethical issues associated with VBDs, with perspectives from multiple disciplines and contexts. The meeting brought together key WHO stakeholders in VBDs, vector control, maternal and child health, ecology and climate change, research and vaccine development, communication in disease outbreaks, and independent external experts (**Annex 2**). The external experts were selected for their contributions to technical aspects of vector biology and disease control and/or infectious disease ethics. The final aim of the project is to produce, within two years, a guidance document providing the first comprehensive analysis of the ethical issues raised by VBD prevention and control.

Presentations and discussions on day 1 provided background information on the biology, epidemiology and control of VBDs and the ways in which these aspects give rise to important ethical considerations. Participants focused on the ethical implications of social and environmental determinants of health in the context of VBDs. They discussed the roles of gender, pregnancy and childhood in the epidemiology and control of VBDs, and the impact of climate change. These considerations were supplemented by presentations of field experience in the surveillance and control of VBDs. Initial discussions addressed several cross-cutting issues, including community engagement and risk communication and vulnerability as well as important gaps in research, surveillance and control.

Presentations and discussions on day 2 addressed ethical issues in vector control, surveillance and research priorities, VBD research methods and new vector control technologies. The ethical issues that were raised in standard vector control included equity of access, vector resistance, risks of rebound disease, vector elimination and potential conflicts between the benefits and risks at individual and community levels in certain contexts (e.g. vaccination, mass drug administration and antimicrobial resistance). The issues discussed in surveillance and research ethics included human landing catches, human challenge studies, and responding to important gaps in order to sustain and increase the benefits of disease control. New vector control technologies were reviewed and preliminary discussions held on governance and decision-making for future deployment.

2. Background

2.1 Vectors, burdens and transmission

Although billions of people are at risk for VBDs, those with multiple sources of vulnerability, such as poverty, insufficient access to high-quality housing and sanitation, and rural habitation (although urban vectors such as *Aedes* are increasingly important) are at greatest risk. While vectors usually transmit diseases between people (or between animals and people) over short distances, the range and speed of global travel play an increasingly important role in widespread VBD transmission. Long-distance travel by infected humans and accidental transport of infected vectors can give rise to international epidemics – as evidenced by the recent outbreaks of Zika virus infection and yellow fever.

Effective control measures require an understanding of the changing epidemiology of VBDs in humans. Several factors influence transmission patterns: the biology and evolutionary history of VBDs; vector behaviour and climate sensitivity; and human risks and behaviour.

VBDs are associated with multiple biological phyla (**Table 1**), and VBD pathogens have complex life cycles involving humans, vectors and (in some cases) intermediate animal hosts. Many VBD pathogens evolved from zoonoses in parallel with the development of human settlements, and this evolutionary history underlies the complex life cycles and transmission patterns of VBDs, such as the way in which yellow fever outbreaks in humans follow from a cycle in monkey populations. Therefore, contemporary environmental and socioeconomic changes (e.g. in land use, agricultural expansion and climate) may increase the likelihood of animal–human transmission (“spillover”), for example by altering the dynamics of transmission among natural reservoir hosts, the geographical footprint of endemic areas, and the type and frequency of human–animal interactions. These phenomena call for multi-sector surveillance, including strengthening veterinary and wild animal surveillance and enhancing intersectoral coordination with public health agencies to improve the prediction of human epidemics.

Blood-feeding arthropods are the chief vectors involved (Table 2), although meeting participants also discussed non-arthropod-transmitted pathogens (e.g. schistosomiasis), which may raise similar ethical issues. Mosquitoes, which are extremely sensitive to environmental factors such as temperature and rainfall, transmit around 80% of human vector-borne infections. Environmental changes and resulting effects on agricultural practices can thus affect transmission. Disease control is complicated by vector behaviour, such as the long-term evolutionary adaptation of *Aedes* mosquitoes to breeding in artificial containers and, more recently, changing biting times in response to control interventions.

The epidemiology, and therefore the control, of VBDs depends on whether transmission via the vector is primarily human-to-human (e.g. malaria and dengue) or only animal-to-human (e.g. Rift Valley fever and West Nile fever) and on the rate of asymptomatic infection. The high prevalence of asymptomatic infections in many VBDs raises distinct ethical issues. For example, many cases of arboviral infection, including with Zika (about 80% asymptomatic), yellow fever and dengue viruses, produce mild or no symptoms. It is important to recognize that even infections with no or mild symptoms can contribute to disease transmission and therefore pose a risk to others.

Better understanding of the complex interactions among animals, humans, vectors and the environment has improved vector control strategies, but numerous challenges remain (Box 1).

Table 1. Vector-borne diseases by biological category

Virus	Bacteria	Parasite
Dengue	Plague	Malaria
Yellow fever	Rickettsiosis	Chagas disease
Zika	Borreliosis	Dracunculiasis (guinea-worm disease)
Chikungunya	Tularaemia	Lymphatic filariasis
Japanese encephalitis	Evaluate contamination effects	Leishmaniasis
Crimean–Congo haemorrhagic fever	Assess blinding	Onchocerciasis (river blindness)
Rift Valley fever		Schistosomiasis
Sandfly fever (phlebotomus fever)		Human African trypanosomiasis (sleeping sickness)
West Nile fever		
Tick-borne encephalitis		

Table 2. Major vector-borne diseases and their vectors

Disease	Main vector
Malaria	<i>Anopheles</i> mosquitoes
Arboviruses: dengue, yellow fever, chikungunya, Zika, Japanese encephalitis	<i>Aedes</i> mosquitoes
Japanese encephalitis	<i>Culex</i> mosquitoes
Lymphatic filariasis	Various mosquitoes
Rift Valley fever	<i>Aedes</i> mosquitoes
West Nile fever	<i>Culex</i> mosquitoes
Leishmaniasis	Sandflies
Onchocerciasis (river blindness)	Black flies
Human African trypanosomiasis (sleeping sickness)	Tsetse flies
Sandfly fever (phlebotomus fever)	Sandflies
Dracunculiasis (guinea-worm disease)	Water fleas
Chagas disease	Triatomine bugs
Crimean–Congo haemorrhagic fever	Ticks
Tick-borne encephalitis	Ticks
Borreliosis (Lyme disease)	Ticks
Schistosomiasis	Freshwater snails
Plague	Fleas
Tularaemia	Ticks, deer flies
Scrub typhus	Mites

Box 1. Challenges to control of vector-borne diseases

- gaps in access to (existing) control measures;
 - effective vaccines and/or treatments have not been developed;
 - effective vaccines and/or treatments have been developed but production, and thus supply, is inadequate;
 - resistance of pathogens to treatment;
 - resistance of vectors to insecticides;
 - prevalence of asymptomatic infection driving transmission; and
 - difficulty in predicting the emergence of new vector-borne diseases (e.g. zoonoses) and/or their geographical spread (e.g. due to globalization and/or environmental change).
-

2.2 Framing the ethical issues

Vector-borne diseases raise unique ethical issues because pathogens are transmitted between humans by a third party – the vector – and because of the unique aspects of vector control, including with novel techniques. VBDs are also an especially important topic for ethical analysis because they have severe consequences: large disease burdens, potential international spread (wherever vectors are present) and significant rates of asymptomatic infection driving outbreaks. Like other infectious diseases, VBDs are closely linked to poverty and the environmental and social determinants of health, raising issues of global health injustice.

Participants agreed that the scope of the meeting, and a future VBD ethics guidance document, should include both ethical issues that are essential and/or unique to VBDs and those that are highly salient in the context of VBDs but contingent in the sense that they are not necessarily, or solely, raised by VBDs. They acknowledged that some ethical considerations might be specific to a particular VBD, while others might apply to VBDs in general.

Box 2. Ethical importance of vector-borne diseases

Severe consequences or harms:

- large disease burden;
- international spread and public health emergencies;
- high economic costs and effects on economic development; and
- large pool of asymptomatic carriers.

Issues of justice:

- inequitable burden (disproportionately affecting vulnerable populations);
- ethical implications of social determinants of health;
- inequitable access to treatment and control;
- unequal distribution of benefits and burdens in community interventions; and
- disproportionately low research resources relative to disease burden.

Issues unique to vector-borne diseases:

- ethics of vector surveillance, control and research; and
 - new technologies for vector control.
-

Many interventions for VBDs, from long-lasting insecticidal nets and eliminating domestic vector breeding sites to mass drug administration, have benefits that extend from one individual to others by a reduction in disease transmission. Thus, VBD control with population-level benefits often requires collective action by many community members in addition to centralized public health interventions. Prevention and vector control initiatives should be ethically motivated by a collective moral responsibility to prevent harm and achieve public health benefits. The distribution of eventual benefits from collective action to prevent and

control VBDs is likely to be concentrated first and foremost among the most vulnerable (e.g. pregnant women and infants). The pattern is similar to that of (other) vaccine-preventable diseases, where vulnerable groups may benefit most from herd immunity. The social distribution of health benefits provides additional moral reasons for intervening at the community level in order to decrease the harm of VBDs in vulnerable groups.

The unique issues raised by VBD-specific interventions are important topics, but no previous document has provided comprehensive coverage of ethical issues associated with vector control. New techniques for VBD control (such as genetically modified mosquitoes) raise new ethical issues. While the governance mechanisms appropriate to such technology may parallel those applied elsewhere (for example, covering genetic modification of organisms more generally), the potentially significant, geographically widespread effects of vector modification warrant especially careful attention.

3. Environmental and social determinants of health

3.1 Gender

Understanding how gender issues contribute to risk for VBDs requires more than aggregate statistics of the disease burden among females and males. Analysing VBD incidence, prevalence and control “through a gender lens” can help improve policies and programmes. By identifying barriers to access and control over relevant resources, a gender analysis can help identify solutions that help to promote equity.

The “gender roles framework” (or “Harvard analytical framework”) is a useful approach that was fruitfully applied to the analysis of malaria incidence in the Ghana demographic health survey, and is now being applied to analyses of schistosomiasis and Rift Valley fever. The framework has three components (**Box 3**). Answering its detailed questions about socioeconomic activity, access and control as well as other factors that influence disease burden can provide more detailed data (9) – which should be used to improve research and control programmes. For some VBDs, public health interventions should target women or men differently according to their roles and exposure.

Box 3. Implementing the “gender roles framework” for vector-borne diseases

Components:

- socioeconomic activity: “Who does what, when, where and for how long?”;
- access and control: “Who has access to resources (land, equipment, capital) and benefits (education, health, political)? Who has control over these resources and benefits?”;
- influencing factors: “What political, economic, cultural and social factors determine the gender differences in socioeconomic activity, access and control?”.

Examples:

- analysing access to and control of long-lasting insecticidal nets for malaria as a way of addressing implementation gaps;
 - risk for schistosomiasis of women collecting water; and
 - risk for Rift Valley fever of men with occupational exposure to infected animals.
-

Opportunities for intervention depend on social roles. For example, the risk for schistosomiasis is associated with exposure to water and infected freshwater snails. Thus, in many communities women will be at higher risk, especially where they are primarily responsible for collecting water and doing laundry. Educating women about the risks of exposure to water and educating the general community about the consequences of urinating or defecating upstream from areas in which water is collected may help to reduce the disease burden, but these factors will depend on the context, requiring a nuanced approach. Furthermore, as environmental factors and agricultural practices change, risks will change. The trend of increasing female participation in the (often unpaid) agricultural workforce of sub-Saharan Africa and the increasing use of irrigation to combat severe drought mean that the role- and context-dependent risks of exposure to water will evolve over time.

In contrast, the risk for Rift Valley fever is due primarily to mosquitoes or direct contact with the blood of infected animals. Because the occupational risk groups in this case include male-dominant roles such as herders, farmers, slaughterers and veterinarians, a “gender roles framework” may also be useful for improving education and control programmes for men.

3.2 Pregnancy

The public health emergency of international concern associated with the epidemic of Zika virus in 2015–2016, which was centred in Brazil, brought into sharp focus the ethical importance of reproductive freedom for women, especially those infected with neglected VBDs during pregnancy. Vulnerability is a product of numerous social determinants of health (e.g. poverty, malnutrition and insufficient access to health care); and the infected woman of reproductive age in a poor community represents a case of exceptional, multifactorial vulnerability.

Zika virus infection is not, however, the only VBD prevalent in these communities: pregnant women and their unborn children and infants are key risk groups for other mosquito-borne diseases, such as malaria and dengue (Table 3). More research is urgently required to clarify the complex interactions between these diseases and pregnancy (including coinfection with multiple pathogens), and the full consequences of such infections for women and their children.

Table 3. Pregnancy and vector-borne diseases

Effects of vector-borne diseases in pregnancy	Example
Higher risks for severe disease	Severe or fatal malaria in pregnancy
Increased pregnancy-related morbidity and mortality	Malaria exacerbating anaemia of pregnancy
Increased adverse pregnancy outcomes	Dengue producing low birth weight or miscarriage
Vertical transmission	Chikungunya
Congenital infection	Congenital Zika virus syndrome, congenital West Nile virus syndrome
Relative immunosuppression of pregnancy as a predisposition to chronic infection	Schistosomiasis
Sexual transmission of infection to pregnant women	Consideration of partner screening and barrier contraception for women with Zika virus infection
Effective treatments not used in pregnancy because of lack of data on safety	Lack of research on safety of novel antimalarials in pregnancy

During the meeting, the WHO team for Maternal and Perinatal Health and Preventing Unsafe Abortion commented on the importance of protecting both the mother and the child in providing an even stronger ethical rationale for improving access to vector control (e.g. long-lasting insecticidal nets) and treatment during pregnancy and the perinatal period. Some interventions are known to have significant, immediate benefits – for example, mass drug administration for malaria in pregnancy – but the long-term outcomes of such policies should be monitored more closely, as drug resistance is an increasing problem. This problem is even greater in pregnancy because of longstanding, exceptional neglect of research with pregnant women, so that the safety and efficacy of new drugs during pregnancy are unknown.

For similar reasons, the consequences of infection during pregnancy are unknown for many VBDs. Furthermore, research with pregnant women requires early confirmation of pregnancy, i.e. universal access to antenatal care, which is still lacking in many regions and populations. The participants agreed that there is a strong rationale for extending access to antenatal care and conducting more, safe, ethical research involving pregnant women in order to address these gaps.

The importance of such efforts has been highlighted by the ethical imperatives in research and development of a Zika vaccine (**Box 4**) (10). As congenital Zika virus syndrome is the most severe outcome of Zika virus infection, vaccine research should particularly be aimed at reducing the risk of infection in pregnant women – although a significant challenge is that Zika infection could occur before a woman realizes that she is pregnant.

Box 4. Key ethical imperatives for research on a vaccine against Zika virus infection in pregnancy

Components:

- Develop a vaccine, ideally one that is safe in pregnancy and/or protects pregnant women (e.g. by vaccinating girls before childbearing age).
 - Allow pregnant women and women of childbearing age to access trials of vaccines against Zika virus infection, with ethical oversight.
 - Collect data on the safety of vaccines against Zika virus infection in pregnancy (e.g. data regarding women who are accidentally vaccinated in early pregnancy), even if they are not intended for pregnant women.
-

The Zika virus epidemic highlighted important policy gaps in terms of reproductive freedom and access to reproductive health care, for example in Latin America. In order to protect pregnant women and their children, a number of ethical duties were identified in a consultation on ethical guidance on key issues raised by the Zika virus outbreak (Washington (DC), April 2016) (11) (Table 4), which were widely endorsed at the current meeting. For example, there is a strong ethical rationale to allow women to choose among all relevant reproductive options and to avoid unsafe abortions by providing access to contraception and safe termination of pregnancy. More broadly, pregnant women should have priority for access to effective interventions. Because participation of pregnant women in research is needed to answer especially important scientific questions about VBDs, future guidelines must clarify the ways in which ethics committees and researchers can promote safe inclusion of pregnant women in research.

Table 4. Ethical duties identified in the public health emergency associated with Zika virus

Domain	Example
Research	High standards of ethics oversight for emergency research Community engagement to build trust Duty to involve pregnant women in research Capacity-building in research ethics
Public health	Access to effective interventions in vector control, prevention and treatment Surveillance and data-sharing Clear risk communication, updated with rapidly changing scientific knowledge
Service delivery	Universal access to contraception and reproductive health care Availability of safe abortion Facilitation of informed decision-making
Government and communities	Support of reproductive liberty Support of women's choices Support for parents and caregivers of affected children

3.3 Childhood

Infants and children are important risk groups for many VBDs, and they are dependent on their parents and their local communities for meeting general needs, including access to VBD prevention and treatment. Children are vulnerable to VBDs (and other health problems), partly as a result of their dependence and partly due to physiological factors. Meeting participants emphasized that illness or chronic infection in early childhood can have significant long-term effects on development, which could be prevented by early intervention. Thus, there is a moral imperative for access to prevention and treatment for children of all ages and developmental stages, for more research to improve these interventions further, and for additional public health interventions designed to reduce social and environmental impediments to healthy development.

Several social and environmental determinants directly affect the exposure and vulnerability of children to VBDs. Social norms on bedtime, for example, may make children more vulnerable than adults to exposure to triatomid vectors (e.g. in the early evening) and Chagas disease, and norms of water storage and waste management affect breeding of and exposure to mosquito and other vectors, often increasing exposure in locations where, and at times of day when, children are outdoors. Likewise, children, their mothers and their caregivers are among the groups most vulnerable to the effects of climate change on vectors.

Vector-borne and other diseases may disrupt childhood neurodevelopment by causing episodes of recurrent illness or more immediately, as seen with congenital Zika virus syndrome. Like interventions to improve access to nutrition, social services, education and health care, those aimed at reducing exposure to vectors help to fulfill responsibilities to improve conditions for neurodevelopment and lead to significant long-term benefits.

Meeting participants agreed that policy decisions should address not only current children but also future generations. Despite the difficulties and uncertainties of projecting future benefits, long-term objectives such as sustainably reducing, eliminating and eradicating vectors and VBDs should be actively pursued via evidence-based, socially sensitive means.

3.4 Environment and climate change

Broad environmental mechanisms that affect the epidemiology of VBDs include climate change, biodiversity loss, changes in hydrological systems, urbanization and coastal depletion. Climate change is expected to alter the prevalence and geographical range of many relevant vectors, resulting in intensification of transmission, extension of transmission seasons and/or re-emergence of disease(s). WHO projections based on a subset of climate-related health impacts are 250 000 excess deaths attributable to climate change per year between 2030 and 2050, including 60 000 due to malaria (12). Separate analyses suggest that the effects of climate change on *Aedes* mosquito vectors will increase the proportion of the global population at risk for dengue from 35% to 50–60% by 2085 (13).

The populations of low- and middle-income countries have contributed least to the causes of climate change yet remain the most vulnerable to the harms of climate change, including potentially increased exposure to VBDs (7, 12). This inequity is of profound ethical concern, as the future epidemiology of VBDs (and other climate-sensitive diseases) will likely show exacerbation of the existing stark global injustices in health and other contexts. Indeed, projections of excess mortality in future climate scenarios are strongly influenced by assumptions of continued economic growth and health progress, which could be further threatened by increased exposure of the most vulnerable to VBDs and climate-related harm (12).

The meeting was briefed on relevant work of the Vectors, Environment and Society unit of the WHO Special Programme for Research and Training in Tropical Diseases. The aim of the unit is to promote research, build capacity and develop collaborations to enhance community access to improved control interventions that would reduce the burden of disease (including VBDs) among the most vulnerable people. It focuses on translation of research findings into a beneficial public health impact. The unit also manages

and coordinates a research initiative comprising projects designed to fill gaps in knowledge on the effects of a changing climate and social factors on disease transmission. The aims of these projects are to (i) characterize local social-ecological systems; (ii) assess risks associated with various conditions of exposure (climate variation and environmental factors) and vulnerability (social determinants of health); (iii) develop practical frameworks, processes and tools for policy- and decision-making, for better risk management; and (iv) build African capacity for interdisciplinary policy-oriented research. In a promising link between these and the topics discussed above, gender is mainstreamed across the projects to better understand gender dynamics, how these influence patterns of disease and to ensure successful control measures.

At a broader policy level, the overall ethical priorities regarding potential adverse VBD impacts of climate change are (i) to obtain further evidence of the impact of climate change on VBDs and (ii) to accelerate VBD prevention and control and/or elimination in order to reduce the incidence associated with climate change. Likewise, improving surveillance in areas where the disease burden is poorly characterized would have the additional benefit of improving preparedness and response to future epidemics, potentially averting significant harm.

Strengthening the adaptive capacity and resilience of communities and health systems and promoting climate change mitigation strategies are critical to protecting human health. A reduction in greenhouse gas emissions would have important co-benefits to health, particularly in light of the global health risks from air pollution that causes around 7 million deaths per year (14, 15).

4. Field experience

The meeting benefitted from detailed presentations (summarized below) of field experience in Burkina Faso (African Region), Cambodia (Western Pacific Region) and Singapore (Western Pacific Region) and also incidental discussions of experience elsewhere (e.g. Zika virus infection in Latin America).

4.1 Burkina Faso

Practical and ethical issues in the control of malaria, arboviral diseases and neglected tropical diseases

This presentation focused on current issues in local VBD control. In recent decades, the country's public health programmes have eliminated onchocerciasis and human African trypanosomiasis. Current challenges have included the 2016–2017 yellow fever epidemic and endemic VBDs.

The yellow fever epidemic demonstrated that vaccination against VBDs cannot entirely replace vector control unless the vaccine is highly effective and the access of populations at risk is almost universal. A number of recent cases among unvaccinated individuals exposed the vulnerability of the vaccine supply, and use of fractional dosing raised the issue of uncertain long-term effectiveness. It was noted that the International Health Regulations (2005) yellow fever vaccination requirements were not always enforced at border crossings, especially at land borders.

Use of the first partially effective vaccine against malaria also showed that vaccination will be only one tool among many in VBD control, albeit a potentially valuable, cost-effective one. The mainstays of malaria

control in Burkina Faso are long-lasting insecticidal nets and mass drug administration. Groups at risk for malaria, such as pregnant women and children, are priorities for bed net distribution, but inequities in access persist in some areas, as does the problem of inappropriate net use. One positive outcome of community engagement has been the use of bed nets of culturally appropriate colours; for example, as white is associated with local death rituals, use of green nets (Fig. 1) led to greater uptake, showing that culturally appropriate public health programmes and community engagement can improve the coverage of vector control interventions.

Mass drug administration is widely used for multiple purposes in Burkina Faso, including intermittent preventive treatment for malaria in pregnancy and in infancy and against schistosomiasis, lymphatic filariasis and onchocerciasis. The challenges include access, compliance, counterfeit drugs, drug resistance and long-term surveillance for effectiveness. Some vulnerable pregnant women may be difficult to reach with intermittent preventive treatment as they have minimal or no antenatal care into which the intervention can be integrated. Genetic mutations that confer resistance to antimalarial drugs have been identified in research settings, but the tests have not yet been widely used in surveillance.

Challenges to the control of other VBDs include shortages of diagnostic tests for dengue, resulting in nonspecific treatment for febrile illnesses in areas co-endemic for malaria and dengue. Local health authorities encounter many ethically relevant policy questions associated with priority setting (e.g. prevention versus treatment) in the context of limited resources, most of which are obtained externally.

Fig. 1. Culturally appropriate bed net in Burkina Faso



4.2 Cambodia

Ethical challenges in outbreak investigation

This presentation focused on outbreak investigations, for which the country maintains public health teams ready for deployment. Reference was made to vigilant surveillance for local cases of Zika virus infection, given the presence of vector mosquitoes and the international spread of infection during 2016. Malaria and dengue are addressed in one programme in order to benefit from cross-cutting mosquito control interventions and other (mainly parasitic) VBDs in a separate programme.

The challenges of outbreak investigation were discussed extensively. It was noted that a false-positive result for a high-profile VBD such as Zika virus infection could have significant consequences, including not only the expenditure of public health resources but also stigmatization and economic consequences for individuals and communities and, in some cases, even far-reaching political consequences.

The participants noted that maintaining a balance between transparency about public health activities and protecting the privacy of individuals and/or the confidentiality of their health information could be difficult. When infection of one person poses serious risks to others, the balance may be in favour of public health interventions to prevent an outbreak, during which care must be taken to protect individual privacy when possible; it was acknowledged that this is not always possible. Any unavoidable violation of privacy by a public health activity should be weighed against its probable public health benefits and the possibility of alternative control measures.

Given the possibility of false-positive results in early outbreak investigations, care should be taken to confirm any suspected diagnosis and the associated public health risks before launching a full-scale intervention. It was noted that the large proportion of asymptomatic cases in diseases such as Zika virus infection means that, in many circumstances, a suspected index case would probably be only one among many, so that targeting one individual might be neither effective nor ethical. Thus, the intervention(s) to be used in a possible outbreak should be a matter of careful technical and ethical deliberation on the probable risks, benefits and costs.

4.3 Singapore

Combining high-quality dengue surveillance with public engagement

Over several decades, Singapore has made significant gains in VBD control by improving housing, with well-resourced surveillance and control programmes and public engagement. Dengue control is a prime example, although dengue outbreaks persist despite excellent vector control. A rigorous system for dengue control has had cross-cutting benefits for control of chikungunya and Zika virus infection.

Singapore employs about 800 mosquito inspectors in a resource-intensive “search-and-destroy” approach to ensure full participation in vector control strategies. Households with active mosquito breeding sites are rare (about 1%), so that inspectors have to “knock on 100 doors to find one breeding ground”. Penalties are imposed on the owners of premises that enable breeding of disease vectors. The authority has legal powers to inspect premises, including when they are unoccupied, after advance notice. This is required only rarely, when the owner is absent for a long time and there is active transmission around the premises.

At the other end of the technological spectrum, the availability of accurate diagnostic testing, virus characterization and integrated public health data systems results in high-quality surveillance, which has been extended to year-round inter-epidemic prevention and epidemic prediction strategies. Intensified control measures are applied when the predicted risk of an outbreak is high (making interventions more cost-effective) and the risk of an outbreak is also communicated to the public early, potentially averting many cases.

Public engagement and public health publicity have become core activities in Singapore's dengue campaign. Education has focused on preventing mosquito breeding in households and neighbourhoods, with the long-term aim of forming habits in the majority of the population that will promote public health. In the near future, Singapore plans to deploy *Wolbachia* for arboviral vector control (see **section 7.5.1**), explicitly considering this to be part of an overall policy of adaptation to climate change.

5. Engagement with the community

Engagement with the community and with the public was identified as a cross-cutting issue in many contexts. Participants were briefed on methodological and ethical issues in community engagement and risk communication, including how they have evolved in some contexts with modern communications technology, i.e. the Internet and social media.

Participants commented that people in populations affected by VBDs have a right to be aware of public health responses and to be involved in decision-making at all stages, including in the design and implementation of surveillance and early detection, policies for outbreak preparedness and containment, strategies to mitigate epidemics and for continuous disease control. VBD control is immensely complex and often involves significant uncertainty. This does not, however, remove the ethical obligation to respect and to communicate clearly with the members of the communities in which the activities are conducted; nor does it remove the ethical obligation of public health agencies to use calculated policies (e.g. mass vaccination) for the general good.

In trans-national outbreaks, international coordination between multiple public health actors is crucial for appropriate and effective interventions. Responses to outbreaks should include public engagement aimed at raising awareness in the international community in order to foster trust and encourage data-sharing, both of which enhance global surveillance and research. Communication on travel during outbreaks and the ethics of travel bans were briefly discussed in the context of the recent epidemic outbreaks of Zika virus infection and yellow fever. When there is a significant rate of asymptomatic infection, travel bans are unlikely to result in long-term protection against the international spread of a disease; and, for political and economic reasons, travel bans should be used with caution and only after international consultation. In general, policy-makers who are considering restricting travel or imposing mandates on travellers should weigh the importance of free individual movement (and thus the direct and indirect burdens of travel bans) against the

likely benefits of such a policy. When the risk to others is significant (e.g. a potentially large outbreak due to the arrival of an infected individual in a country without the disease but with relevant vectors), there may be good prima facie moral reasons to curtail individual liberty, but this should be considered only when doing so will actually reduce harm to others and when less restrictive options are unlikely to be sufficiently effective.

As access to modern communication increases, some people obtain health information (or misinformation) online, such as through social media. While public health agencies would do well to make use of such technologies, some people might still prefer and/or place greater trust in face-to-face oral communication, as was the case during the epidemic of Ebola virus disease in 2014–2015. This is another area in which context-specific sociocultural information obtained before and during an outbreak can be invaluable.

6. Vector control

6.1 Vector control and elimination

The aim of public health interventions for VBDs may be eradication, elimination or control of vectors. In some cases, achieving such objectives involves concerted efforts to eliminate a vector population locally or perhaps globally by the use of insecticides or other measures. Historical examples include the elimination of *Anopheles gambiae* mosquitoes from Brazil and of *Aedes aegypti* mosquitoes in large areas of South America during the twentieth century. More recently, sustained campaigns have succeeded in eliminating Chagas disease vectors from parts of South America and onchocerciasis vectors from parts of Africa. Meeting participants were briefed on the possible ecological consequences of such programmes. These are not always well described, but there is some evidence that other mosquito species commonly replace those that have been eliminated. This is beneficial when the new species has less vectorial capacity or is not a vector for the disease in question. Elimination of a vector is not, however, necessary for eliminating a VBD.

Important ethical issues raised at the meeting regarding vector elimination included the need for specified objectives (e.g. disease reduction, control or elimination), long-term political commitment to ensure sustained activities and international governance mechanisms when one country's vector elimination strategy may affect or be affected by the policies of its neighbours. Surveillance for vector resistance to insecticides or the reintroduction of vectors was identified as important in order to prevent a potential rebound in disease burden.

6.2 Vector control measures

The global vector control response (2017–2030) was recently reviewed comprehensively (16), and WHO recommends integrated vector management in the control of VBDs. The aim of this strategy is to ensure effective, locally adapted, sustainable vector control to reduce the burden and threat of VBDs. Vector control frequently involves use of an insecticide (or molluscicides for snail vectors), but other approaches are also important (e.g. covering water containers to prevent vector breeding).

Mosquitoes are the main targets, as most of the more than 1 million VBD deaths annually are caused by mosquito-borne diseases (1, 17). Vectors can be targeted throughout their life cycle, from larvae to adults, by measures such as removing or placing netting over household water storage vessels, larger-scale environmental interventions at breeding sites, larvicides, insecticides, bed nets and, potentially, novel technologies (see **section 7.5**). The overall effectiveness of a given strategy usually depends, among other things, on its acceptance by local communities (e.g. its compatibility with local customs).

In some cases, insecticides have other benefits that may increase their acceptance in a community. For example, residual indoor insecticide spraying or use of treated bed nets in a single household can reduce the capacity of vectors for malaria, leishmaniasis, lymphatic filariasis and arbovirus diseases, and the incidental benefits include a reduction in “nuisance insects”, such as head lice, ticks, bedbugs and cockroaches. Emphasizing these benefits may improve acceptance of indoor residual spraying, as one of the challenges to sustainable vector control is “community fatigue” (**Box 5**). There is nevertheless concern that, by similar mechanisms, outdoor spraying could kill beneficial insects, such as bees, potentially reducing biodiversity, pollination and food yields in some contexts.

Box 5. Challenges to standard vector control measures

Bed nets and long-lasting insecticide-treated nets:

- sustainability
- suitability for sleeping situation (hammock nets or blankets for sylvatic malaria)
- biting times (before or after sleep)
- insecticide resistance

Indoor residual spraying of insecticides:

- no effect on outdoor biting
- replastering of sprayed surfaces
- houses with minimal walls
- insecticide resistance
- community acceptance
- community fatigue after repeated spraying

Outdoor space spraying

- community consent or involvement in decision-making
 - training
 - appropriate targeting (requires excellent surveillance, case histories and prediction of onward spread)
 - potential adverse effects on beneficial insects or other fauna (e.g. honey bees)
-

An urgent gap in vector control is the need for longitudinal, long-term, international surveillance and research to determine entomological and epidemiological effectiveness, to clarify which benefits can be attributed to which interventions (when several are used simultaneously) and to assess insecticide resistance.

6.2.1 Insecticide evaluation and entomological trials

Meeting participants were briefed on evaluations of the safety and efficacy of insecticides for vector control. The WHO Pesticide Evaluation Scheme assesses vector control products by evaluating evidence for their efficacy (e.g. whether a given insecticide reduces vector capacity or would probably be useful in achieving public health benefits) and safety (e.g. the likelihood of short- or long-term adverse effects on humans, biodiversity and ecosystems). New pesticides are evaluated in four phases, from the laboratory to widespread use.

Ethical oversight of such evaluations should include consideration of equitable benefit-sharing among the communities and individuals involved (whether in the intervention or control arm of a trial), the provision of comprehensive information and the right to refuse or withdraw from a trial (although this may be difficult in community field trials). The health of volunteers sleeping in experimental huts, spray operators and net washers must be closely monitored to identify and mitigate risks. Some form of collective decision-making should be in place for interventions that are applied to whole communities. Meeting participants noted that similar ethical issues regarding consent have arisen and been discussed in other contexts, such as cluster-randomized trials (18, 19).

Once insecticides are declared safe for use, by WHO and/or local bodies, numerous ethical issues arise. Meeting participants noted that, in general, household interventions such as long-lasting insecticide-treated bed nets and indoor residual insecticide spraying are voluntary or are encouraged by free provision and community engagement. In the case of outdoor insecticide spraying, careful attention should be paid to obtaining consent (e.g. from individual households and/or the community). Further ethical analysis of policy options is warranted.

6.2.2 Insecticide resistance

Another issue in the use of insecticides for vector control is the growing problem of resistance. The problem is similar to that of antimicrobial resistance, in that frequent or inappropriate use of an insecticide against a vector population (or against agricultural pests) often results in selection of resistant vectors. The mechanism is perhaps best understood in the context of *Anopheles* (malaria vector) mosquitoes and to a lesser degree in that of *Aedes* (arboviral vector) mosquitoes. Yet, there are critical gaps in surveillance and research on vector resistance. The empirical questions include the context-specific consequences of insecticide resistance for public health objectives (i.e. disease control) and the global patterns of resistance in different regions. Ethically, it is important to weigh short-term gains in disease control against the long-term harm of control failure due to resistance. More research (including implementation research) should be done to predict and avert such harm, which could be significant if VBDs resurge when current insecticides fail and other options (e.g. non-insecticide environmental vector management) are not used in time.

In the absence of an integrated platform for surveillance and research on insecticide resistance, a promising recent development is the Worldwide Insecticide Resistance Network (<https://win-network.ird.fr/>), which connects 18 internationally recognized institutions in vector research to track insecticide resistance patterns in arbovirus-transmitting mosquitoes globally. The aims are to identify gaps in surveillance for resistance, identify failure of control due to resistance, fill gaps in knowledge on insecticide resistance and assist decision-making in the management of resistance.

6.2.3 Summary of meeting on Zika virus vector control

The scoping meeting was briefed on similar gaps identified in arbovirus vector control at a recent meeting on Zika virus vector control (Geneva, 21–23 February 2017), which included:

- lack of a standard, evidence-based protocol for *Aedes* vector control;
- inadequate laboratory capacity, especially in endemic areas;
- absence of a well-defined entomological threshold to predict epidemics; and
- gaps in research to characterize the complex effects of herd immunity, viral serotype and local environmental factors, on transmission.

These gaps in arbovirus control exemplify the complexity and neglect of VBDs as well as the difficulty of predicting the consequences of rare pathogens that suddenly become epidemic. The recent Zika virus emergency and the longstanding global arboviral disease burden illustrate the ethical imperative that more must be done to fill the gaps so that more harm can be averted sooner.

6.2.4 Coercive or mandated interventions

The participants raised a key ethical question for policy-makers: When is it justifiable to coerce, mandate or enforce participation in vector control measures? Examples of means used to improve participation are listed in **Box 6**.

Box 6. Incentives, coercion and enforcement used to implement vector control measures

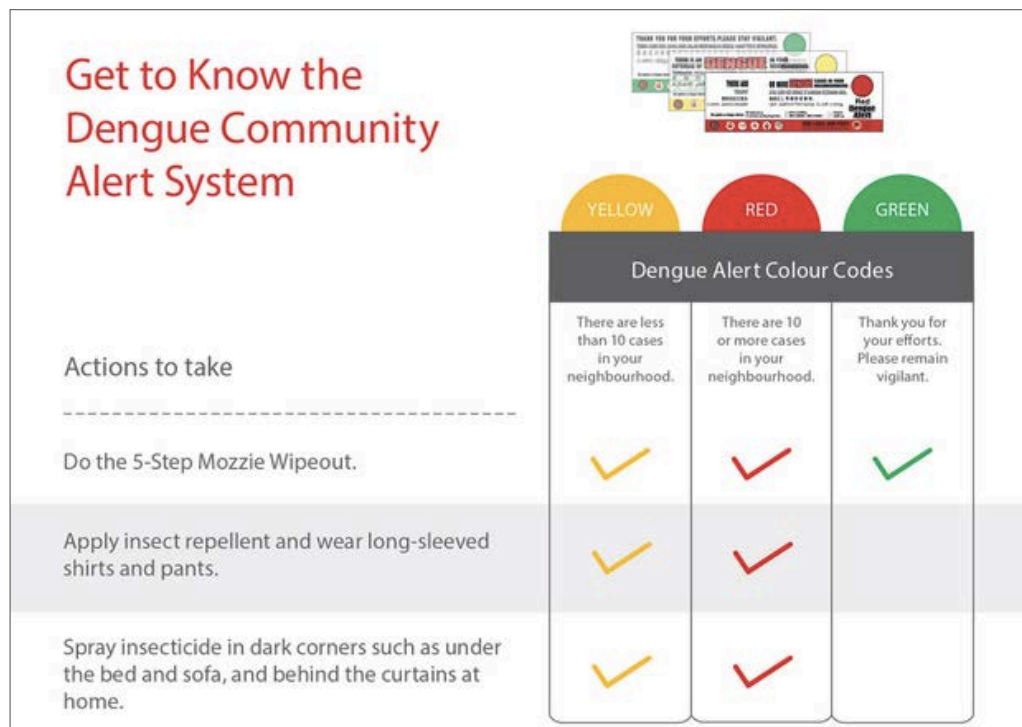
- incentives to participate;
 - fines or disincentives for not participating;
 - public reporting of vector and/or disease prevalence by location;
 - intervention in a household by public health officers;
 - prosecution for non-participation; or
 - prison or severe sanctions for non-participation.
-

Meeting participants discussed in which coercive measures are used. In the past, a coercive vector control policy was used in the yellow fever campaigns (e.g. in Brazil in the 1930s (20)), when inspectors had the power to enter households and intervene at mosquito breeding sites. Similar policies persist, especially for control of arbovirus diseases for which there is no therapeutic option (e.g. dengue). Cuba and Singapore employ large numbers of mosquito inspectors with powers including entry onto a property without the owner's consent if the risk for mosquito breeding is considered high. Similarly, several states have legal provisions to enforce community compliance with mosquito control. For example, India, Malaysia, Singapore, Sri Lanka and the state of Florida (USA) have enacted legislation to fine or otherwise prosecute individuals or government entities who fail to intervene against mosquito breeding on their property (21–23). Prison terms have been considered in some jurisdictions but have rarely, if ever, been applied, partly because other types of pressure are usually sufficient to achieve public health objectives.

Identifying poor compliance with mosquito control can motivate change, but ethical considerations (e.g. the risk of stigmatization) should inform policy development. The meeting discussed examples in which individuals have been harmed (e.g. losing their livelihoods) when others in the community believe that one household is the source of a VBD outbreak. To overcome such tensions, Singapore has a “dengue community alert system” (Fig. 2), in which the value of public health objectives is implicitly balanced against those of privacy and avoiding individual stigmatization. Rather than targeting individual residences or buildings in which mosquito breeding has been identified, the system identifies neighbourhoods (to provide anonymity for individuals) with colour codes representing the number of cases of dengue. One important consideration is that this could nonetheless stigmatize individuals living in these neighbourhoods, whether or not they are compliant.

Meeting experts noted that multiple strategies could potentially be justified in different contexts, differentiating between response to epidemic outbreaks and routine control, and identified coercion in vector control as an issue warranting comprehensive ethical analysis.

Fig. 2. Community alert system for dengue in Singapore



6.3 Human landing catches

Human landing catches involve human beings acting as mosquito “traps”. These are currently the “gold standard” in many entomological surveillance and VBD research programmes. They have allowed invaluable insight into the biology, entomology and transmission of disease vectors that could not have been obtained by other means (24). The meeting experts recognized, however, an ethical imperative to prevent harm to volunteers or employees working as human landing catches. Possible safeguards include selecting volunteers with low risks for severe disease, limiting the length of shifts, assuring priority access to prophylaxis and treatment and, ultimately, developing mechanical traps.

No mechanical trap is currently available that can provide the same information, and the absolute harm to volunteers and employees appears to be low, even after frequent contact with infected vectors (25). One potential problem that was highlighted is considerable variation in laws, ethical oversight and practice in different jurisdictions (26). For example, Brazil has banned human landing catches, which has impaired malaria surveillance, and institutional review boards in the USA rarely approve studies involving human landing catches. Centralized ethical guidelines and local ethics capacity-building should be established to ensure that the public health and research benefits of human landing catches are balanced against any risk to individuals.

7. Prevention, treatment and research

7.1 Prevention and treatment of malaria

Global malaria control has improved dramatically since the turn of the twenty-first century, with renewed funding, research and public health initiatives, after recognition of the severe consequences of the longstanding neglect of this globally important disease. For example, since 2000, the proportion of children under 5 years of age who are at risk and who sleep under long-lasting insecticidal nets in sub-Saharan Africa has increased from 2% to about 68%, and 30–80% of these children have access to artemisinin combination therapy if they become infected. This has resulted in a dramatic reduction in malaria-related child mortality and the overall number of malaria cases (8).

Yet, many gaps remain. Of the 91 countries at risk in Africa, 84 have ongoing malaria transmission. Mass administration of intermittent preventive treatment is widely used, but implementation is variable (e.g. only 31% of pregnant women in sub-Saharan Africa received two or more doses of intermittent preventive treatment in 2015), and there are significant gaps in data collection and surveillance after mass administration (8). Meanwhile, the resistance of mosquitoes to insecticides is an increasing, probably under-recognized problem. There is thus an urgent need to accurately characterize the links between insecticide resistance and public health outcomes. Furthermore, the public health implications of the spread of artemisinin resistance (of malarial parasites), from South-East Asia to Africa (27), are unknown and warrant vigilant surveillance and further research.

Vivax malaria is another looming challenge. As control of falciparum malaria (the most deadly form of the disease) increases, so does the relative importance of vivax, which is the most widespread, more difficult to treat definitively, and more frequently causes asymptomatic infection. Priorities with respect to control of vivax malaria include better understanding of asymptomatic epidemiology and transmission (and thus understanding of how the asymptomatic reservoir should be targeted) and research into and implementation of, new, less toxic, treatments.

7.2 Research priorities for *Aedes*-borne diseases

Gaps in clinical and epidemiological understanding of VBDs are not inevitable but are due, rather, to their long neglect. More research (from basic science to implementation research) should be conducted to achieve maximal health benefits for individuals and communities. As VBD public health programmes move towards ambitious targets such as elimination, more gaps will have to be filled in order to prevent programme failure and a future rebound in harm.

Meeting participants were briefed on a number of important research gaps, including the lack of vaccines against most VBDs. As mentioned above, more implementation research should be conducted when new vaccines are ready for deployment, and the long-term effectiveness of new vaccines should be monitored prospectively.

Research to improve surveillance techniques is another priority. The thresholds of insecticide and antimicrobial resistance that threaten public health should be defined. Feasible methods of vector surveillance are required that provide relevant data in all transmission settings, ideally with a reduction in the use of human landing catches. Likewise, human surveillance requires accurate, reliable tests and rapid integration of new data; therefore, new tests and analytical capacity-building are much needed. Although longitudinal cohort studies would be methodologically ideal, they are costly and complex, and the utility of cross-sectional seroprevalence surveys in determining disease epidemiology should be tested.

Technical and ethics experts emphasized the need to improve the use of data to predict disease outbreaks and disease severity. For example, climate change and other environmental conditions may increase the probability and magnitude of disease outbreaks. Promising early research involves integrating existing data on climate to develop predictive models, which have been shown to improve the cost-effectiveness of vector control interventions, resulting in more harm averted for each unit of funding and effort invested. In the long term, such models should be used to anticipate hotspots for increased risk of VBDs due to climate change and to better prevent or mitigate harm.

A number of participants further stressed the need for more implementation and operational research, including social science research, to improve understanding of the role of human behaviour in disease transmission and participation in vector control interventions. The research should include more context-specific work on the ethical, social and cultural aspects of vector control and public health interventions; as diseases spread across large areas within and between nations, different populations in different environments will have to work together to achieve and maintain the public health benefit of reducing the burden of VBDs.

7.3 WHO research and development observatory

While only eight VBDs are formally classified by WHO as neglected (**Table 5**), in the broader ethical sense, neglect of VBDs is still widespread, and there is an ethical imperative to reverse the neglect. Recent positive trends include more funding for malaria control, which has halved the global burden over a decade, and more funding for other diseases, such as dengue and Zika virus infection. Yet, the outbreak of Zika virus could have been better predicted and significant harm averted had the virus been less neglected in the past. Likewise, a lapse in yellow fever vaccination and inadequate vaccine stockpiles were major contributors to the 2016 outbreak, which, at the time of the meeting, had caused 1538 cases in Brazil and a case fatality rate of 34% among confirmed cases (28). More generally, underfunding of VBD research and control programmes impedes development and use of the tools required to reduce or eliminate significant global disease burdens.

Table 5. WHO classification of vector-borne and neglected vector-borne diseases

Vector-borne	Neglected vector-borne
Malaria	Chagas disease
Yellow fever	Dengue
Zika virus	Dracunculiasis (guinea-worm disease)
Japanese encephalitis	Lymphatic filariasis
Chikungunya	Leishmaniasis
Relapsing fever (borreliosis)	Onchocerciasis (river blindness)
Crimean–Congo haemorrhagic fever	Schistosomiasis
Lyme disease	Human African trypanosomiasis (sleeping sickness)
Plague	
Rickettsiosis	
Rift Valley fever	
Sandfly fever (phlebotomus fever)	
Tick-borne encephalitis	
Tularaemia	
West Nile fever	

Source: reference (30)

Means for describing and responding to neglect, such as the WHO Global Observatory on Health Research and Development (<http://www.who.int/research-observatory/en/>), are extremely welcome. The Observatory, “a centralized and comprehensive source of information and analyses on global health R&D activities for human diseases”, allows review of international trends in research funding. For example, according to the latest figures available at the time of the meeting, the financial investment (US\$) per disability-adjusted life year was 10–13 for HIV infection, tuberculosis and malaria, 50 for dengue, 43 for Chagas disease, 16.7 for onchocerciasis, 16 for leishmaniasis, 6.6 for schistosomiasis and 5.2 for lymphatic filariasis. Ideally, resources such as the Observatory will ensure better matching between disease burdens and funding by focusing on market failures and identifying situations in which a small additional investment could yield significant public health gains.

7.4 Human challenge studies

In challenge studies, or controlled human infection models, research participants are intentionally infected with a given pathogen. Such studies are used to study both vector- and non-vector-borne diseases (e.g. influenza). More than 6500 volunteers have safely participated in challenge studies, which have improved understanding of VBD biology and control. The ethical aspects of such studies have recently received

attention in the academic literature (29,30) and have been the subject of WHO guidance (31). Many of the ethical issues are common to challenge studies of VBDs and other infectious diseases. Specific issues identified at the meeting were use of challenge studies for VBDs for which there is no treatment (e.g. dengue), or where there are long-term risks associated with infection (e.g. future risk of severe dengue if a research participant is later re-infected with another dengue serotype) and use of challenge studies for testing vaccine efficacy when the end-point is unethical or difficult to measure (e.g. Zika challenge, with the end-point of decreasing the risk for congenital Zika virus syndrome).

Despite strategies to mitigate the risks for diseases such as dengue (e.g. informed consent about future risk for severe dengue, use of attenuated virus with the end-point of viraemia but not clinical disease, and dose escalation from a very low dose), meeting participants generally agreed that caution should be exercised in using human challenge studies for untreatable, potentially severe vector-borne pathogens and that each case would require careful assessment. Similarly, in the context of Zika virus, a recent report from the National Institute of Allergy and Infectious Diseases in the USA (32) on human challenge studies with Zika virus concluded that the risks posed by such studies were not outweighed by the expected benefits of such research, given current understanding of the biology and epidemiology of Zika.

The relevant general research ethics requirements discussed included pre-registration of studies, adequate training of the relevant ethics committee, a thorough assessment of the risks of subjects and of the wider population, mitigation of risks by safeguards such as treatment and a thorough overall risk–benefit assessment, including consideration of less risky ways to obtain the same scientific information or public health benefits.

7.5 New technologies for vector control

The WHO Vector Control Advisory Group assists groups conducting innovative research by assessing the likely entomological and public health efficacy of new concepts and provides advice on development, from laboratory studies to field release and wider public health implementation.

The meeting was briefed on a number of novel technological approaches that could potentially be more widely used to improve current vector control strategies. Examples include the use of data on human movements to predict gaps in the coverage of control measures for outbreaks and the use of climate data to predict outbreaks associated with weather events. Other strategies include new insecticide-treated products, such as whole-house insect nets (rather than bed nets), “attract-and-kill” baits and applying insecticides to rodents in order to kill the vectors that feed on them.

More radical technological solutions have been proposed for mosquito-borne disease control, including *Wolbachia* and genetic modification of mosquitoes. The technical aspects of these approaches are summarized below, followed by a discussion of the relevant ethical issues.

7.5.1 *Wolbachia*

Wolbachia is a common genus of bacteria that symbiotically infect mosquitoes and other insects, with no known adverse effects on humans bitten by infected mosquitoes. Infection of *Ae. aegypti* with certain strains can reduce transmission of dengue, inhibit reproduction between infected males and uninfected females and spread through mosquito populations via transmission of *Wolbachia* from infected females to their offspring (33). It is hoped that interventions using *Wolbachia* could ultimately lead to a dramatic reduction in the transmission of *Aedes*-borne pathogens, especially dengue – potentially making a major contribution

towards disease elimination. *Wolbachia*-infected *Ae. aegypti* have been released into the wild as part of research and dengue control, e.g. in northern Australia (34), Singapore, Viet Nam and Brazil (35–37). Definitive results on efficacy, practicality and any unforeseen long-term consequences are pending.

7.5.2 Genetically modified mosquitoes

Several current research programmes aim to genetically modify mosquitoes in order to reduce mosquito populations and/or disease transmission. One research programme that is particularly close to implementation uses OX513A *Aedes* mosquitoes modified by the addition of a gene that causes stage-specific killing. When male OX513A mosquitoes are released, the offspring of genetically modified males and wild-type females are programmed to die at an early stage of development, thereby reducing the total mosquito population. As for *Wolbachia*, the objective of releasing OX513A mosquitoes is to reduce transmission of *Aedes*-borne diseases such as dengue. Field trials with entomological outcomes have been performed, and trials with public health outcomes (e.g. effect on dengue transmission) are planned (33). Unlike gene drives (discussed below), this technique is not intended to result in the persistence of genetically-modified mosquitoes in the wild (after the death of released genetically-modified mosquitoes and their offspring), and thus would require periodic releases and recurrent expense.

Other research programmes include the use of clustered, regularly interspaced, short palindromic repeats-associated protein 9 (CRISPR-Cas9), a novel method of gene editing with a wide variety of applications. The principle aim of CRISPR-Cas9 use in vector control research so far has been to construct gene drives – a method of introducing new genes (e.g. into mosquito populations) that are intended to be preferentially inherited by subsequent generations and thus increase in frequency over time. Such genes could contribute to reducing mosquito populations (e.g. by creating sterile females) or disease transmission (e.g. by reducing the propensity of mosquitoes or animal hosts to carry pathogens) and thus lead to significant improvements in public health, eventually across multiple VBDs (if gene drives are successfully developed for relevant vectors). Technical challenges include the sustainability of gene drives in the face of evolutionary fitness costs and biological barriers to mating between populations, which could limit the spread and persistence of genetically-modified vectors in the wild. The most advanced models target *Anopheles* (aiming to reduce the burden of malaria), but the technical experts agreed that these constructs are not yet ready for field release. Preparations for public trials will take time and will have to be carefully assessed prospectively (33).

7.5.3 Ethical considerations

If they are effective, novel technologies for vector control such as those detailed above could result in major public health benefits in terms of reducing disease burdens. A number of concerns have, however, been raised. Guidance for researchers, particularly for genetic techniques, has been issued by the WHO Special Programme for Research and Training in Tropical Diseases (38), the French National Institute of Health and Medical Research (39,40) and the National Academy of Sciences in the USA (41). Whether it would be ethical to eradicate a vector species via a gene drive has also been considered in the academic ethics literature (42).

The main ethical concerns include potential ecological risks, unforeseen harm to humans and other species, and the likelihood that the effects of an intervention could spread rapidly across national borders. These concerns are perhaps greatest for gene drives, because, if they were successful, they would have long-term, potentially irreversible, and potentially widespread effects on vector populations. The US National Academy of Sciences' report highlighted that current governance mechanisms may not address all aspects of gene drive research, particularly because of rapid scientific development and the uncertain, potentially international, effects of field trials in wild vector populations.

Meeting participants discussed possible responses, including the need to identify or create an international body and/or international governance mechanisms to determine how risk-benefit assessments regarding genetically modified vectors should inform decisions made under conditions of non-trivial uncertainty and, ultimately, to decide on whether to proceed with release trials. A key point will be whether the benefits could be achieved with less risky strategies, and how to balance funding of new technologies with support of traditional methods.

Participants generally supported the recommendations of the US National Academy of Sciences' report but noted that public engagement would probably have to be expanded to transnational or global levels. An additional idea raised and supported at the meeting was establishment of a gene drive registry in order to better coordinate and monitor multiple, parallel research programmes.

8. Conclusions and next steps

Participants were given thorough technical information, including on advances in vector control and recent developments related to the outbreaks of Zika virus infection and yellow fever. Technical and ethics experts and WHO representatives had an opportunity to discuss the ethical issues that arise in the context of VBDs, noting a number of neglected topics that require further work and other topics that overlap partially with ethical analyses in infectious diseases and bioethics more generally.

The main broad issues identified in the closing discussions as requiring further consideration were:

- **the ethics of vector control** (including coercive and mandated interventions, insecticide resistance and new technologies);
- **the ethics of the environmental and social determinants of health** in VBDs and the need for a more nuanced, context-specific approach to control;
- **the ethics of VBD research** (including human challenge studies, human landing catches and genetic modification of mosquitoes);
- **risk-benefit analyses and ethical mechanisms for decision-making**, especially in international epidemics and interventions; and
- **community engagement** and risk communication.

The meeting laid the foundation for preparation of a WHO guidance document on ethical issues associated with VBDs. The next step will be to define the issues for which guidance is required and on which further research and analysis should be undertaken. Decisions on the scope of this project will be coordinated by the Global Health Ethics unit (at WHO headquarters) and be informed by discussions at the meeting and the content of this report, which maps the issues identified and discussed to date.

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Annexes

Annex 1. Agenda

Day 1. Thursday, 23 February 2017

Time	Topic	Presenters
08:30–09:00	Arrival and registration	
09:00–09:10	Welcome and opening of the meeting	Ties Boerma
09:10–09:20	Declarations of interest	Patrik Hummel
09:20–09:30	Objectives of the meeting	Andreas Reis
GENERAL TOPICS		
Chair: Christiane Drum		
09:30–10:00	Challenges in VBDs vis-à-vis other infectious diseases: vectors, burdens and transmission	Ron Rosenberg
10:00–10:30	Reflections from ethicists	Michael Selgelid
10:30–11:00	Coffee break	
11:00–11:30	Challenges in VBDs: host issues: pregnancy	Ronnie Johnson, Caron Kim
11:30–12:00	Reflections from ethicists	Florencia Luna
12:00–12:30	Challenges in VBDs: host issues: childhood	Nigel Rollins
12:30–13:00	Reflections from ethicists	Cheryl Cox Macpherson
13:00–14:00	Lunch	
Chair: Aamir Jafarey		
14:00–14:15	Gender and vector-borne diseases	Florencia Luna
14:15–14:45	Climate change and VBDs	Mariam Otmani del Barrio
14:45–15:15	Reflections from ethicists	Zeb Jamrozik
FIELD EXPERIENCE		
15:15–15:30	Field perspectives from Burkina Faso	Bocar Kouyaté
15:30–15:45	Coffee break	
15:45–16:00	Field investigations in Cambodia	Vanna Kab
16:00–16:15	Preventive measures: case study of Singapore	Lee Ching Ng
COMMUNITY INVOLVEMENT		
16:15–17:00	Community involvement and communication	Gaya Gamhewage
17:00–17:45	General discussion	

Day 2. Friday, 24 February 2017

Time	Topic	Presenters
VECTOR CONTROL		
Chair: Cheryl Cox Macpherson		
09:00–09:30	Overview of vector control measures	Raman Velayudhan
09:30–10:00	Summary of international meeting to review vector control options for control of Zika virus	Raman Velayudhan
10:00–10:15	Entomological trials	Rajpal Yadav, Anna Drexler
10:15–10:30	Vector elimination	Martha Quinones
10:30–10:45	Coffee break	
10:45–11:15	Reflections from ethicists	Jerome Singh
13:00–14:00	Lunch	
PREVENTION, TREATMENT AND RESEARCH ON VBDS		
11:15–11:30	Prevention and treatment of malaria	Francine Ntoumi
11:30–11:45	Research priorities for <i>Aedes</i> -borne diseases	Lee Ching Ng
11:45–12:00	Reflections from ethicists	Bernhard Baertschi
12:00–12:15	WHO research and development observatory	Vasee Moorthy
12:15–12:45	General discussion	
12:45–13:45	Lunch	
Chair: Michael Selgelid		
13:45–14:00	Vaccines and human challenge studies	Kirsten Vannice
14:00–14:30	Reflections from ethicists	Christiane Druml
14:30–15:00	New technologies for vector control	Thomas Scott
15:00–15:15	Coffee break	
15:15–15:45	Funding principles for gene drive technologies	Katherine Littler
15:45–16:00	Reflections from ethicists	François Hirsch
16:00–16:45	Open discussion on new technologies for vector control	
16:45–17:00	Summarizing discussion	Zeb Jamrozik
17:00–17:30	Pillars of a future guidance document, outlook	Abha Saxena; Andreas Reis; Michael Selgelid

Annex 2. List of participants

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