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# Ethical implications of fighting malaria with CRISPR/Cas9

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**Summary box**

- Genome editing is a new, cheap and versatile technique which has great promise to combat vector-borne diseases. The current ethical debate worldwide is mainly concentrating on the dangers of germline intervention and less so on the potential for fighting vector-borne diseases.
- Gene drive technology has been significantly boosted by the CRISPR/Cas9 gene editing tool which may be able to combat malaria by targeting specific stretches of vector DNA and editing genomes at precise locations, working like a molecular scissors. However, CRISPR/Cas9 is currently not a 'silver bullet' and needs further research and consideration of the ethical aspects and consequences of its use.
- In September 2016, the UNESCO Chair of Bioethics at the Medical University of Vienna convened a meeting entitled 'Fighting Malaria with CRISPR/Cas9: Ethical Implications', which gathered together infectious disease experts with a focus on malaria, entomologists and ethicists to discuss the advantages and disadvantages of genome editing applied to mosquitoes to fight malaria.
- Although there was no formal consensus, some general conclusions were reached, in particular that any ethical debate needs to involve African stakeholders living in malaria areas and to consider future generations and the environment. The precautionary principle should be taken into account in any discussion, as should be the human cost of doing nothing.

## THE BURDEN OF VECTOR-BORNE DISEASES

In 2014, WHO dedicated its World Health Day to vector-borne diseases as they account for more than 17% of all infectious diseases, causing more than 1 million deaths annually, with a high economic impact.[1] About half a million people with Dengue fever are hospitalised each year, while Zika, responsible for an unprecedented rise in the number of children born with congenital brain abnormalities, and also triggering Guillain-Barré syndrome (a neurological disorder that can lead to paralysis and death), was estimated to cost US$ 3.5 billion globally in 2016, due to direct costs, lost productivity, deaths and avoidance measures.[2]

Insects, particularly mosquitoes, can transmit devastating diseases like malaria, West Nile fever, Dengue fever, yellow fever, trypanosomiasis, Chikungunya and Zika. Among these vector-borne diseases, malaria poses a severe public health challenge worldwide. It is spread by the bite of female mosquitoes infected with a Plasmodium parasite. There are approximately 214 million cases of malaria worldwide, mostly in Africa, affecting vulnerable groups such as children, pregnant women, travellers and migrants, with an estimated 438 000 deaths per year.[3] Climate change will tend to worsen these numbers.

## CRISPR/CAS9 PRESENTS NEW HOPE

In addition to existing means of combating malaria, such as insecticide-treated nets, indoor residual spraying, and artemisinin-based combined treatments, which have all reduced mortality rates, new methods aimed at eradication must be developed. Research on vector control measures must continue as long as an effective vaccine remains elusive. An additional challenge is increasing antimalarial drug resistance. The goal has to be to reduce malaria transmission to a level where it is no longer a public health problem. None of the many past and present efforts to fight the disease have succeeded so far, but recent advances in genetic engineering, namely CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats/Cas9), a system which can target specific stretches of DNA and edit genomes at precise locations (working like a molecular scissors), provide new hope.[4]

CRISPR/Cas9 is a new and versatile technology for altering genes. Simple and cheap, it can be used to permanently modify the genome of almost any organism, significantly impacting many areas from medicine to crop seed enhancement. Its has huge potential for autologous treatments, teaching cells to fight disease in one's own body, to delete

hereditary diseases for one's self and one's offspring, and to shape new generations of organisms as genetic modifications are passed to future generations. It can be used for ecological genetic control, and thus as a gene drive, replacing or suppressing populations of insects by targeting an anti-parasite effector gene placed inside the gene drive construct (replacement of the population) or the single female fertility gene (suppressing the population).

In September 2016, the UNESCO Chair of Bioethics at the Medical University of Vienna organised a meeting entitled 'Fighting Malaria with CRISPR/Cas9: Ethical Implications'. A gathering of infectious disease experts in malaria, entomologists and ethicists, the meeting provided an opportunity to discuss the advantages and disadvantages of genome editing specifically applied to mosquitoes to fight malaria. In this commentary, we report on some of the discussions held during the conference.[5]

## ETHICAL CONSIDERATIONS

Innovative biotechnologies, namely gene drive technology, which has been greatly enhanced by the CRISPR/Cas9 tool, require ethical analysis before implementation. These technologies modify life itself, at the individual and at the species level (acting at the germ line, and thus passing down all modifications from one generation to the next).

Ethical consideration of biotechnological developments should be conducted under the presupposition that ethics and sciences can and ought to work together for the good of individuals , for the well-being of societies, and for the protection of all forms of life and ecosystems. Ethics is not a barrier to science and should not limit scientific progress. On the other hand, the sciences are not ends in themselves and are not autonomous endeavours, standing apart from the consensual objectives of societies. On the contrary, while the sciences should continue to develop, discover and implement the best means for pursuing the goals of society, ethics should work at the societal level, helping to establish the best results for a fair and equal society. The decision to use CRISPR/Cas9 to fight malaria, or genome editing in general, does not belong solely to science, but also requires public engagement, especially from the African communities living in malaria-endemic areas. These communities suffer from chronic poverty and are particularly vulnerable to foreign economic interests, and having low levels of education, they lack the capacity for informed debate and free decision-making.

Ethical considerations of the use of CRISRP/Cas9 have been few. We here outline four major areas for ethical consideration regarding the use of CRISRP/Cas9 to fight malaria.

### Scientific hazards

Sound science is the first ethical requirement for scientific research.

CRISPR/Cas9 has large range of applications and huge possibilities for life transformation, which will take decades to perfect. The correct use of this biotechnology requires careful forethought and tight control, which is far from being a reality.

Altering a gene can generate unpredictable and undesirable consequences in the modified species, as well as in other species, and give rise to new and unknown animal and human diseases.

### Promotion of public health

The impact on human health is a major concern in the ethical evaluation of new biotechnologies. At this level, ethical analysis demands evaluation of the benefits and risks and that the former outweigh the latter.

The potential immediate benefits of CRISPR/Cas9 for public health are vast: it can be employed to fight malaria, but can also be used to combat in many other pathologies that cause suffering and death, namely genetic diseases.

However, there are considerable risks. Can science guarantee that incidental exposure to mosquitoes, apart from their bite, through inhalation or ingestion does not result in harm, that no novel genes will transfer to humans, and that there will no alterations in disease transmission or altered transmission of other diseases with unpredicted consequences? Is it possible to avoid all side effects through control strategies?

Regrettably, these and many other questions do not yet have an objective and accurate answer; therefore, gene editing should be introduced cautiously and accompanied by thorough scientific research.

### Protection of biodiversity and the ecosystems

The impact on biodiversity and on ecosystems has to be considered when dealing with biotechnologies that interfere with biological entities. At this level, ethical analysis demands respect for all forms of life as valuable in themselves.[6]

Gene editing technologies could reduce biodiversity or damage ecosystems. Although scientists claim that the ecological risks from eradication by gene drive are less than the detrimental effects of conventional mosquito control, they also recognise that more research on risk assessment is needed. Conversely, it has been suggested that both genome editing technologies and gene drive can be used for conservation (e.g. by targeting invasive species), although this would conflict with notions of naturalness and the idea of 'nature', which is understood as what is independent of human purposes.

Human beings are an integral part of the biosphere, as reflected in the UNESCO Declaration on Bioethics and Human Rights. Under which criteria and how far do we have the right to modify biological entities? Is there a way to accurately predict the impact of the modification of or

removal from the ecosystem of a single animal species? And would there be a way to control the negative effects?

### The slippery slope threat

In the last 50 years, all new biotechnologies have been subjected to the slippery slope phenomena, that is, they were produced for a specific goal but were quickly used for other objectives,[7] some good and some bad depending on their impact on personal well-being and on societal development.

The fight against malaria using CRISPR/Cas9 will unavoidably lead to its application to other insects, to other animals, in a growing generalisation of its use with unpredictable consequences. In addition, the free use of CRISPR/Cas9 in fighting animal-transmitted diseases will likely spread to other human diseases where it can also offer some hope. Furthermore, evidence shows that when new biotechnological resources are designed and applied to human beings for therapeutic reasons, which are good in themselves, they ended up being mostly used to fulfil individual and/or public desires, exchanging the original therapeutic telos for a social telos.[8]

In this predictable scenario, the diversity of possible uses for gene drive technology (namely the production of bioweapons) and their impacts are, indeed, unpredictable.

## CONCLUSIONS

Although there was no formal consensus, the debate came to some general conclusions:

1. Gene drive technology, boosted by the rise of CRISPR/Cas9, should be considered together with interventions that are already having a positive impact in fighting malaria.
2. Genome editing technologies should only proceed when their side effects and societal impacts are sufficiently understood. An advisory group of European research institutions should be established to oversee and report on the progress of these technologies, and shared European or worldwide guidelines should be developed. This work should proceed at the scientific, ethical and legal levels.[9]
3. Some ethical principles laid down in the UNESCO Declaration on Bioethics and Human Rights (2005) are important in promoting global justice, namely Social Responsibility and Health (art. 14), Sharing of Benefits (art. 15), Protection of the Environment, the Biosphere and Biodiversity (art. 17) and Protecting Future Generations (art. 16). The precautionary principle should be considered, as should the human cost of doing nothing.[10]
4. The ethical discussion should continue, empowering and involving African stakeholders, and reflecting on the risks and benefits for people living in areas endemic for malaria, for future generations and for ecosystems. Capacity building, public engagement and acceptance should be arranged before any intervention, thus contributing to fairer decisions for the people and communities involved. Africans will have the ultimate say in when and how these technologies will be used by them to tackle malaria.

Few other new technologies have given us more hope for alleviating the burden of disease but, at the same time, few have raised more fears regarding their potential to bring about permanent changes which might be harmful to mankind and the biosphere. The ethics of fighting malaria with CRISPR/CAS9 is, and will continue to be for quite a while, an open debate.

**Contributors** The only contributors are the corresponding author and co-author.

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