Target Malaria

Submission to Nuffield Bioethics Council

In response to the call for evidence on genome editing

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Note: Given Target Malaria's expertise and remit, we have focused our answer to this enquiry to the application of gene drive approaches for the purpose of vector control, specifically in the case of malaria. Our submissions focuses on part 1 (general considerations) and part 3 (genome editing in animals).

Introduction

With over 200 million new infections each year, malaria imposes huge social and economic costs in Africa and globally. Efforts to tackle the disease, through vector control and increased access to drugs, have had a positive impact. However, current approaches to malaria control face some important challenges: increasing resistance to insecticides and drugs is making some interventions less successful, and the very significant cost to governments of carrying out malaria campaigns places a heavy burden on the public finances of developing countries.

Target Malaria is a global not-for-profit research alliance, whose aim is to find a long-term, sustainable and cost-effective solution to malaria prevention, in order to help save millions of lives. Our research currently targets the two species of mosquitoes (out of 3400 species worldwide) most important for malaria transmission in Africa – *Anopheles gambiae* and *Anopheles arabiensis*. We aim to inactivate specific genes in malaria-transmitting mosquitoes to suppress their ability to reproduce. This would reduce the number of mosquitoes able to transmit malaria.

As one of the first, and few, programmes of research aiming to develop an effective tool for malaria control using gene drive, we are committed to the ethical and effective application of gene drive as a method of genome editing. New tools for gene drive, in particular CRISPR, make genome editing more accessible and relatively easier to apply than previous methods.

However, gene editing remains a complex field and the new tools do not guarantee successful, or similar, outcomes. It is important that, as gene drive is used in more fields, we assess each application of this new technology on a case by case basis, considering the specific characteristics of each product developed, its intended use and conditions of use. This will help avoid oversimplification and generalization about gene drive that are based on speculation about the potential of a tool, rather than on concrete and specific assessment of a product. This is particularly important in regards to risk discussions, which can only be effectively done when risk assessments can be carried out.

1- Perspectives on genome modification

The distinctive significance of genome interventions

- *Is there anything special about the genome that makes intervening in it different from other ways of manipulating nature (e.g. selective breeding of plants or animals)?*
- *To what extent can the development of genome editing techniques be regarded as distinct from or continuous with existing techniques? In what way are the differences significant?*

Genome editing through the use of very specific nucleases allows extremely precise and controlled changes to be made to the genome of the target organism in a way that for many organisms, particularly pest or medically relevant insects, was not previously possible. Such precise interventions minimize the likelihood of undesirable, off-target effects associated with other regimes of mutagenesis and selection. In many ways this can be regarded as an extension of breeding and selection regimes designed to produce organisms with a particular desirable trait.

One application of genome editing techniques is in the generation of a gene drive - the inheritance of a genetic element to a disproportionately high frequency of offspring – based on a phenomenon displayed by an existing naturally occurring class of genes called homing endonuclease genes that are found in a range of single celled organisms.

Science and society

- *What obligations do scientists involved in developing and using genome editing technologies owe to society and what freedoms should society allow to these scientists? Do genome scientists have any special obligations to society that are distinct from those of other scientists?*

Scientists engaged in developing and using genome editing technologies have a responsibility to ensure that their research is undertaken with scientific integrity and to the highest standards of ethical research conduct. This responsibility is incumbent on all scientists, irrespective of the technology in use or aims of the research. There is no reason in principle, or by virtue of the science itself, that genome scientists should face special or different obligations. All scientists should conduct their work with integrity, transparency, and accountability, and strive to align their work with the values of society that supports and benefits from their work. Similarly, the importance of stakeholders' informed consent is not specific to genome editing technologies but rather a shared standard for all ethical research. There is a responsibility for scientists to disclose information about their research in an inclusive, meaningful and relevant way to empower stakeholders to make an informed decision about any technology.

- *To what extent is the development of genome editing valuable as a pure research tool, and to what extent is its value dependent on envisaged practical applications?*

Genome editing technology can be valued for both its intrinsic value as a knowledge-generating research tool, and its instrumental value as a tool with practical applications that lead to benefit. Target Malaria aims to achieve both objectives: to contribute to knowledge and scientific progress and to develop a tool of value for controlling the malaria vector populations in Africa. The main beneficiaries of Target Malaria's research will be people living in endemic countries where malaria causes hundred thousands of deaths and millions of dollars of economic loss every year.

The project proposes an approach that responds to the ethical requirement of equity and access to scientific innovation. All researchers of Target Malaria have made a "global access" promise that specifies that the technology will be made available and accessible to developing world countries at an affordable price. In addition, the technology profile would provide equal access regardless of economic status, and would not require behavioural changes.

One of the ethical challenges is the fact that the populations that would potentially benefit the most from the technology are not necessarily the ones making decisions or being able to influence these decisions directly. Malaria affects largely poor and rural populations, which are generally lack influence on national and international decision-making. The project intends to address this gap by ensuring that it engages all stakeholders affected by its work and places those who are most directly affected by malaria at the heart of its engagement. For this reason, Target Malaria is engaging the communities, formal and informal leaders, civil society groups and other stakeholders in rural villages of Burkina Faso, Mali and Uganda where it is currently carrying out fieldwork, and similarly in the neighbourhoods around its insectaries. This engagement aims at enabling stakeholders to make an informed decision about the research and to get an appropriate level of public acceptance and to respond to all concerns in the sites where the project operates.

The second important challenge for technologies such as those from Target Malaria is the impossibility to "opt out" from use at an individual level. This is an issue that will be more relevant if research successfully leads to the availability of a new tool for malaria control, but is also pertinent to the research phase. The decision made by regulators and health authorities to deploy a gene-drive based malaria vector control tool would affect all individuals, regardless of their personal views on the subject. Unlike vaccines or other medicines where individuals often have the opportunity to express their values through their choice to accept treatment or be vaccinated, the adoption of this technology would not be based on an individual decision. This is not a new situation and not linked specifically to the use of gene drive as similar issues exist with the deployment of other vector control methods such as spraying, but it is nonetheless an important ethical consideration that needs to inform stakeholder engagement both during research and possibly later if a product was to be deployed.

- *What obligations do governments have towards society to ensure 'safe' science or otherwise to shape the scientific research and development?*

Governments have an obligation to set standards and norms that support innovation, consistent with international standards of ethical research conduct, and consistent with societal values. As perspectives on what is 'safe' can vary significantly in society, it is important for policymakers to examine scientific evidence and to set requirements for stakeholder engagement to help guide researchers and ensure new tools can be developed and used. Governments should also set priorities for the development of scientifically valid technologies to support public health and social welfare, and other values that may be challenged by disease or other harmful organisms.

Science, morality and law

- *To what extent are laws and legal frameworks necessary or desirable in seeking to ensure adherence to the moral principles that should inform genome editing?*

Research using genome editing should be guided by the same principles as other research. The ethical principles that guide other research, such as respect, integrity, fairness, proportionality in weighing risk against benefit – apply to research considering genome editing. The questions raised by genome editing technologies, e.g. concerns about minimizing risk and maximizing benefit, informed consent, community acceptance, equality in access,

transparency, accountability, redress, etc., are the same questions raised by many other technologies.

The work by Target Malaria illustrates the potential for gene editing to provide powerful tools to help address some of the most important current public health issues. Hence it is important to consider 'genome editing' not in abstract terms but through each of its applications. Weighing each practical use of the technology is essential to understand its risks and benefits and inform the decision to use, or not, a given tool.

Target Malaria recognizes the novelty of its proposed approach for malaria vector population reduction. For this reason, it proposes a step-wise testing process, to ensure that it learns from each step, and is able to build capacity and confidence along the way. The project is working within existing national standards for conducting research with recombinant DNA that are administered by institutional biosafety committees - such as containment standards (Arthropod Containment Level 2[1]) - and to international standards, including the WHO guidelines on modified mosquitoes[2]. These frameworks mostly address practical questions about quality research on modified insects, as well as safety and efficacy of testing.

Target Malaria welcomes initiatives such as the enquiry from the UK House of Lords about genetically modified insects, or the study from the US National Academy of Science on gene drive technologies. The project believes that it is important to gather expert opinions about this technology in order to ensure that the research is done according to best practices, and that concerns and expectations are taken into account and uncertainties related to such research addressed in a satisfactory manner. For this reason, several Target Malaria members have been providing written and oral contributions to these processes. It is an important opportunity for researchers to participate to a public discussion and ensure acceptance from experts and general public for the research and the technology.

While all initiatives to examine genome editing, its legal framework or ethical issues, must by their nature be directed at several research projects and sectors, Target Malaria highlights the need to consider each project and application of this technology on a case-by-case basis. The context of this technology implementation, its aim for malaria vector reduction, and its approach based on co-creation with African endemic countries' stakeholders are specific and therefore concerns and expectations need to be analysed according to this specificity.

2- Genome editing in animals

Current research

- *What is the current state of the art in the field? What are the current technical limitations and constraints/ bottlenecks?*
- *What are the main directions of travel? What are the envisaged endpoints/ applications?*
- *What is the rate of travel? What are the expected timescales for realising the envisaged endpoints?*
- *Are gene drives an area of particular interest or concern and, if so, why?*

Our particular area of interest is in modifying the genetic makeup of the mosquito vectors of malaria in ways that make populations unable to support malaria transmission. This is based

[1] http://www.astmh.org/AM/Template.cfm?Section=ACME&Template=/CM/ContentDisplay.cfm&ContentID=1444

[2] http://www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/

on the precedent that all successful malaria control programs to date have relied on attacking the mosquito vector rather than the parasite itself.

A genetic transformation technology for the malarial mosquito has existed since 2000, though this relies on transposon-based insertions that insert into the genome in semi-random locations. Once an insertion has been created, it can be secondarily modified to include additional transgenes and compare different genetic loads at the same locus, however until recently there has not been a way to modify a specific gene of choice.

The advent of new nuclease technologies such as TALENs and CRISPR-Cas9 allow very specific gene editing in the mosquito and the validation of genes that are expected to be essential in processes of interest for malaria control such as reproductive capacity, mate-seeking behavior, immunity against parasites and sex determination.

In terms of modifying natural populations of mosquitoes, a method is required to rapidly increase the frequency of the genetic modification with each generation. In an African context, it is not logistically feasible to rear sufficient numbers of modified mosquitoes required for an inundative approach that would otherwise be required to ensure high frequency of the modification in the target population. For these reasons gene drive, which ensures the favorable bias inheritance of a genetic modification in each generation, offers a powerful technology for transforming a population over epidemiologically relevant time and space.

We have shown recently that nucleases including CRISPR can also be adapted for the purposes of generating gene drive. We were able to show close to 100% inheritance of a CRISPR-based gene drive element at three different genetic loci that cause a disruption of female fertility and that could therefore ultimately cause a reduction in population numbers. Others have shown similar rates of biased inheritance of gene drive element designed to increase immunity of the mosquito against the malaria parasite.

Though the technology has great transformative power and can act relatively quickly once deployed, it is still in the early stages and a timeframe of 5-10 years is envisaged before deployment to allow safety and efficacy testing and a full risk assessment.

Conditions of research and innovation

- *What are the main 'drivers' and 'obstacles' for genome editing in relation to envisaged endpoints?*

Gene editing itself allows unambiguous determination of gene function such that key genes can be identified as targets when manipulating the capacity of mosquitoes to sustain malaria transmission. Coupling this knowledge to an efficient gene drive having a desirable impact on malaria transmission would provide a low-cost, self-sustaining technology since the mosquito population would be rapidly transformed through reproduction of the mosquitoes themselves. As such it would be available to all, regardless of economic status or access to healthcare. Moreover, because the spread of the gene drive relies on the process of mating, it is species-specific and should only affect the targeted mosquito species. This is contrast to other approaches such as clearance of breeding sites and insecticide spraying, both of which are indiscriminate in eliminating non-target organisms in addition to the target species.

Impacts

- *Are there particular issues relating to ecological stability, biological diversity, technology transfer between countries, and equitable sharing of the benefits of research?*

Genome editing is a tool that could be used for many different applications and therefore issues relating to ecological stability, biological diversity, technology transfer between countries, and equitable sharing of benefits will depend on the characteristics in question. Any

technological interventions that have an impact on species population levels or genetic composition will have consequences for ecology and biological diversity. Interventions directed at pest or vector control may be specifically intended to disrupt natural ecological balances involving undesirable harmful organisms in order to provide a public benefit. This is also true of technologies that are considered conventional (e.g. pesticides, biological control), or the more recent developments that make genetic manipulation of wild populations more feasible. Some of the impacts will require evaluation and approval by regulatory authorities, if the protection goals of a particular government are affected. From a regulatory perspective, maintenance of biological diversity or ecological stability themselves are not a protection goal. Instead, the impact on specific valued species (e.g. endangered, charismatic, or agriculturally beneficial) are the focus. Therefore, the considerations that presently come into play when evaluating other technological interventions will remain the same, with specific issues dictated by the nature of the genetic constructs, species manipulated, and the receiving environment.

It should be noted that gene drives are not new phenomena; natural gene drives have been known for over 50 years. For example, in *Drosophila* the segregation distorter locus and P element spread has been studied since the 1950's. Other natural gene drives have been studied in various species, and the research on those examples could give insight into the expected behaviour of synthetic drives. Thus, the use of a gene drive intervention *per se* should not be of concern, but rather the potential consequences (risks and benefits) of this intervention.

Because of the potential for spread of mosquitoes beyond political borders which can occur once released, decisions to release mosquitoes with gene drive constructs will affect more than one country. The Cartagena Protocol on Biosafety provides for advanced informed assessment of the transboundary movement of living modified organisms (and implemented by individual countries via national laws and regulations). In the case of driving constructs, it is potentially possible that mosquitoes could transfer to countries that have not authorized their use. The Cartagena Protocol provides a mechanism (the Biosafety Clearing House) for party countries to inform other countries of regulatory decisions, and therefore allows a country of first release to notify neighbors of potential intentional or unintentional transboundary movement. However, it is likely that other multi-country mechanisms for review and approval, such as those now being developed for genetically modified organisms in at least two African regions could also address the need for cross-boundary regulatory approvals, and consequently, the legal transfer of technology from one jurisdiction to another. These regional approaches could facilitate the sharing of benefits, which would otherwise be difficult to achieve if country-by-country approvals were required. However, different approaches to regulation in different regions could create imbalances in the development and adoption of new technologies.

The scientific advances occurring in this field are centered in laboratories in the developed world, in particular North America and Europe, with research in China also proceeding. Research in methods of gene editing and construction of gene drives is, to the best of our knowledge, absent in Africa. On the other hand, there is much benefit that could accrue to developing countries, where mosquito-borne diseases, notably malaria, are more prevalent than in developed countries. Thus, while research capability might be predominantly in the hands of developed country laboratories, it can be argued that the most important and valuable benefits would be experienced by developing countries, with relatively little local investment. This situation changes the benefit sharing conversation, since typically the concern has been the exploitation of developing country resources for the benefit of developed countries. In a sense, the applications of gene drive approaches for malaria control could reverse the traditional benefit sharing equation.

Appendix: About Target Malaria

Target Malaria started as university-based research program in 2005 and now brings together scientists, experts in community engagement, regulatory affairs, and risk assessment across Africa, Europe and North America. Three teams are based in countries that are affected by malaria: Burkina Faso, Mali and Uganda.

Our approach is focused on reducing the number of female malaria mosquitoes. Only female mosquitoes bite and are therefore able to transmit malaria when they take a blood meal, and the number of productive females in a population will usually determine future population size.

Currently, we are evaluating two approaches to reduce the number of *Anopheles gambiae* by creating strains of genetically modified malaria mosquitoes. This work is still at an early stage, but our models indicate that this method has the potential to significantly reduce the numbers of these mosquitoes, and the transmission of malaria, within epidemiologically relevant time and space dimensions. We are taking a step-wise approach working with regulators and communities to ensure acceptance and approval at each step.

As a mechanism to reduce the number of female *Anopheles gambiae* mosquitoes, we are investigating the use of genes that produce enzymes (called nucleases) that cut specific sequences of DNA. The concept for these nucleases is based on Homing Endonuclease Genes (HEGs). HEGs are a class of nuclease genes, found in simple single celled organisms, which are capable of copying themselves from one chromosome to another. In principle there are several types of endonuclease that could be re-programmed to act in a similar way to HEGs and we are testing a wide range of these nucleases.

We are exploring different strategies to use these nucleases to reduce or modify populations of *Anopheles* mosquitoes. When introduced into the malaria mosquito, they work by identifying and cutting through essential genes targeted by our researchers, such as fertility genes or genes key to pathogen transmission. The interrupted gene will no longer function, and modified mosquitoes will be affected according to the nature and importance of the gene. It is possible that enzyme-based gene drive could also be used to change mosquito populations such that they are no longer able to transmit malaria.

The ultimate goal of all of the strategies is to produce modified malaria mosquitoes that can pass these genes on to a disproportionately high percentage of their offspring, so the modification is spread throughout the specific population relatively quickly and is effectively "self-sustaining". This makes the reduction of the malaria mosquito vector population cost effective and relatively simple to implement because the mosquitoes themselves do the work. Two of the main areas we are currently focusing on are biasing the sex ratio of mosquito populations and reducing female fertility.

Target Malaria works within the national regulatory requirements of each country in which it is active and adheres to international guidelines on good practice for research and deployment of genetically modified insects. The project has an active stakeholder engagement process and supports capacity building in its partner countries. Outputs of the project are subject to a Global Access Agreement to ensure that their use is facilitated for the public good.

For more information: www.targetmalaria.org