Convention on Biological Diversity, 14th Conference of the Parties (COP14)

Gene Drive Research: Fact check

A number of claims and concerns around gene drive were raised during side events and other discussions at the UN's Convention on Biological Diveristy COP14 in Sharm el Sheikh, Egypt (November 17-29 2018). Experts from around the world offer some explanations and clarifications on these important topics.

Claim: We can address malaria with existing tools such as bed nets.

Fact: Bed nets alongside other malaria control tools such as indoor residual spraying (IRS) and case management with antimalarial drugs have contributed significantly to the decrease in Malaria morbidity and mortality over the last decade. However, these interventions are facing challenges such as resistance by the mosquito to the insecticides used in bed nets and IRS, and by the parasite to the antimalarial drugs. A reduction in global malaria cases and deaths has stalled since 2015. Furthermore, the current tools do not address the issue of outdoor biting mosquitoes which have been shown to contribute significantly to malaria transmission. Under the most optimistic projections for malaria incidence in 2030 (Griffin et al., 2016), malaria will not be eradicated using existing tools. This is why, as articulated by the WHO, we need to invest in new, complementary tools to be used alongside existing methods - *Brian B. Tarimo, Ifakara Health Institute*

Claim: Malaria is uncommon in Nigeria and can be controlled, so there's no need for additional malaria control tools.

Fact: In 2017, there were 219 million cases of Malaria globally and of these 200 million cases (92%) happened in the WHO region of Africa (World Malaria Report, 2018). In Africa, Nigeria carried the highest burden of Malaria cases with 25% followed by the Democratic Republic of Congo (11%), Mozambique (5%), and Uganda (4%). Furthermore, there were 443, 000 malaria deaths globally and of these 93% happened in the WHO region of Africa. In Africa, the highest number of deaths occurred in Nigeria (19%) followed by the Democratic Republic of Congo (11%), Burkina Faso (6%), United Republic of Tanzania (5%), Sierra Leone (4%), and Niger (4%). In conclusion, to say that malaria Is under control in Nigeria is premature. If there was no malaria in Nigeria and the Democratic Republic of Congo then the burden of malaria cases and mortality in Africa would have approximately halved from the current numbers - *Brian B. Tarimo, Ifakara Health Institute*

Claim: Fish feed on mosquitoes so gene-drive mosquitoes would impact the food chain.

Fact: The most recent research from the Centre for Environmental Policy at Imperial College, London found that removing the dominant malaria-carrying mosquitoes from Africa would have little impact on

ecosystems, as they are not found to be vital to the diet of any species. Malaria carrying mosquitoes avoid laying eggs where they find predators and prefer simple, small puddles where fish are not present.

Gene-drive technology enables specific interventions that offer the potential to be more environmentally benign than broad scale methods such as insecticides. Genetic control of specific mosquito species would leave many other species of mosquito which develop in complex, permanent water habitats for fish to consume.

For mosquitoes genetically modified to prevent the transmission of malaria, any impact on the food chain would form part of a risk assessment. This would involve assessing their consumption by predators and whether any consumption might have adverse consequences - *Dr. C. M. Collins, Imperial College London*

Claim: we can eliminate malaria using the same approach as we did for Sri Lanka, which has been declared malaria free.

Fact: Malaria vectors are very different around the world. *Anopheles gambiae* complex is an extremely good vector because it has a preference for human sources of blood feeding. It is a very different vector than the one in Sri Lanka. Sadly, all models from WHO show that the current tools will not be sufficient for Africa. This is a well-established fact and the reason why so many researchers in Africa and abroad are working hard on new and complementary tools to eliminate malaria – *Delphine* Thizy, *Target Malaria*

Claim: Gene drive is an agribusiness technology, not a public health technology.

Fact: Since Austin Burt first proposed the idea of this type of gene drive in 2003 (based on DNA nucleases that exploit the cell's DNA repair machinery to copy themselves into a particular target sequence) the sole focus of the work that he has led has been with the aim of mosquito control, recognising the huge need for this in malaria control and the evidence that reducing mosquito numbers is the best approach we have for eliminating this disease. In 2005 he set up the first, and for a long time the only, research consortium using this technology, with the specific aim of developing a program for control of the mosquito responsible for the majority of malaria transmission in Africa, where the majority of the world's malaria burden falls. Recent advances in the field over the last 3 to 4 years have opened up the technology to sectors other than malaria control. However, the need, and analysis of potential benefits against risk, for the development and deployment of this technology in any given application should be evaluated on a case by case basis – *Dr. Tony Nolan, Imperial Collegel London*

Claim: If modified individuals containing gene drives from one species of the Anopheles gambiae complex are released, the gene drive modification will spread to all seven species of the complex and beyond, to less closely related species.

Fact: Gene drive is a process of biased inheritance. More than a dozen ways of using this process to control pest and vector populations have been proposed by different researchers. Most of these have not yet been built in the lab, and researchers use mathematical and computer modelling to understand the differences between them: for example, to understand how efficient they are (i.e., how many gene drive organisms

would need to be released to have a desired impact), and how likely they are to spread from one location to another when there is some movement, or from one species to another when there is some hybridisation. In general, the more efficient systems are more likely to spread, though there are exceptions.

In the specific context of potentially introducing a gene drive construct into one member of the *Anopheles gambiae* species complex, the question of whether it is likely to spread to another species in the complex must be addressed on a case-by-case basis, as some gene drive constructs would be likely to spread, and others not. Note that most species in the complex are vectors of malaria, so already subject to control measures, and hybridisation with species outside the complex is probably impossible.

More research, cautiously done, is needed to test which of the most promising ideas can be made to work in the lab and, eventually, in the field. More discussions are also needed about which (if any) of the workable ideas is worth proceeding with to implementation. The answer may differ from one location to another, and may involve combinations of strategies. Target Malaria is committed to proceeding in a cautious, step-by-step manner, and to consulting with a wide range of stakeholders to co-develop safe, effective, and acceptable interventions - *Prof. Austin Burt, Imperial College London*

Claim: Resistance will render gene drive technologies ineffective.

Fact: Any type of intervention targeting a biological pathogen or pest engenders the evolution of resistance. For example, insect resistance against all major insecticide classes for malaria vector control has now been reported. However, not only is the use of insecticides in the form of bed-nets and indoor formulations the foundation for much of the recent success in pushing back malaria cases and deaths, but these same insecticides can remain effective if combined or applied against selected susceptible vector populations. Knowledge about resistance thus requires careful planning as to where, when and how to deploy insecticides and simultaneously calls for the development of new compounds. Another example are vaccines. Vaccines rarely provide full protection from disease and can trigger the development or pathogen resistance and the evolution of pathogen virulence. This does not mean we should stop developing vaccines or that vaccines are automatically ineffective - after all vaccines are a scientific success story and avert an estimated 2 to 3 million deaths each year. It merely means that care has to be taken on when and how to apply vaccines and that better vaccines need to be developed continually.

The same logic applies to gene drives. Early gene drives aimed at reducing mosquito numbers (population suppression) triggered resistance in laboratory cage experiments thus limiting their effectiveness. More recent iterations of the technology were able to remain effective in the lab for longer and would be expected to suppress vector populations in the field. Combinations of gene drives, carefully applied, could thus reduce the number of mosquito vectors and the transmission of Malaria even if any particular gene drive cannot be expected to remain effective indefinitely - *Dr. Nikolai Windbichler, Imperial College London, Dr. Alekos Simoni, Imperial College London, & Dr. Tony Nolan, Imperial College London*

Claim: Gene drive organisms pose a threat to non-target populations and species through uncontrolled spread

Fact: Compared to other insect control approaches and particularly insecticides, which usually target a range of insects relatively indiscriminately, gene drives are much more specific in targeting the organism of interest. This potentially makes gene drives an environmentally friendly intervention, unlike for example the area-wide use of some insecticides recently implicated in the loss of biological diversity of insects and other species.

The mechanism that allows a gene drive to increase in frequency in a target population requires mating. Mating occurs only between members of the same species or very closely related species that can interbreed in the wild. In the case of the malaria mosquito being targeted by gene drives it forms part of a species complex of closely related mosquito species where rare events of interbreeding have been documented. In this case those interbreeding species are malaria vectors as well.

So, for a gene drive to be active in a non-target organism all of the following conditions need to be met:

- the target species and the non-target species need to mate (very unlikely outside of closely related species)
- the offspring of matings between the target and non-target species need to be viable and fertile (extremely rare outside of very closely related species)
- the genetic sequence being targeted needs to be fully conserved (this may or may not be the case, depending on the gene drive)
- the control elements that direct the expression of the gene drive need to work in the same way in the non-target organism
- the gene drive needs to be inserted in a precise genomic location inside the target gene in the non-target organism (highly unlikely)

All these aspects together contribute to make a carefully designed gene drive extremely specific to the target organisms that it is designed to invade. In the case of gene drives designed to target malaria-transmitting mosquitoes, spread to unrelated insects or other non-malarial mosquitoes is incredibly unlikely - *Dr. Nikolai Windbichler, Imperial College London, Dr. Alekos Simoni, Imperial College London, & Dr. Tony Nolan, Imperial College London*

Claim: Local communities in Africa are not being properly consulted over the potential use of gene drive technology for malaria control.

Fact: Community, public and stakeholder engagement is one of the three pillars alongside the Science and Regulatory pillars in Target Malaria's research, which aims at developing a novel accessible, sustainable, cost effective gene drive technology for malaria control.

Target Malaria has dedicated stakeholder engagement teams that work in communities to consult and get feedback concerning the research. A stepwise approach for both the research and engagements takes into consideration the need to provide sufficient evidence based information for a particular phase before proceeding to the next.

Stakeholder teams conduct feedback sessions for local communities to raise their concerns and have their questions answered. This promotes the co-development value of Target Malaria. Furthermore, the stepwise approach ensures that there is no information overload. We conduct the engagement activities in local communities using the local languages. We have taken care to translate some of the scientific terminologies into local languages through consultations and the help of linguists. Open-days provide opportunities for local communities to visit the laboratories – an avenue to have their questions and concerns answered by the experts.

Prior to our engagements with communities, we obtain individual household permission to collect mosquitoes from homes or compounds, as well as community acceptance for village-wide activities through local authorities. Our "relay" staff, who live in the communities, also provide information even when researchers are not there. We have also developed grievance/complaint mechanisms that include the participation of local communities - *Elinor Wanyama Chemonges, National Stakeholder Engagement Lead, Target Malaria Uganda*