Genetically modified mosquitoes

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1. Preface

We attempted to choose a topic which is still in development. The genetically modified mosquitoes need improvements and currently get in use to fight well known diseases like the Zika virus, dengue fever or malaria. Today GMO's (genetically modified organisms) show plenty of side effects. Some GMO's used for agriculture demonstrated instabilities of health (especially in developed countries) and the weeds get with time resistant to the genetically modified seeds. People are worried the same outcome could happen with the genetically modified mosquitoes. We wanted to find out how much is needed to progress with this technology. This cure method saved numerous human lives so far and has the potential to increase its effect.

2. Introduction

Our topic deals with genetically-engineered mosquitoes which have the ability to fight effective tropical diseases such as the dengue fever and maybe soon the newcomer Zika virus or malaria. „Genetically-engineered“ means organisms which have been genetically modified for diverse reasons such as agriculture production, oil production or pest control. The infectious disease dengue fever (infects 50-100 million people each year) gets transferred through mosquitoes (especially by *Aedes egypti)* and is caused by the dengue virus, so scientists started using genes to control the insects. Malaria is more difficult, about 100 different species of the genus *Anopheles* can transmit human malaria through parasitic protozoans which complicates the methods. Alternative treatments and controls are vaccines, pesticides (could cause environmental problems e.g. the lasting remains of DDT). Today, a next disease causes difficulties in many countries in Middle and South America called the Zika virus. It spreads itself with the help of the mosquito *Aedes egypti*, causing microcephaly and other birth defects which show up severe symptoms like skull deformation on the newborn of the infected mothers. Researches believe that also other members of the *Aedes* family transmit the Zika virus (WHO, 2016).

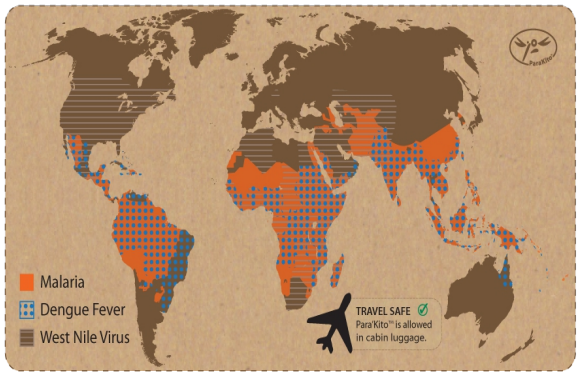

Fig. 1: Distribution of the diseases malaria and dengue fever (PK 1, 2011)

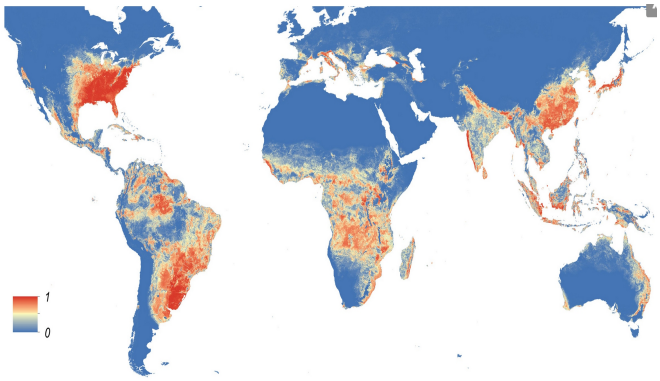

Fig. 2: Global map of the predicted distribution of Aedes albopictus, another mosquito of Aedes family that researchers believe transmits Zika virus (Elife 1, 2015)

Symptoms of the diseases malaria and dengue fever:

Dengue symptoms appear 4 to 5 days after being infected. It remains for a long time and causes strong headache and bone pain. If the fever disappears, it can show up again with skin rashes. Malaria fever shows other symptoms like joint pain, vomiting, sweating, anaemia, chills and sweating (Luis, V., 2014).

2.1 Alternative Treatments

Wolbachia:

Wolbachia are microscopic organisms that live in insect cells and are passed on from the male sperm to the female egg. Already 60% of the different insect species that bite us have Wolbachia in their cycle. When Wolbachia gets inserted into the *Aedes egypti* or other mosquitoes, the transmission of the dengue fever and other diseases gets reduced. A team of scientists all over the world deal with the project called „Eliminate Dengue“ lead by Professor Scott O'Neill (E, D., 2016).

Vaccines:

A vaccination is an inactivated type of microorganisms or infection that is infused into the body to recreate a genuine disease. Since the infused microorganisms are "dead," they don't bring about a man to end sick. Rather, vaccination stimulates a safe reaction by the body that will battle off that sort of sickness. The complexity of the malaria parasite makes it an extremely difficult task. There is no fix available malaria vaccination, the making of malaria vaccines is still in development.

People in third world nations use protective clothing and *mosquito nets* against the insects.

3. Engineering technique methods

3.1. 1950s, Sterile Insect Technique (SIT)

There was a technique in development. The males got a dose of radiation which made them sterile, although they still could produce sperm, the offspring died in a very early stage. As a result, the population reduced. This SIT was succesfully fighting a pest of cattle called screw-worm. This technique also reduced the Tsetse fly population and did not harm other insects. But this technique does not work well on other/all species, because of the irradiated males which get very sick by this radiation, so the females decide to not mate with them.

3.2. Genetic engineering (SIT)

The firm *Oxitec* developed a method on modifying insects called The Oxitec Solution, applying genetic modification to birth control of *Aedes egypti*.
Oxitec created male mosquitoes that contain a special gene in their DNA. When they release these mosquitoes, the females can not tell the difference between the modified mosquitoes and the wild type mosquitoes. When they mate, the offspring inherits that gene and does not survive. With this technique the males do not suffer from irradiation.

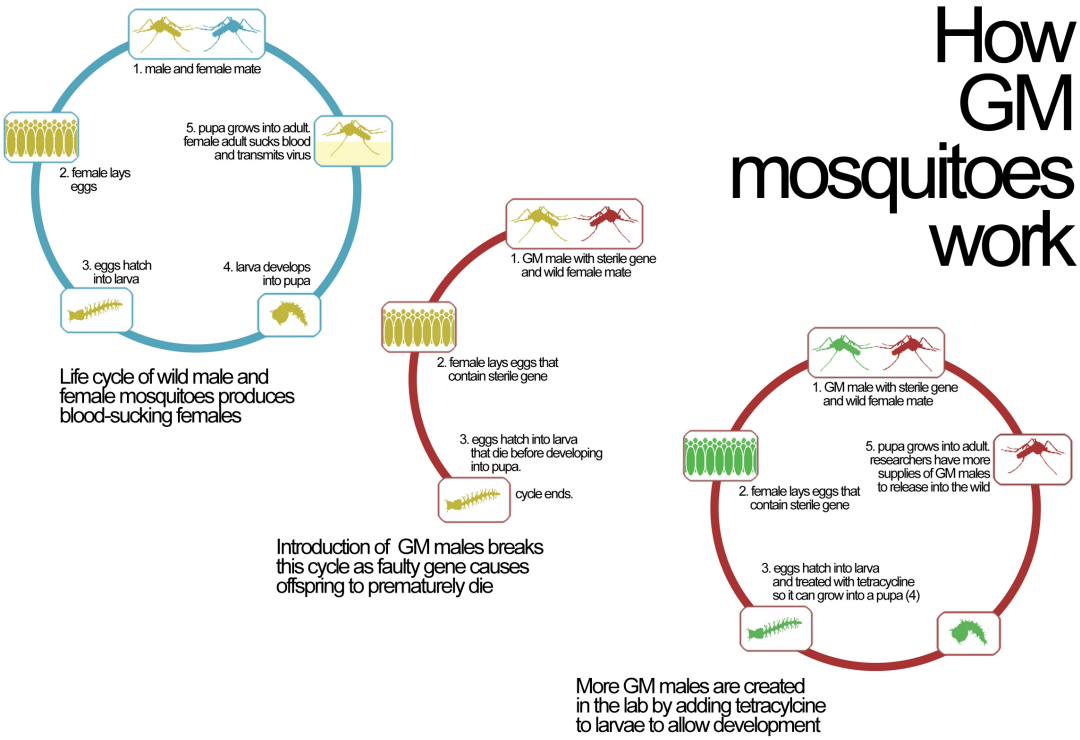

Fig. 3: How genetically modified mosquitoes work (OneinSeven, 2011)

Scientists isolate the sterility gene of interest (we do not know where it comes from) and insert it into a vector such as a plasmid.
The mosquitoes get the gene by adding it to their DNA. This modified DNA produces a protein that stops the functioning of the cells. This protein is called tTA and it acts as a switch that controls the activity of other genes. This means that the modified mosquitoes become sick and die before they mature. So how do the scientists breed 'sterile' males ?
The scientists rear the male mosquitoes in the presence of tetracycline, the protein tTA stops working for a while (until they die), as a matter of fact it acts as an antidote. The offspring inherits that lethal gene and dies, because the 'antidote' is not present in the nature. This technique is very effective and reduces the population as well.
How proceeds this method ?
Using special glass needles with a point that can only be seen under a high-powered microscope, the scientists inject small fragments (the gene of interest) of the DNA into the mosquito eggs. Only a few mosquito cells take the DNA fragments up into the own genome. These can then pass it on to their offspring. With only one sterile mosquito, the scientists can get many more by breeding it with others (O, S., 2016).

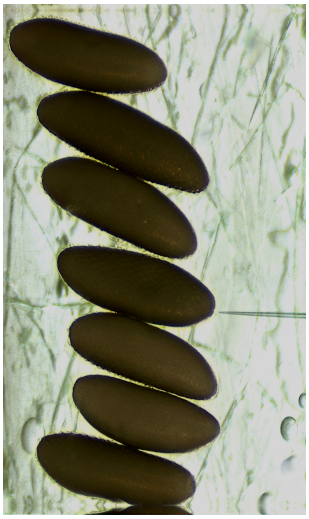

Fig. 4: DNA Injection of the mosquito eggs with special glass needles (Oxitec 1, 2016)

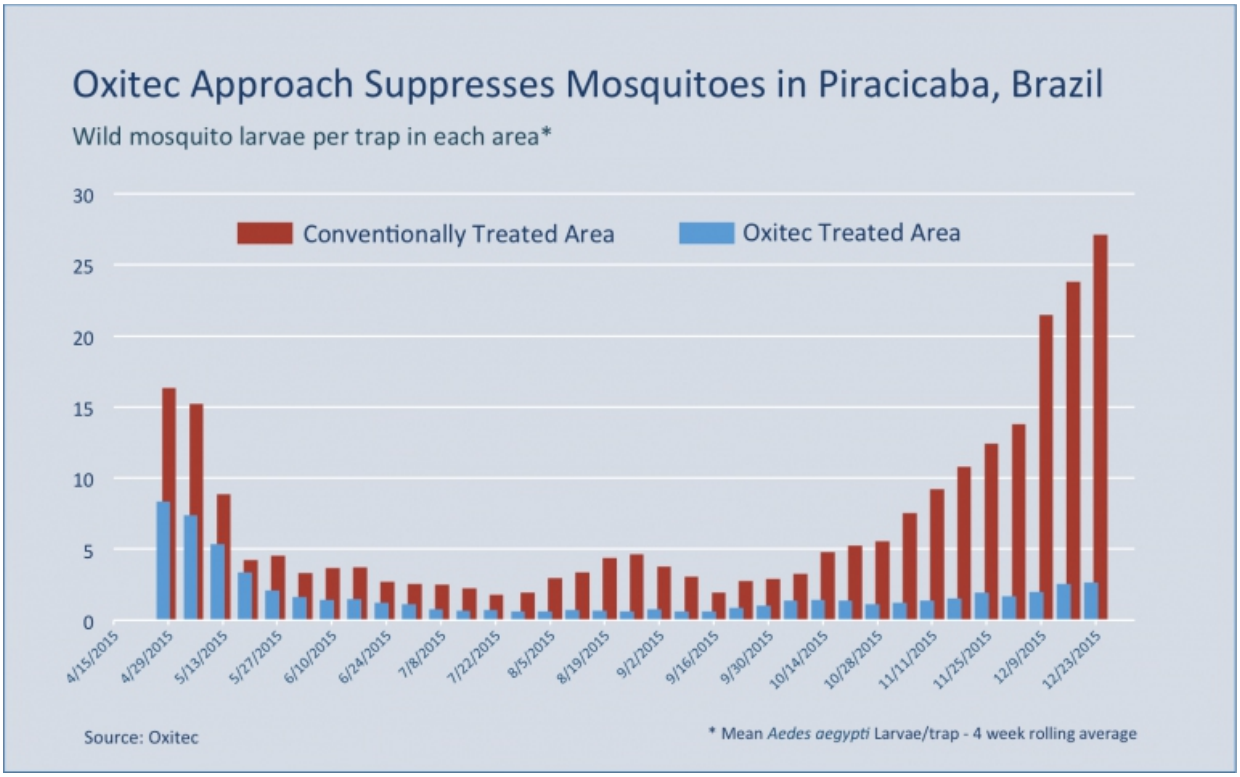

Fig. 5: Distribution of wild mosquito larvae in Piracicaba (Vox 1, 2016)

3.3 Heritable sex distortion

Many articles are about discoveries of new methods to fight malaria, but there is neither information about the explanation of the technique nor a list of pros and cons. However, there was a discovery about a method which induces extreme reproductive sex ratios. That can minimise or even eliminate pest populations. Distorting the sex ratio of malaria populations, using a genetic modification strategy could increase the production of male progeny and eventually control the spread of malaria. Here the endonuclease I-PpoI gets exploited which is then able to selectively break ribosomal gene sequences of the malaria carrier *Anopheles gambiae* that are found on the mosquito's X chromosome. The destruction of the paternal X chromosome makes its offspring male, because female mosquitoes get one of their two X chromosomes from the male parent and the other from the female parent. There is no realisation of this technique, because it presents many problems which will be explained in the discussion. The modified mosquitoes in this process and in the oxitec solution are transgenic meaning there was a transfer of a beneficial gene from an unrelated organism to the mosquito (I, SIS., 2014).

4. Interview

We tried to contact Oxitec and the Swiss Tropical Institute. Unfortunately, we did not get an answer from Oxitec and the Specialist of the Swiss Tropical Institute Pie Müller is out of his office. So we decided to ask questions to the author of an article on TechTimes about genetically modified mosquitoes and the Zika virus. It is about the assumption that the genetically modified mosquitoes are responsible for the Zika virus since it is very widespread in Brazil where Oxitec released their mosquitoes. A survey conducted for the Annenberg Public Policy Center (APPC, 2016) shows that 35% of the respondents believe that this theory is true. The interview with the author called Angela Betsaida Laguipo conducted electronically (T, T., 2016).

1. Do you agree that genetically modified mosquitoes are responsible for the Zika virus and are there enough meaningful arguments to proof the hypothesis ?

There has been not enough evidence that genetically modified mosquitoes were the ones which caused the Zika virus outbreak. Another study which I wrote an article about, has found that the zika virus could evolve and mutate in a fast rate. So, the virus that has been not harmful in decades ago, could have mutated into a robust one which has been linked to microcephaly. Here's the article http://www.techtimes.com/articles/150728/20160417/another-reason-to-fear-zika-mosquito-borne-virus-mutates-quickly.htm.

2. Do you think the survey is trustworthy ?

I think so yes, since the survey was randomized and a sample was appropriate. Also, it's about the perception of Americans if they believe these mosquitoes have caused the complications. Well, the findings of the study shows that a lot of people have not been well-informed on GM mosquitoes, why are they useful and how can they curb mosquito-borne illnesses. People today are a little reluctant when it comes to science breakthroughs but also, they could be right considering the timing of events. Also, because it happened in Brazil, including the cases of microcephaly and the GM mosquitoes were released there.

3. Are there any other projects planned to prove this hypothesis ?

I haven't been informed or I haven't read any article that proposes future projects for this.

4. Do you think there is a way to fight the disease by modifying the mosquitoes on another way ?

Zika virus is a relatively new virus and a lot of science experts are now considering ways to curb the disease. However, if there are other ways why not. The most important thing is, to eradicate breeding sites of mosquitoes and wear protective clothing. Dengue fever has been there for a lot of years and even if they used GM mosquitoes in Brazil, they are still suffering from cases of dengue and yellow fever.

4.1 Conclusion of the interview

The survey proves that people are reluctant to new technology as Mrs Laguipo said. Oxitec in Brazil still works on new projects to fight also the Zika virus. The virus undergoes genetic changes since many years and still continues. Mutation of pathogenic microorganisms is difficult to battle against. Logically speaking there is a possibility that genetically modified mosquitoes are responsible for that since the people do not know many other reasons for the fast outbreak of Zika virus and its bad sides like microcephaly.

5. Discussion

With the genetically modified mosquitoes, oxitec managed to control the birth of *Aedes egypti* and stop the distribution of dengue fever in some affected areas. This environmentally friendly method demonstrates a new opportunity of using non-toxic ways to fight tropical diseases in the world like malaria. In the interview, there are surveys, assumptions (and in the future maybe even evidences) that expose the genetically modified mosquitoes as the causation of the Zika virus which is currently present in many countries like Brazil and even in the USA. The possibility exists since we do not know everything about the genetically modified mosquitoes. Many accidents in the lab could have happened to which we would not know the consequences. It could happen that a modified female is released. We do not know what that gene (which is lethal to the mosquito offspring) causes to our bodies (even though Oxitec claims it does not harm humans). Another risk would be the chance that the mosquitoes mutate from the lethal gene and become even more dangerous to as humans. Oxitec is a company looking for profit since we assume that the cost for the production of these mosquitoes is very high. They try to kill the mosquito population and that could harm the biodiversity and change the ecosystem in the surrounding. Also, Oxitec always informs about their success, other aspects are left out. *Aeges egypti* lives in the same ecological niche as *Stegomyia albopicta*. The two mosquitoes share the same habitat and carry both dengue, Chikungunya and the yellow fever. *Stegomyia albopicta* will take advantage if *A. egypti* dies out. In contrary, other organisations of scientists attempt to eliminate diseases like dengue fever by using the Wolbachia bacteria and not harming the mosquito population. The question is if the goal is to wipe out the mosquito population completely, just lower it or only eliminate the disease. However, there are no accurate publications of other engineering techniques. Sex distortion of the organisms is not quite a good option since this method provokes unflattering results. The female survivors of the transgenic offspring show up to be very damaged due to the inherited and altered X chromosome. This transgenic female could then bite a human or another mammal and transmit the potentially lethal endonuclease I-PpoI.
Aeges egypti carries both the dengue fever and Zika virus. Until now Oxitec mainly worked with the *Aeges egypti* to fight the dengue fever. As said in the conclusion of the interview it is only logical to assume that the modified DNA of Oxitec's mosquitoes could have a connection to the Zika virus since this virus is still mutating. Today, Oxitec works on next projects against the Zika virus. There is also the chance that some other factors influenced the mutation of the Zika virus as we know it today.
We think that Oxitec's procedure to fight dengue fever, yellow fever and Chikunguya is a good solution. As the name says the Oxitec solution seems ideal and should not have any disadvantages but difficulties show up when looking at the topic more precise.

6. Summary

Genetically engineered in general means organisms that have been genetically modified for different reasons such as oil production, agricultural production or pest control. The genetically modified mosquitoes are transgenic. They still need improvements but they could get us involved in fighting diseases like malaria or the Zika virus. Organisations all around the world now encourage affected countries to boost their researches for genetically modified mosquitoes so it gets as successful as Wolbachia which are microorganisms that live inside a cell and reduce the transmission of the dengue fever and other diseases. In 1950s the first technique was developed to make males sperm sterile by using a dose of radiation. They could still produce sperm but the offspring died in a very early stage. It successfully fought a so called cattle screwworm and reduced the Tstetse fly population. Nowadays there is a technique to control the birth rate of *Aedes egypti*. The method called The Oxitec Solution makes male mosquitoes contain a special gene in their DNA. As in the Wolbachia the offspring does not survive. For this the scientists rear the male mosquitoes in the presence of tetracycline, the protein tTA stops working for a while. The offspring inherits that lethal gene and dies, because the 'antidote' is not present in the nature. This technique is veryeffective and reduces the population as well. Another method is a sex distortion of the mosquitoes or vaccination. Side effects and complications show up with the methods.

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