1. These are the five key strategies for combating insecticide resistance as mentioned in the WHO document *Global plan for insecticide resistance management in malaria vectors*, published in 2012. It is still the same document that is mentioned in the WHO map gallery page in the section on insecticide resistance. Since 9 years have passed, I wonder what are the main measures taken by IRAC to combat insecticide resistance in the current practical situation?

As a technical working group of the Agrochemical Industry association CropLife International, IRAC does not undertake Insecticide Resistance Management per se, but makes recommendations for, and provides information on, IRM, that we hope the users of insecticides will follow. IRAC supports the recommendations within the WHO GPIRM document.

2. In the document *Global plan for insecticide resistance management in malaria vectors*, published by WHO, Dr Margaret Chan mentioned that we urge affected countries and stakeholders to take immediate action to preserve the effectiveness of current vector control methods, and to ensure that a new generation of public health insecticides is made available as soon as possible.genetically modified mosquitoes, have demonstrated the need to develop new chemical insecticides.

But this is the content of guidelines from many years ago. According to the latest WHO report, there is a new technology that may be used to address the transmission of mosquito-borne diseases, genetically modified mosquitoes, do you think it is still meaningful to develop new chemical insecticides in the current situation?

Since the GPIRM was published, there has been a lot of activity, especially around pillar III. Insecticides have been repurposed from agricultural use, for use against mosquitoes. Mosquito bed nets containing pyrethroid insecticides, plus PBO, a synergist that mitigates some of the pyrethroid resistance mechanism, have been developed and introduced. These nets have been shown to be more effective against pyrethroid resistant mosquitoes that pyrethroid alone nets.

Nets containing the insecticide chlorfenapyr, in addition to a pyrethroid, have also been introduced, and have been shown to be effective against pyrethroid resistant mosquitoes. Other nets containing the Insect Growth Regulator (IGR) pyriproxyfen, in addition to a pyrethroid, have also been introduced. These sterilise the female mosquitoes reducing the number of mosquitoes in the next

generation. Again, these have been shown to be effective against pyrethroid resistant mosquitoes.

The neonicotinoid insecticide chlothianidin has been recommended for use as an Indoor Residual wall Spray (IRS). This provides a completely new insecticide mode of action class to be used in rotations with the existing IRS insecticides, such as organophosphate or carbamate insecticides.

Completely novel insecticides are also being developed for the Vector Control market, some sponsored by the IVCC https://www.ivcc.com/ It is hoped that in the near future there will be an even wider choice of insecticide mode of action classes for use against mosquitoes, and which will allow IRM programmes to be implemented.

So overall, the situation looks better now, than it did in 2012.

Genetically modified mosquitoes potentially offer a great new tool for malaria control. However, their use is still contentious, and there are many hurdles to get over before they can be used on a large scale. Malaria can be vectored by a number of different mosquito species, which may be present together in the same region. A GM approach would therefore need to address each mosquito species separately. I think that GM mosquitoes will play an important part in the control of vector borne disease, but they will not completely replace the need for insecticide use.

3、Developing new chemical insecticides may have a lot of investment, but resistance may soon emerge, how do you see this situation?

Development of novel insecticides is a very expensive and time consuming activity. One of the reasons that this has historically not been undertaken for mosquito vector control, is that the vector control market is not large enough to give a return on the investment required to bring such an insecticide to market. To address this, the IVCC, and others, have formed Public Private Partnerships to fund the early research and development of VC insecticides. This reduces some of the financial hurdles, and will hopefully lead to novel insecticides specifically for use against mosquitoes to reach the market in the next few years.

So the main hurdle is the financial return on investment in what is a relatively small market, compared to the agricultural insecticide market, rather than the immediate threat of resistance. It is also very difficult to find insecticides that have the right properties for mosquito control, whilst also being safe to humans and the environment.

Any new insecticide for VC will have been evaluated against pyrethroid resistant mosquitoes, so the developers would be confident that cross resistance wouldn't be a problem in the short term.

4、Nootkatone is a mosquito-repellent chemical that we produce in large quantities by means of synthetic biology. "Having a new effective ingredient for insecticide available will assist in addressing the growing levels of insecticide-resistance to other products currently in use", according to EPA. But some people believe that the emergence of new chemical repellents only briefly alleviates the current dilemma caused by insecticide resistance, but does not really solve the problem. What do you think?

Mosquito repellents are not widely used in institutional malaria control programmes. As repellents are relatively volatile, they need to be regularly replaced to maintain an effective concentration in the area protected from mosquitoes. This is logistically difficult to achieve in many regions where malaria vector control is undertaken. A Long Lasting Insecticide treated bed Net (LLIN) should remain effective for up to three years, and IRS sprays should work for 6 - 12 months before reapplication is needed. Volatile insecticide repellents would need to be reapplied much more frequently, which may be a logistical and financial challenge.

Whilst theoretically mosquitoes could become 'resistant' to repellents, there is little evidence to suggest this has happened with the repellent DEET, which has been used as a topical repellent for many years.

5、At present, the specific repellent and mosquito-killing mechanism of noscapone is still unclear, if we want to determine whether nootkatone can really be a solution to insecticide resistance, what should be done?

To evaluate whether a potential insecticide has cross resistance with existing insecticide resistance mechanisms, bioassays are the first steps to take. This would involve identifying the dose response of, in this case, nootkatone against a susceptible strain of mosquito. This could either evaluate repellent of killing effects. Then the study is repeated with strains of mosquitoes known to be resistant to other insecticides. If there is no significant difference in the dose response, then there is unlikely to be any cross resistance. If however, there is a significant change in the dose response, then you may have cross resistance between the new insecticide and an existing one. More information on cross resistance bioassays can be found here https://irac-online.org/documents/irm-vector-manual/?ext=pdf