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Malaria, Mosquitoes and Models

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Although there are excellent ways of controlling malaria now, there is a real risk that these will break down. We therefore need new strategies to save lives in the future. Professor Godfray described some of the exciting possibilities currently being researched – and alluded to the important role being played by mathematical modelling in trying to combat this deadly disease.

Malaria is a major problem, causing at least a million deaths and up to 500 million clinical episodes a year. About 60 per cent of cases and 80 per cent of deaths occur in sub-Saharan Africa. There are good and effective ways of combating malaria – although poor health infrastructure in developing countries challenges their implementation – but there will always be a need for new strategies. Professor Godfray's lecture was, as he said, not so much about saving the lives of children in Africa now, but about providing possible means of doing so in the future. There is a need to have 'things on the shelf' for the day when current methods fail.

Professor Godfray began by describing the life cycle of malaria and of the mosquito, a vector which transmits the disease. He outlined the scale of the problem and current control methods, before going on to look at novel control measures. These include ways of stopping mosquitoes transmitting malaria and causing early death in the mosquito itself, thus reducing the opportunities for transmission.

He also spoke about the importance of an inter-disciplinary approach to the problem, making particular reference to the role of mathematical modelling. Malaria is caused by a single-celled micro-organism called *Plasmodium*, and is transmitted only by female mosquitoes of the *Anopheles* genus. The mosquito injects malaria sporozoites into the human when taking the blood meal essential for successful reproduction. This then reproduces in the (human) body, causing illness and possible death – and passing the disease on when the mosquito bites again.

Current strategies include insecticide-treated bed nets and indoor residual spraying – where the walls of huts are sprayed with a long-lasting insecticide which kills off the mosquito, a creature which will often 'rest' on the wall while maturing her eggs prior to laying them in suitable water bodies. There are also effective drug treatments which act against the pathogen, particular the recently-introduced drug artemisinin and its derivatives. There are several problems with both strategies, however, in that health infrastructure of countries afflicted by malaria is variable and often poor, so getting control methods out to populations is a challenge. In addition, mosquitoes and malaria itself are good at becoming resistant to insecticides and drug treatments respectively, making it a constant struggle to keep ahead.

As well as making current strategies work better – particularly by improving health infrastructure – we have to look to the future, said Professor Godfray. “There are good current strategies and we can save children today, but we have to prepare for these strategies failing,” he said. “We need to have other things on the shelf.” Researching new methods requires significant investment in molecular biology and biochemistry, and mathematical modelling plays an important role in deciding what are the most promising strategies.

Strategies on which people are working include new drugs and possible vaccines, but also novel ways of tackling the vector – the mosquito itself. Professor Godfray outlined some novel anti-mosquito tactics. These include driving genes through the mosquito populations which make them unable or less able to transmit disease, and causing the mosquito to die before it can transmit malaria.

Researchers have created a refractory mosquito – one which cannot pass on malaria – but how do you “drive” this gene through a wild insect population? As was first realised by Austin Burt at Imperial College, homing endocuclease genes (HEGs) are a promising avenue of research. These are selfish genes, found naturally in single-celled micro-organisms, that are able to spread rapidly through a population by cheating Mendel’s laws – ensuring they are over-represented in the next generation. A useful gene, such as one that interrupts mosquito transmission, can be attached to the HEG and hence driven through the population. Alternatively, the HEG can be engineered to spread in a manner that knocks out a gene in the mosquito essential to the malaria pathogen, or for the mosquito itself. In the last case the aim is to drive down mosquito population numbers. Mathematical modelling has been and is an important tool in predicting how these different strategies would work and in finding the best ways of making it possible.

HEGs can also be used to cut or ‘shred’ the X chromosome, which means there would be significantly more males (XY) than females (XX). Mathematical models show this can significantly reduce population densities and hence disease spread. Although it has been demonstrated in the lab that this technique works in mosquitoes, one problem is that currently it works too well (X chromosomes in offspring are also shredded), so means of modifying X shredding activity are being explored.

Parasitic bacteria use is another promising approach. Professor Godfray described research into *Wolbachia pipiens*, abundant intra-cellular bacteria, found in around 20 per cent of all insect species, including some mosquitoes. Females who are uninfected with *Wolbachia* cannot use sperm from infected males, again cutting down on reproductive chances. There has also been research into, for example, using the bacteria to carry a useful gene and spread it through the mosquito population. This is possible in principle, but we can’t yet get genes into *Wolbachia*.

Another strategy is trying to reduce the lifespan of the mosquito. Only a small fraction of the insects live as long as ten days – the life cycle of malaria infection – so anything that can speed death reduces transmission. This has been confirmed by mathematical modelling. Work on the fruit fly has shown that some *Wolbachia* can cause what is colloquially known as ‘popcorn’ in the brain – essentially damaging it and causing early death. Getting ‘popcorn’ into the brains of malarial mosquitoes could shorten their lives, but we’re not there yet, he said. This would have the advantage, however, of not involving genetic modification, which opens up ethical and regulatory dilemmas.

Another approach would be using fungi as an insecticide. Again, mathematical modelling provides answers on the optimum way to do this, including getting the balance between efficacy and avoiding the development of resistance. The disadvantage is that it doesn’t kill immediately, but does accelerate senescence.

Professor Godfray concluded by stressing that there are excellent ways of saving lives and controlling malaria now, although getting the health infrastructure working remains a major challenge. There is, however, a real risk of current control measures breaking down, so novel methods are needed. Many exciting ideas are being explored – both GM and non-GM – and mathematical modelling is essential to these research programmes.

Questions

Questions ranged from the political to the biological. Asked about differences in responses of governments to the malaria problem, Professor Godfray said it was variable. The important thing was to build up health infrastructure, but political instability and war were the enemies. The World Health Organisation and other bodies, including the Gates Foundation, were playing an important role, he said.

One questioner asked about how long the proposed strategies would last before they became obsolete. Professor Godfray said strategies could be designed to minimise the probability of mosquitoes developing resistance. For example, there could be an evolutionary advantage in targeting older mosquitoes, as natural selection gets weaker as creatures age.

Asked how modified genes could be spread into the field, Professor Godfray said that seven or eight labs were working on it, and there were a number of exciting possible ways, including the use of HEGs and *Wolbachia*.

Bringing the topic closer to home, he was asked if the proposed strategies could be transferrable to other biting insects – for example, the Scottish midgie. Professor Godfray said there was work going on into the vectors of diseases other than malaria, including dengue fever. If a means were found to target biting midges, he was sure it would be taken up in Scotland!

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