The Zika Virus, Dengue and the Yellow Fever Mosquito
Transcript

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Professor Francis Cox and
Professor Christopher Whitty

Part 1: The Human Diseases - Professor Christopher Whitty

In Thomas Gresham's time insect transmitted diseases were common and feared everywhere in the world. Many of these are now historical memories such as plague transmitted by fleas and louse-borne typhus; others remain significant public health problems of the tropics but are in retreat such as malaria and sleeping sickness. A group of diseases transmitted by one genus of mosquito, *Aedes*, is however expanding steadily around the world. Four major viral diseases in particular cause increasing problems for human health: Zika virus, dengue, Yellow Fever and chikungunya. In the first half of this lecture I will concentrate on two of these; Zika and dengue. There are however major current outbreaks of the potentially fatal disease Yellow Fever in Africa, and of chikungunya, a disease which can cause severe arthritis in areas including the Caribbean. Professor Cox will in the second half of the lecture cover the *Aedes* mosquito and how we might control it.

Zika has recently led to worldwide and sometimes lurid headlines. It is not a new disease, having first been described in Uganda in 1947. Since then it has spread through Africa, up to South and Southeast Asia and then hitchhiked across the Pacific to Latin America. It is during a major outbreak in Brazil over the last year that it acquired its notoriety. In non-pregnant adults and children Zika generally causes either no symptoms (the majority) or minor viral symptoms such as headache, rash and fever which resolve uneventfully over a week. In less than 1:1000 cases it can give rise to the potentially serious complication of Guillain-Barre syndrome. This occasionally occurs following a number of infections, and leads to the immune system attacking the myelin sheath around peripheral nerves.

What gave rise to very justifiable concerns however was the association between Zika in women who are pregnant, and microcephaly (small head) in their babies. A big spike in microcephaly cases in a region of Brazil coincided with a Zika outbreak. Subsequent virological investigations showed that the virus is capable of crossing the placenta and infecting the fetus. The association currently appears only to occur in the first trimester of pregnancy and if women contract Zika in this period there is a 1-13% risk of microcephaly.

Microcephaly is associated with neurological damage. Zika in early pregnancy also seems to cause problems with hearing and vision and may cause more subtle neurological problems in children without microcephaly which will become apparent as they grow older. Current estimates are that around 1.7 million women who are pregnant will be infected in the Americas in the first wave with potentially tens of thousands of affected babies.

Although men are very unlikely to become seriously affected by Zika, there are rare but definite cases of men transmitting Zika sexually. This is an understandable concern to families who are trying to have children. Men are infectious not only many have the disease but probably for several weeks and possibly several months afterwards and the virus can persist for a lot longer although is not clear whether it is at high enough levels to be infectious. Current advice is therefore to delay unprotected sex with women who might become pregnant for at least eight weeks following return from an affected area, and WHO has recently changed its advice to either men or women returning from affected areas avoiding unprotected sex for 6 months.

The big Zika outbreak of 2015/2016 in Brazil and surrounding countries appears to have reduced very substantially. It is important however we are not lulled into a full sense of security by this. Because Zika is transmitted by mosquitoes which are highly affected by rainfall, temperature and other seasonal factors in common with other mosquito borne diseases there is a strong seasonal element. Dengue virus, which is transmitted by the same mosquitoes in the same places in Latin America also tends to peak in the early part of the year. There is therefore likely to be another outbreak, probably in slightly different areas, in the Latin American summer of 2017.

For a mosquito transmitted infection the things which determine the long-term epidemiology include: the geographical range of the mosquito species; seasonal factors; the proportion of the population who are immune to infection either through previous infection or vaccination; travel by infected people. It is much more likely that the infections will move around the world in people who are then bitten by *Aedes* mosquitoes and have the virus than mosquitoes moving around the world.

In the short term the most important predictor is seasonality of mosquito biting, but in the medium term the key question is what proportion of the population are immune. If no one in the population is immune anybody who is infected is likely to spread the disease to many other people. Once a high proportion of the population is immune there is what is called the herd effect; there are not enough susceptible people in the population for an epidemic to take off. It is likely therefore that there will be several waves of initial infection with Zika, but since it looks likely that an infection leads to long-lived or lifelong immunity as a high proportion of the population become infected the epidemics will die out. They may then occur again several years into the future when a high enough proportion of susceptible people (generally children not born during the current epidemic) exist to sustain an epidemic.

For Zika we can try to model mathematically what will happen in the future. We have however a much easier task with dengue as that has been around and been reported for several decades so we have a lot of past data. There are four types of dengue (serotypes), and once a person has had one of them, they remain immune for a long time and probably for life to that type but not to the others. For this reason dengue serotypes take it in turns to cause epidemics. Dengue has however spread very substantially over the last three decades both in terms of numbers of countries affected, and numbers of people infected. Anywhere where dengue outbreaks have occurred is likely to be susceptible to Zika outbreaks. This includes much of Latin America, Southeast Asia, South Asia and more limited areas of Africa.

Unlike Zika, dengue is an unpleasant and potentially severe disease of children and adults. Like Zika around three quarters of those infected show no symptoms. Of those who have non-severe dengue it can still be an extremely debilitating infection with very painful muscle aches and headaches, and can leave people exhausted for weeks or months afterwards. Dengue can also cause very severe disease; WHO estimates 3.2 million severe cases and 5000 deaths a year. Two overlapping syndromes cause severe disease: dengue haemorrhagic fever and dengue shock syndrome. In dengue haemorrhagic fever people can bruise and bleed, sometimes catastrophically. In dengue shock syndrome fluid rapidly leaks from the blood system into the body, causing the blood pressure to plummet. Untreated the case fatality can be up to 20%, and even with good treatment there is a 1% mortality from severe dengue.

In common with most viruses, there are no specific drug treatments for Zika or dengue. The key to reducing the public health impact is to prevent the disease, and broadly there are two ways to do this. The first is to develop vaccines which mean that even when people are bitten by infected mosquitoes they do not develop disease. The second is to reduce the transmission from mosquitoes by attacking the mosquitoes themselves. Because it is an exploding and dangerous epidemic there have for many years now been attempts to develop a dengue vaccine.

Dengue presents a unique challenge for a vaccine. There are 4 serotypes, and infection with one of them appears to provide long (probably lifelong) immunity to that serotype. For a short while there is also some protection against other forms of dengue. A second infection with one of the other three serotypes however seems to give a significantly higher chance of a severe disease. Mechanisms behind this are not fully understood, but it makes developing a vaccine more hazardous as almost uniquely some degree of previous immunity increases severity of disease. Once someone has two infections the risk of severe disease seems to drop substantially.

In 2016 the first dengue vaccine has been recommended by WHO; CYD-TDV. This contains all four dengue serotypes. In trials over 31,000 children in Latin America and Southeast Asia have been vaccinated. Around 60% efficacy over two years. Efficacy against hospitalisation was 73%. Efficacy varied from 40% (serotype 2) to 76% (serotype 4). It is, however, less effective in children under 5 (34%) and more effective in people with previous exposure (78%) than those without (38%). Importantly, there is some evidence more hospitalisations of children <5 in the vaccine group. Models predict in very low transmission intensity settings vaccination of 9 year-olds was likely to increase dengue hospitalization rates. Duration of protection is unknown. As a result, the vaccine is currently only recommended by WHO for high-transmission settings.

A Zika vaccine is potentially less difficult because there is not the complication of the four serotypes of dengue. Immunity from natural infection appears to be long and probably lifelong so in principle a vaccine should be possible. Initial trials in animals appear promising. There is however at least a theoretical risk of interaction of immunity between dengue and Zika so it would be difficult to predict what the efficacy would be in the countries where Zika is a major problem and dengue coexists. The priority is a vaccine which is effective in women before they become pregnant. Even if everything goes right it usually takes years to get a vaccine properly trialled, assessed for safety, licenced and deployed. We therefore have to face the major Zika epidemic in Latin America, which is likely to expand to parts of Asia, before we get a vaccine. For the short and medium term therefore for both dengue and Zika we are reliant on the other way of controlling the disease: addressing the mosquito vector.

Part 2: *Aedes Aegypti,* The Yellow Fever Mosquito – Professor Francis Cox

There is an old sea shanty that goes something like this:

'*Beware, beware the Bight of Benin, for few come out though many go in'*.

From the earliest times of exploration and exploitation of Africa, particularly during the mid eighteenth century, mariners and traders had good reason to fear this part of the West African coast because of two deadly diseases, malaria and yellow fever both carried by mosquitoes. Malaria, as everyone knows, is carried by the *Anopheles* mosquito but yellow fever is transmitted by a very different mosquito, *Aedes aegypti*, the yellow fever mosquito. The mosquito itself is a striking creature immediately recognisable from its black and white striped legs and a lyre pattern on it back. This mosquito originated in Africa and was transported in trade ships particularly to the New World with slaves and is now established throughout the tropics and parts of the subtropics where, as you have already heard, it is the carrier of a number of viruses including Zika.

The mosquito and its life cycle.

Most of what everyone know about mosquitoes is based on our knowledge of the malaria vector, *Anopheles*, but the biology of *Aedes aegypti* is very different and it is necessary to know something about its life cycle in order to understand why it is such a superefficient vector.

The life cycles of all mosquitoes are basically the same. The female mosquito lays her eggs in water, the free-living stages, larvae, emerge, feed and transform into pupae and the male and female adult mosquitoes emerge and begin their aerial existence. This whole process takes from about 6 days depending on various factors particularly the temperature, the higher the temperature the shorter the life cycle. Although these statements are broadly true for *Aedes aegypti* they obscure the actual details that make this mosquito such a dangerous vector and one that is so difficult to control. First the egg. Unlike other mosquitoes, the female does not lay her eggs in open water but in temporary or damp places. The eggs are laid in batches of 100-200 over a period of several days and in different sites a process repeated about five times during her lifetime. The choice of laying site is very important and can be anywhere where small amounts of water accumulate. These vary from water butts, puddles and gutters to coconuts, egg shells, bottle tops and even damp filter paper (a bonus for scientists working with this mosquito). In one series of observations, over 50 possible laying sites were found in one village. Surprisingly, on a worldwide scale, the most important breeding sites are discarded tyres and it has been estimated that there is one used tyre for every ten people on the planet. The trade in used tyres is massive and Japan, for example, exports tyres to over 130 different countries. Tyres are virtually indestructible and nearly always contain some water and are therefore important vehicles for spreading the mosquito around the world. *Aedes aegypti* eggs have one very important survival strategy-they can survive desiccation for over six months. The female mosquito lays her eggs in temporary water that dries up but as soon as the site becomes flooded the larvae emerge possibly thousands of miles from where the eggs were deposited. This explains how *Aedes aegypti* reached the New World. Ships anchored in African ports took on barrels of freshwater where the mosquitoes laid their eggs just above the water line and, as the level of water in the barrels fell, the eggs dried up. On arrival at their destination, the barrels were emptied and refilled whereupon the eggs hatched out, the larvae emerged, the life cycle was completed and the mosquitoes migrated to other sites where they became infected with local diseases such as dengue and Zika. It is difficult to imagine a more efficient method for the widespread dissemination of any disease carrying mosquito.

The next stages in the life cycle are the larvae and they exhibit another important survival characteristic: they are able to starve for several months, which is an obvious evolutionary advantage. There is another less obvious survival strategy; they are not prey to predators such as larviverous fish that cannot live in the temporary habitats favoured by the yellow fever mosquito. The next stages are the pupae that eventually reach somewhere safe where the adult mosquitoes emerge. Both the males and females feed on plant juices, but only the female mosquito feeds on blood that it needs to nourish its eggs. Unlike other mosquitoes, *Aedes aegypti* can feed on a wide range of hosts including amphibians, reptiles, birds and mammals so never needs to go short of blood. In any case, females can survive on plant juices so it is not essential to find a host at least in the short term. The hosts of choice, however, are humans which the mosquito homes on down a plume of attractant odours including carbon dioxide. Unlike the malaria mosquito, the *Aedes aegypti* female feeds during the day and does so both indoors and outdoors so it is very difficult to avoid being bitten. It also tends to rest out of doors so it is difficult to find. Female mosquitoes live for several weeks and need to feed frequently thus increasing the chances of transmitting any disease that they are carrying. As pointed out earlier, the mosquito lays its eggs in a wide variety of wet or damp places and, as these are frequently available close to human habitations, it does not have to fly very far to find someone to feed on.

Nightmare scenarios

The Zika virus, transmitted by *Aedes aegypti*, is already a threat to human health in over 40 countries in Central and South America and the Caribbean. A recent study (September 2016) by Oliver Brady at the London School of Hygiene and Tropical Medicine has identified a number of countries with the conditions necessary to sustain the Zika virus. These include China, the Philippines, Indonesia, Vietnam, Bangladesh, Pakistan and Nigeria. As if this wasn't bad enough, there are also two nightmare scenarios. The first is that the Zika virus could switch to other mosquitoes, *Aedes albopictus*, a mosquito with a very wide distribution, and also *Aedes africanus* in Africa and *Aedes hensilli* in Micronesia We already know that the Zika virus can be transmitted by these mosquitoes. The second nightmare scenario is the effect of global warming. It is best to take these two scenarios together because, although very different, they both have the same potential outcome. The one chink in the *Aedes aegypti* armoury is that it is confined to the tropics and subtropics and cannot survive below about 25^{0}C. *Aedes albopictus*, on the other hand, is able to survive temperatures as low as 17^{0}C. In order to understand what might happen it is easiest to consider Europe rather than the world as a whole. *Aedes aegypti* and the diseases it carries are no real threat in Europe. However if we now look at the distribution of *Aedes albopictus* we can see that much of Southern Europe could be at risk. Making conservative estimations about global warming, we can envisage that *Aedes aegypti* could also occupy a similar range of temperatures. This is already happening in parts of North America. The threat to those living in the tropics and subtopics is going to affect those living in the warmer temperate zones. It is no use pretending that we have sufficient tools to prevent this threat and all we need to do is to look at Singapore, one of the richest countries in the world, to see that the *Aedes aegypti* mosquito and dengue still present major health risks. Someone at a conference recently said that 'if Zika reaches Stockholm we are in real trouble' and this would inevitably affect us. We are confident, however, that this will not happen but remember that the weather forecaster, Michael Fish, once said that gales were not on their way just before the cyclonic great storm of 1987.

Controlling the mosquito

Epidemiologists no longer talk about eradication and the best we can hope for is elimination of a particular disease as a health risk in a well-defined region and control as a short term means towards elimination. As we have seen, the *Aedes aegypti* mosquito is perfectly adapted to living with humans and, as a consequence, is an ideal vector of yellow fever, dengue, chickungunya and the Zika virus. It is likely to extend its range with the inevitable disease consequences. The challenge, therefore, is how to control it. This is not impossible and there have been successes in the past. Early in the last century, yellow fever threatened the completion of the Panama Canal and the mosquito was eliminated by about 1910 and in the 1950s Brazil successfully eliminated both *Aedes aegypti* and the malaria *Anopheles* mosquito by employing draconian methods and vast amounts of DDT. Unfortunately, Brazil failed to sustain its mosquito control programme hence today's problems. Much of what we know about methods of mosquito control has been derived from work on dengue about which there is no shortage of information. The general consensus is that very few intervention measures work as far as disease control is concerned and the best results have come from community managed campaigns, water covers and house screening.

If conventional methods don't work, what about novel methods for mosquito control? Here there is no lack of possible candidates. One possibility is the use of genetically modified mosquitoes, particularly sterile males. This involves the release of large numbers of irradiated sterile male insects and the theory is that when the females mate with these sterile males, which they only do once, their offspring either do not reach maturity or are sterile. The use of sterile males to control insect pests has been very successful against a limited number of crop pests but has been less successful with mosquitoes particularly *Aedes aegypti*. In 2010 the release of sterile males eliminated his mosquito from the Cayman Islands, and in 2015 in a small trial in North East Brazil this technique reduced the mosquito population by 95%. There have been similar successes in Panama and Malaysia. These, however, have been small trials and the real problem is the need to swamp the natural populations of mosquitoes with sterile males. This could be an insuperable problem and one that would have to involve cooperation between several countries some actually in conflict with each other.

Another more recent technique involving male mosquitoes, and one that has not yet been field trialled for Zika, is the introduction of the gene for maleness into the population. This results in female to male conversion and, as males cannot transmit the virus, this could be a very useful addition to our armoury. The major constraint for the use genetically modified males, however, is likely to be the prohibitive cost.

Other possible methods of control involve biologicals including a toxin derived from the bacterium *Bacillus thuringiensis* (Bti) which has proved to be useful in controlling mosquito larvae in several trials. There is also a natural insect pathogen, *Wohlbachia,* which could be very useful if introduced into natural populations and is now being used experimentally for its potential in the control of Zika. These methods of control are in their infancy and all we can do is to wait and see.

The future

The question is not whether *Aedes aegypti* will spread beyond its present range, bringing with it the diseases it transmits, but when, so it is very important to understand how and why this might happen. The main problems are likely to be, spread of urbanization, spread of farming, deforestation, encroachment on jungles, global travel, lack of planning, wars and conflicts, ignorance and political inaction and incompetence. The fact that Zika could have threatened the Olympic Games, and the subsequent publicity, might just be the wakeup call that the world needs in order to prevent or limit future disasters.