Title	*HIV: Will there ever be a vaccine?*
Description	This talk looks at the University's work in China and Africa and its attempts to identify the key determinants of protective immunology against HIV infection that should guide future vaccine design
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Contributor My name is Sarah Rowland-Jones. I work here as a Professor of Immunology. I'm based in something called the Weatherall Institute of Molecular medicine which is up on the hill on the John Radcliffe site.

I trained originally- did my first degree in Cambridge, but I'm sure you'll all make allowances for that! Came here as a clinical medical student and trained subsequently in infectious diseases. And I'm an honorary consultant here looking after patients on the John Warin ward which is the infectious disease ward.

But, as quite a junior doctor became very interested in HIV infection. I was a senior house officer in London around the time that the first patients with HIV were being recognised and treated in London. And I think it was the really awful situation for many of these people that convinced me to pursue a career focusing on HIV medicine, and then subsequently research.

The first patient I looked after, whose CT scan we'll see in a little while, was a young man who had recently come to terms with his sexuality and had moved down from Scotland and worked in a gay bar. And he was diagnosed with having HIV, presenting with quite late state AIDS. First of all he lost his job, and then he lost the home that he had, which was living above the bar.

And all his friends stopped visiting, and his family wrote and said they were very sorry but, you know, they had to think of the children and they wouldn't be able to come. And it was the experience of facing a terminal disease whilst losing all the support that people normally experience in that circumstance that really struck me.

I think things have changed a lot since then, that was in the early 1980's, but that's still a very important memory for me.

So, after I'd finished my clinical training I moved to do research. And most of that time I've spent in Oxford, but with a strong interest in HIV in Africa. And, for four years until last summer I worked in West Africa in the MRC, Gambia. And I'm going to talk about HIV vaccine development and the problems and the issues and the recently announced successes.

And my talk is liberally illustrated with pictures of our travels in Africa. So, if the science is not interesting to you, do feel free to enjoy the pictures!

So, this is the brain of the unfortunate man I was telling you about who presented with what was then a very typical presentation of a rather bizarre infection called toxoplasma forming a swelling in the brain. You can immediately see that that's abnormal.

This is now not so commonly seen, because people are treated earlier, and also the drugs that people take to prevent Pneumocystis, another very common presentation in those days, a chest infection, also help prevent toxoplasma. And this- the lower picture is a picture of the AIDS quilts which were very much a feature of the early AIDS conferences.

And people made them in memory of loved ones. This is a fairly obvious couple who had both died of HIV.

As you probably know, the first cases were reported in the early 1980's and, when I was a medical student, we saw HIV very much in terms of risk groups. That there were certain kinds of people that got HIV infection and other kinds of people were not as vulnerable to the infection.

Of course now we know that really HIV is a disease of anybody who has sex which, I think, counts for an awful lot of people in the world! And also many people who don't, if we think about the children who have become infected through mother to baby transmission, which I'll talk about a bit later.

So we got to indentifying the virus very quickly, only a couple of years later after the first syndrome was described, the virus was identified. And we then learnt quite a lot about it, because we knew something about the family of viruses it belonged to. And the key thing is that it uses an enzyme which we call reverse transcriptase to make a copy,

And that copy of itself becomes integrated. That's a fancy word to explain it actually becoming an inherent part of the DNA of the host infected cell. One of the important points to make is that this enzyme in HIV is inherently prone to making mistakes. And that would be a problem for many organisms, we have many checks and balances to make sure that when we reproduce or our cells reproduce we don't make mistakes.

But the making mistakes in HIV comes alongside a very rapid replication rate. So that the virus doesn't really mind if it makes a whole lot of rubbish. And, in fact, what we now know is that it makes a mistake pretty much every time it copies itself, and perhaps more than 90% of the virus in an infected person is unable to replicate any further, what I'd referred to as rubbish.

But the advantage of this to the virus is that any time something comes along that threatens it, such as anti-retroviral drugs, or, as we'll see, the immune response to the virus, then the virus has up its sleeve a variant that can potentially escape that. And this makes it a particularly difficult target for both the immune response and for drugs.

And it's thought that every possible variant of the virus that could be made is made within the first few weeks of infection. So, if you want to tackle this, you have to do it at a very early stage. And, of course, most people don't get recognised at a very early stage of infection.

The first cases in Africa were reported around the same time. And one of the virus- a second strain of HIV, which I've been very interested in because it's particularly prominent in West Africa, was picked up in 1986.

And we think that more than 45 million people have been infected just in these last two to three decades, and around 33 million are currently living with HIV and AIDS.

So this is a virus that, from a very small beginning, has taken a massive toll. And I think that's why it's attracted so much attention, because this is something that really could devastate the human race, and, in many parts of the world, is already doing so.

And these are the start figures which I think hide a lot of human suffering. And this is something that the United Nations AIDS group put out every year in incorporation with the WHO, the estimates for different parts of the world.

And most people will know that sub-Saharan Africa is the worst affected, and accounts for the vast majority of people with HIV infection. But there are some hot spots, and a few years ago you wouldn't have had any figures for Eastern Europe, but in the former Soviet states, HIV has taken

off with a vengeance. And that's probably one of the fastest growing areas, with many different strains circulate- co-circulating.

And we're almost certainly underestimating the epidemic in China, which also has the potential to grow huge. India has- because it has a very large population, has the most infected patients of people of any single country.

And the figures in North America, Latin America and the Caribbean and Europe have been stable really for the past couple of decades. So, if you think particularly – if you break down those figures into the number of new infections, the WHO estimates 7,400 per day in 2007, which is their last data. And the vast majority of those are people from what we would think of as the developing world.

A significant proportion of those are children and the burden of HIV falls particularly heavily on children in sub-Saharan Africa. The disease is very rapid in African children, 50% of children without children will die by the age of two in Africa.

But, also it has a disproportionate effect on... by removing the adults, so many households in Africa are led by children, who have to take on responsibilities at a very early age, And, now, about half the infected population are women, and particularly worrying are the figures in young people.

And it seems that adolescents are maybe unusually vulnerable to HIV infection, so there's a very rapid rate of increase, particularly in sub-Saharan Africa, in teenagers.

Over the years I've seen all sorts of things said about HIV infection, and you've probably seen some of those. The one thing I think we can disprove pretty quickly is that it's a CIA plot! This is a very intelligent virus, and couldn't possibly have been invented by the Americans!

But, apart from that, all sorts of things may be possible. I think one of the most bizarre headlines I've seen comes from a daily newspaper in Africa, which I still can't really explain. And the text has sort of disappeared over time. But that was the headline.

So, where did HIV come from? Well, the family that HIV belongs to is a retrovirus and most animals, most mammals, have a retrovirus. Mice have them, cats have them, most different monkey species have their own. And often they don't cause disease in that particular species. In fact, in most cases they don't, the animal has learnt to live with them quite happily.

Whether that's taken many years of co-evolution with the virus and the host is not known, but that's probably the case. The HIV-2, which is really very much limited to West Africa, we know came from a particular virus of West African monkeys which are called Sooty Mangabeys, And the molecular virologist suggests that its come into the human population on several occasions, and probably through the bush meat trade.

Monkeys, parts of monkeys are sold widely in rural markets in West Africa, and probably through catching or preparing monkey meat and contact with blood, is likely to be how these viruses have come in. And there are probably many more viruses out there. A new species of HIV was recently reported that came in from gorillas, and there are others circulating, particularly in central West Africa, and all of these have the capacity to be the next big HIV epidemic.

HIV-1 looks like the virus that infects chimps in Central Africa, around Cameroon and the Democratic Republic of Congo, which is where the virus probably first surfaced in Africa. And the monkeys that are infected with the virus naturally don't usually get sick.

The mathematical biologists, who understand these things, have developed a molecular plot to try and work out when HIV might have come into the human population and then started to spread out. And the estimate is that it came into the humans around 1930, and probably then started developing into its many different families.

The first case that we absolutely are sure about is from a sample that was collected from a man in what's now the Democratic Republic of Congo, and goes back to 1959. Earlier samples, we don't know that they didn't have HIV, they're just not of a high enough quality to determine.

In Africa where I've had a particular concern, many hospitals would contain people looking a bit like this man. He has- you can't see very well from this picture, but he has widespread shingles, which is often an early sign of HIV infection. These are orphans in a Nairobi orphanage that we also had some contact with.

So, just to tell you about Africa in particular. By 1986, a survey done in prostitutes working in a Kenyan slum showed that, already more than two thirds of the prostitutes were infected with HIV which was a big surprise to everybody who was working there, and I think was a sort of herald of the scale of the epidemic subsequently.

And, in many parts of sub-Saharan Africa, and it's still the case, up to one in three adults in the major cities are infected with HIV. A colleague of mine recently started at the University of Cape Town. She was told, as part of their induction process, that they should assume that one in three of their fellow students, and one in three of their lecturers would be HIV positive. And I think that kind of brings it home.

Certainly, in much of Africa, it's very much a middle class disease. So it's had a particular toll on the professions and some of the more productive parts of society. And it's continued to climb, and probably the highest rates anywhere are in Southern Africa. And it's particularly sad that South Africa didn't start to have much HIV reported until the early 90's, so quite a long time after East and West Africa. But whilst other good things were going on in that country, there was a fair neglect, really, of the consequences of HIV.

And it spread to very high levels. So, if you go to an anti-natal clinic in KwaZulu-Natal, up to half of the women presenting there will be HIV positive. And, as you can imagine, this has a huge impact on the economy of these countries. And for several years now, this has had a measurable effect on the Gross Domestic Product of many sub-Saharan African countries.

And it's been predicted, and this is only a year away, that all the gains in life expectancy and child survival that were achieved through public health measures in the 20th Century are likely to be reversed by the end of this decade as a consequence of AIDS.

So, this lady gets a very unfortunate press. She was the US Health Secretary in 1984, which was a press conference to announce- if you were American, the identification of the AIDS virus by Bob Gallo. The French would say they identified it a few months previously.

And the main aim of the press conference was to say they now knew what the virus was, they'd be able to screen the blood supply, this would make the blood supply safe. And she was asked about the possibility of a vaccine and she said, as far as she was concerned, a vaccine would be available for testing within two years.

And this has been quoted time and time again, she'd been made to look a real idiot. But she later commented, many years after her retirement, that Bob Gallo, the man who discovered the virus, told her to say that. And he's been very quiet about that.

So this is a baby at a child health clinic in the Gambia, where I, as I mentioned, was working for several years. And he's being weighed and checked over before he receives some of his routine vaccine. And the routine programme of vaccines that is used, really, across the developing world, we call the EPI, the extended programme of immunisation.

And that's really one of our major public health success stories. And the Gambia's one of the poorest countries in Africa, yet it managed to vaccinate well over 90% of its children against these various diseases, and has just introduced pneumococcal vaccination as well.

So it's a huge impact on infectious diseases. So we can do vaccines in general very well. And, I think to understand why we don't have an HIV vaccine, it's probably important to go back to the very original understanding of what we mean by protected immunity.

The idea is if you survive your first attack of measles or Whooping cough, that then- sorry, so you don't die in that first illness, but then you're protected from it lifelong. So nobody gets measles twice. And this was first articulated by a Greek historian who was describing the plague of Athens, which was many millennia ago.

And we still don't really know what the plague of Athens actually was, but it had a pretty devastating effect of wiping out about a third of the population. And they had trouble trying to find people to look after the sick, for obvious reasons. And one of the things that emerged over the course of the plague was that the people who had had it and recovered were the best people to nurse the sick, because, as far as they were concerned, as far as they could see, these people didn't become sick a second time.

And, in fact they received the congratulations of others, believing that they were safe from all known diseases. And I think that- the Greek historian doesn't comment whether that was indeed the case, it seems unlikely.

But, in general, that's the principle of protected immunity on which all our current vaccines are based. So that if you give somebody a small amount, or a weakened form of the original organism, you induce immunity that is like having the first attack of the illness but without the major symptoms.

This became a little bit more sophisticated in England, in the 18th Century, when smallpox was a major problem. And most of you will know the story, Jenner noted that milkmaids who had acquired a related virus, called cowpox, causing pustules on their hands, appeared to be resistant to smallpox.

So, what he did, without any ethics committee approval, was to take material from cowpox blisters and put them into the skin of healthy donors. And we call it vaccination, because this is related to the Latin for cow. And then, even less ethically he performed a live virus challenge on a child, which you would never get through these days. One of his vaccinees was a boy working locally, and he gave him smallpox, and he didn't get sick, so thereby proving the efficacy of his vaccine, which is something that is quite hard to do these days.

And so the smallpox vaccine is based on a related, but much milder form of the illness, and most of our current vaccines, and most successful ones, are live viruses usually, that have been weakened in a laboratory so they don't usually cause disease. Although as all of you will know you sometimes get a fever, or feel a little bit unwell at the time of immunisation.

And the Killed Whole virus vaccines are less effective, but they're still used in certain forms. With some more modern approaches, the Hepatitis B immunisation, which is a very effective vaccine, you simply use the coat, the protein of the virus, as a synthetic protein and that provides long term protection.

So, with that in mind, thinking about an HIV vaccine, the strategies that have been widely used previously are thought to be too risky, and too much of a gamble, particularly for manufacturers and the pharmaceutical companies to use for HIV even though, in practice, in animal models these approaches seem to be effective.

And there are some people who are continuing to pursue Killed HIV vaccines, or Live Attenuated HIV vaccines because of the success in animal models. But ultimately, if this vaccine was going to be used widely, you would need a drug company as a partner, and very few of them would be willing, as far as we can see, to take that kind of approach on.

So, most infections for which we have a successful vaccine, with the possible exception of rabies, we do know that there is protective immunity. But, as far as we can tell, most people infected with

HIV do eventually develop AIDS. So we don't even know if it is possible to generate protective immunity against HIV.

And a question that hasn't needed to be asked for other vaccines is what we need to do in order to get protective immunity. So we've had to understand much more about the immunology and the pathogenesis of this organism than we would necessarily in other settings.

And the same applies, I think to diseases like malaria and TB, and one of my colleagues is talking about the TB vaccine work that they've been developing in Oxford, over the course of the weekend.

So there are other problems that are inherent to HIV as well. I told you how variable it was, because of the tendency to make mistakes as it's copying. As far as we know, when people get infected, they get infected with a single strain and very recent studies have shown really, that usually only one, and very occasionally, two, individual virus' get into an infected person and set up the infection.

But because you wouldn't know what that virus was going to be from your possible contact you have to try and think of making a vaccine that covers all the potential variants, and those are very different in different parts of the world and in different people.

Also the virus, unlike most infections, is transmitted in many different ways. By breast milk, by needles and blood as well as sexually. So you have to think about providing protection at different sites of the body.

Going more about the variability of the virus, the molecular biologists do this thing called a phylogenetic tree where they look at- the length of each of these branches tells you how far the virus has changed. And this is the 1959 sample from the very earliest case that's recorded, and this is where they think the original AIDS virus came into the population.

And even without knowing much about phylogeny, you can see that the virus has changed and also developed into quite distinct families, which are named with different letters of the alphabet.

One of the things that is a particular issue, where there are several strains circulating together as in Central Africa, and now in Eastern Europe which has a whole alphabet going on, is that it's possible for somebody to be infected with two different distinct strains of virus. And these can get together in the course of infection, and create new strains.

So, for example the E clade that's prevalent in Thailand has got a bit of A clade virus and something else, another parent that we don't actually know. And some of these become stronger and more dominant, and set up new infections of their own.

This is just to point out that infection takes place on different routes. Just to explain the picture on the left. A colleague took this photo of an advert for a sex doctor in one of the Francophone African countries. So he was offering to treat an awful lot of interesting things, my French isn't good enough to tell you what all of them are.

But basically, we don't know very much about how to generate immunity at a mucosal surface, that's the site of most HIV infections. So that's something that we really need to understand more about.

Once the infection has established, these are some of the reasons that it causes such a problem, such a long-term, difficult problem. I mentioned earlier the virus becomes part of your own DNA, and the virus can move directly from cell to cell, so antibodies, which are the proteins that we make in the circulation that stick on the outside of pathogens, can't really access the virus very effectively.

So, you can really only get at the virus by destroying the affected cells. And these cells are cells that express a marker on the surface called CD4, which the virus needs to get into cells. And they are really crucial cells for the functioning of the immune system.

So, if we're thinking about actually getting rid of HIV by a curative strategy, it's really very difficult even to conceive of how you might do that. So you might have as many as 10 million virus particles in the blood and you might be able to get at those with a drug that is circulating in the blood.

But you'd also have to rid the body of all the cells expressing this particular receptor, CD4, containing virus. And, as far as we know, even the best therapy that we have which, in the West has made HIV much more of a chronic disease than the life sentence it was originally, that there's a reservoir of cells that are untouched by the drugs, and if you stopped therapy, the virus immediately comes back up again to the level that it was before treatment was started.

So it's really very difficult to see how we might actually cure people of this virus, and it's really difficult to see how we could do so without damaging the rest of the immune system.

There was a case reported last year of a man who had a complication of HIV infection and blood malignancy, and, as part of the treatment for that he had a bone marrow transplant, which involved ablating, giving him very intensive chemotherapy and radiotherapy to get rid of his own immune system.

They weren't trying to treat his HIV, they were trying to treat his lymphoma, but, in fact when he recovered from the bone marrow transplant, he appeared to be HIV uninfected. But this is obviously not a treatment for the vast majority of infected people in the world.

I should mention that the bone marrow transplant he'd been given was from rare people, which I'll talk about shortly, who lack the second receptor that the virus needs to enter the cells. So they'd given him, basically, an HIV resistant bone marrow.

So, just from a simplistic point of view, if this is the infected CD4 T cell, you can attack the virus in two ways. These are the antibodies which are Y shaped and stick on the outside of organisms. And these are cells which are cytotoxic, or 'killer cells', which can recognise and kill virus infected cells.

But both of these depend on assistance from these CD4 healthy cells, which are the ones that are infected and being destroyed by the virus. So it's quite a difficult task to mount an effective immune response if the coordinator of the immune response is being damaged by the virus.

So this is probably the most heavy slide, really. Just trying to explain that even in an infected person, it's not that the immune system isn't trying. It's been estimated that one in five of all of your immune cells are responding to HIV in an infected person. But the response somehow just doesn't quite hit the mark.

So people make antibodies against the virus, but they're not usually the kind that can stop the virus, or 'neutralise' is the technical term, the virus that is transmitted from person to person. I mentioned that these key immune cells are lost very early in infection, and that's partly because the virus preferentially targets those.

And there is another form of immune response, the killer, or cytotoxic T cells. And they do a good job for a long time, but they ultimately fail too. So it's much better to prevent infection before than to try and treat it after it's established.

And the antibody response – it's still not entirely clear why people don't make a very good response to the virus, but there are things that make it particularly difficult to target for antibodies, and this equally applies to antibodies that might be generated with a vaccine. And one of the issues is the virus surface is covered in sugar molecules, which don't have a particular- that aren't particularly critical for the virus, but that makes it a very slippery surface for antibodies.

And the parts that are absolutely crucial, that the virus really can't do without, which are therefore conserved and less likely to vary, are in very deep pockets. And they are overhung by sugar molecules, and really very hard for antibodies to get at. Or other, even more crucial parts, are actually only revealed when the virus docks on to the CD4 molecule, so, for a very short time.

And antibodies usually can't get at the virus at that point. Whereas the rest of the envelope can change quite happily, without really affecting how well the virus functions. So, if you do make good antibodies against it, the virus can evolve very quickly to avoid it.

Now, the killer T cells are the other main arm, and they produce a lot of different things. They do kill the cells, but they also produce soluble factors, antiviral factors that attack the virus as well. And just one technical point is what they see, how they recognise an infected cell is, that small parts of the virus, or any other pathogen or indeed a tumour if this is a cancerous cell, are held on the surface of the cell, a bit like a red rag to a bull, with a little tiny fragment in an HLA molecule.

And all of us have different HLA molecules, and some are more effective than others when presented with particular pathogens. And that's how the T cell sees the affected cell, and that triggers this cascade of reactions, which lead to the death of the infected cell.

And we do know that these T cells can kill the infected cell before it makes new infected virus. So it is an effective way of controlling the virus for much of an infected person's life. So this is potentially one of the routes where the virus might be vulnerable.

So is it better then, if it's so difficult to make an antibody response, which is how we think most of our current vaccines work, is it better then to make a T cell response against the virus? And many people followed this approach, and, in fact, one of the first vaccines of this sort to be tested was developed here in Oxford by a colleague and PhD supervisor, Andrew McMichael.

And this went through a number of animal studies, and eventually tested for the first time in humans. Some of you may recognise the MP for Oxford West and Abingdon, who was the first person to receive the vaccine in Oxford. He'd been a junior doctor on our ward before he went into politics.

You can see a guy with a camera behind, and another one here. In fact he had to have one ampoule of vaccine and four of saline to allow all the cameramen to get their picture! But he got re-elected, so...! And in fact it makes him very useful in debates about genetic manipulation, because he refers to himself as a genetically manipulated human, when this comes up the House.

But it's a question, really, whether this is going to provide enough protection against HIV infection. Although many of our current vaccines do simulate this kind of immune response, they nearly all make a good antibody response as well.

And people became very gloomy around two years ago in the HIV community when a study was published from a company called Merck, working in collaboration with the big HIV vaccines trial network. And they had set up a study of what, to everybody, seemed to be the best candidate, and seemed to have worked in monkeys, and seemed to give the right kind of T cells in a human.

And they had a plan that, if after a certain number of infections in the high-risk groups that they had immunised, they would then analyse the results without continuing the trial further. And so, when they analysed these early infections, they found that not only did the vaccine not protect people but there was a suggestion, in some of the vaccinees, that they may have even been at increased risk of infection.

And this was particularly worrying. The vaccine contained bits of HIV inserted into one of the cold viruses, adenovirus. And it had been made to be replication defective. And the suggestion was that people who had seen this particular cold virus before and had high `[[?? 0:34:37]]` of antibodies appeared to be more susceptible to the HIV infection after the vaccination.

In fact, this was probably a statistical quirk, because as further analysis of the infection in the trial has gone on, this hasn't been confirmed. But people then became very gloomy about the prospect of vaccine altogether, and they felt that T cell vaccines may be doomed, and there was a lot of hand waving and soul searching, and a feeling that the community should return to basic science and try and understand the virus better before trying again with a vaccine.

There are various ways you can try and understand protective immunity against HIV. I mean the obvious way, really, would be if you had a good vaccine and even if it wasn't completely successful, you could look at what correlated with success. But we're not really at that stage, so, at the moment most of the immunologists are looking at people who have encountered HIV and then done relatively well.

And, in particular, people who were exposed to the virus who don't become infected, or people who have remained well despite being infected, and have appeared to control their virus load without the aid of drugs for long periods of time.

And one of the tactics that we employed was to look at people who were exposed but not infected. And, in fact, despite all the gloom in what I told you before, it's actually relatively hard to catch an HIV infection. And if you're in a stable relationship with an HIV infected person, we know from studies of say haemophiliac men and their wives before they were found to be HIV positive that only around 10 or 15% of the wives became infected.

And if you have a needle stick injury with known HIV infected blood, the chances are around 1 in 1000 of acquiring the virus. And the same to children born to infected mothers, even those who are subsequently exposed to HIV in breast milk.

And one of the first examples of this, this was an old paper from when I was a PhD student, was looking at a child who was born to a haemophiliac father, and his wife had become infected in the course of them trying to have a baby. And at that stage we didn't have very sensitive tests to know whether the baby was infected.

We had to wait till the mother's antibody, which the baby carries in the blood for the first year of life, had disappeared, to know whether the baby was actually infected himself. And when the baby was about 9 months old, we had some blood from him and we found that he had these killer T cells circulating in his blood that recognised HIV.

And we were quite depressed about that, we thought that that probably meant that he was going to turn out to be HIV infected. But, when his mother's antibody was cleared from his system, he was virus negative by all the tests. So this suggested that you could make a killer T cell response to the virus without antibodies, and without actual infection.

And, of course, because of confidentiality, I never actually met that baby, this is my own baby. Just showing off some baby photographs!

So one of the causes of not being infected reported here, and I'm sorry I don't have the full cover, but from the Sunday Times, 'This man can't catch AIDS'. This was a gentleman in New York who had done all the things that his friends had, but, whilst they were all getting sick, he had failed to catch HIV infection.

And he offered himself, and his blood to a New York laboratory, and they investigated and found his blood was very difficult to infect in a laboratory. And what it turned out was that this particular gene, called CCR5 is necessary, along with CD4, for the virus to get into cells. And around 1 in 100 Caucasians, particularly of Northern European, Scandinavian and Northern European descent, lack both copies of this gene.

And, if you have no copies of the gene then your cells don't express this receptor, and the virus can't get in. But this isn't present in most African or Asian populations, and it's been speculated that this has been selected in Caucasians in relation to the plagues of the early part of the last millennium.

But this only accounts for a very, very small number of people who are exposed but not infected. One of the studies that we went on to do after the baby study was in the Gambia, where we were looking at people who were exposed- working as sex workers, in a clinic who were exposed to HIV, but hadn't become infected.

And, just as we had with the baby, we could find the same killer T cells in those children. And very extensive testing revealed no evidence for HIV infection. And these women have been exposed to both HIV-1 and HIV-2, and HIV-2 is generally regarded as not being as virulent a strain as HIV-1, and we wondered if exposure to that particular strain had led them to be able to generate protective immunity.

We then set up a collaboration with a group of Canadians working with Kenyan Doctors and researchers in Nairobi. And they had started off a study of a particularly unpleasant genital ulcer disease called chancroid, and I haven't got any pictures of that to show you, you'll be glad to know.

Very early on in their study they thought- which was in the early 1980's, they thought they should just check how much HIV there was in their group, and they found that more than 90% of sex workers in this poor slum called Pumwani-Majengo in Nairobi were HIV infected.

There was an economic incentive not to use condoms, because many of their clients really didn't like condoms, and they would pay the women more for sex without a condom. It was only a few cents difference, but it was an economic driver for unprotected sex. And we estimated that there would be several exposures, a significant number of exposures per year.

And Frank Plummer, the Canadian professor who was leading this study, and his colleagues noticed that if everybody was equally susceptible to HIV, you would start out with 100% of people uninfected and you would have an exponential curve with time down to zero.

But, in fact what happened after about three or four years, this curve started levelling off. So what they concluded was that there was a group, who if they made it through the first three years of prostitution without getting infected, appeared to be relatively resistant to HIV infection.

And they looked- because they were epidemiologists, they looked very closely at behavioural factors, and , in fact the only factor that came out repeatedly was that the more exposure the women had, the more likely they were to be resistant, which obviously is not intuitive.

And we played with cells from the women in a laboratory and found it was very easy to infect their cells. In fact, the only person whose cells were easier to infect in a laboratory with HIV were mine, which is a bit of a worry, but anyway the CCR5 gene was normal in them.

So, it wasn't that they couldn't be infected, or it was certainly not that their cells couldn't be infected. And you remember that I mentioned HLA as one of these key proteins associated with the function of killer T cells. And there were very strong HLA associations with being resistant in these women.

And, what we found, working with the Kenyan and Canadian group was that these women, just as the Gambians and just as the babies we'd seen previously, also had killer T cells and healthy T cells responding to HIV, and we could find them circulating in their blood. But they appeared to be enriched in a genital mucosa, which is where you would like them to be if they were going to lead to protection.

And they did the kind of things that you'd want them to do as a vaccine. They were targeting multiple parts of the virus that seemed to be- particularly targeting those parts that were similar between different African strain. And Rupert Kaul, working with me, found the longer you'd worked as a prostitute, the greater these immune responses became.

It was suggestive of an acquired immunity, rather than something that was present innately. But also he found that some women who previously he'd thought to be resistant, and even had these T cell responses, if they took a break and went back to their families- and usually they hadn't told their families what they did in Nairobi, they may be away for a few months and then came back to prostitution.

These immune responses had gone, and in some cases that led the women to become susceptible to HIV. And this is not dissimilar to what, as a clinician, you would see with people with malaria.

That if you live in a malaria endemic country you build up resistance to malaria over time, but if you come to Oxford for three years and then go back to your malaria endemic country many people are appalled that they become ill with malaria for the first time for a decade or more.

So it's a partial immunity, not a complete immunity. But, of course, the public health message that springs from these kinds of observations are that if you're going to use prostitution as a method of avoiding HIV infection, which is obviously not a good method, then you can't afford to stop!

So, our kind of scenario was that if you had a lot of exposure and you were a susceptible kind of person, then most people can become infected. And, in the Nairobi scenario, was the worst case, really. 90% of people are likely to, in the right circumstances, or wrong circumstances, are likely to acquire HIV.

But probably in some people, perhaps it's the kind of virus they are exposed to initially, or the way their immune system will respond, they can make an immune response that contains the infection. And that subsequently, the exposure appears to boost immunity.

So we thought this was something that encouraged the idea of developing a vaccine, and, with another group of epidemiologists focusing on mother to child transmission, we thought we would look at breast milk which was a particular concern, because it's something that's very important for protecting children against a whole range of diseases, particularly in the developing world, but also a potent way of transmitting HIV.

And breast milk has HIV free in it, and also inside immune cells. And about half of babies that become infected in the developing world get it- acquire infection through breast milk. And it's presumably an oral infection because you can mimic this situation very easily in baby monkeys.

And yet most of the babies who may be drinking hundreds of litres of infected milk don't get infected. So, with my colleagues we reasoned that breast feeding could be just the right kind of exposure to infants that could boost immunity in infants that were exposed to HIV, but not infected.

A lot of the infection is thought to take place as the infant comes through the birth canal and swallows infected secretions, and I'm sorry I've told you that so near tea time. So, what we've tried to do is see whether we could do it on a statistical basis- show whether children who had these kind of immune responses were protected from breast milk transmission.

And my colleague, Grace John-Stewart, designed a study looking at a large group of women, and this was at a time when there wasn't any formal prevention of mother to child transmission programme in Kenya, where mothers were given AZT through the last part of pregnancy and offered formula milk.

But in that part of Kenya, formula feeding is like telling your neighbours that you have HIV, so most women still chose to breast feed. And we looked at the babies through the first year of life using very sensitive assays to see if they were infected and also to look for T cell responses to the virus.

And, what we found was that a disappointingly large number of babies became infected, and I think that's because AZT isn't a very good prevention. And a lot of these infections were very early, particularly in the first month. And, with hindsight we would have designed the study differently.

And the infection was much more likely at birth if the mother had a high viral load. But the late infections were all in breast fed infants. But, looking particularly at what we were trying to identify we found that around half the babies had at least one assay where we could detect a T cell response. And we didn't find it in babies that weren't exposed to HIV.

So these were often very young infants whose immune system is often frequently considered to be immature, and they could be very strong. And statistically the results, just approaching significance. But none of the children that did have these T cell responses acquired breast milk

infection. Whereas, those who didn't have infection, there was a significant rate of infection, suggestion, although this is correlate, not a proof, that these T cells can lead to resistance.

So I was just going to say that most of you will know about the Thai vaccine trial. And what I had put on this side was a picture of a sunset in Thailand, and to tell you a little bit about the news that came out yesterday of a vaccine trail that appears to have succeeded where all previous ones have failed.

And this is a vaccine that was tested by the US army in collaboration with a number of authorities in Thailand. And testing in a cohort, young people in South East Thailand, they studied 16,000 people comparing people given dummy injections with people given the vaccine.

And it was surprisingly difficult to find out in the course of researching this talk what the vaccine actually contains. But it seems to be a canarypox which is an old relative of the smallpox vaccine that infects canaries, and doesn't really infect people. So it is a live virus but doesn't continue replicating. And it contains a few, not many, HIV genes.

And the vaccinees were given four injections of that vaccine followed by two protein boosts which were designed to elicit antibodies, although not the right kind of antibodies, not the kind that would be effective in neutralising a primary isolated virus.

And the figures, which were on this slide and I can't remember off my head were that there were remarkably low rates of infection in the trial. So the figures were something like 54 in the vaccinated group, and 71 in the placebo group. So, really very tiny numbers.

It gives a protection rate of 33%, which is what the big news was about yesterday. And it is just statistically significant. And it is a lot better than no protection. But this has a lot of implications for vaccine. A partially effective vaccine clearly can't be used on a widespread basis, 30% protection simply isn't good enough to make it into a public health- into a regular use.

It does offer the possibility of trying to work out what the difference was between the people who were protected and the people who weren't, and say, what are the things that the vaccine did that correlate with protection.

But the problem that it poses for future vaccine studies is that although it only worked a bit, you would now have to use it instead of a placebo in subsequent vaccine trials, which will make subsequent vaccine trials very large and very cumbersome.

And I just wanted to point out that actually it's quite a laborious process to develop a vaccine, and even if you have something that works, or a good idea, there are a lot of processes that have to be gone through before a vaccine can be developed.

It's five o'clock on a Friday, and before people get completely to this stage I'll stop and see if you have any questions. Thanks very much.
