Title	*Developing an improved TB vaccine*
Description	Dr McShane talks about the University's work in creating an improved vaccine against tuberculosis and she also talks about the urgency of this research
Presenter(s)	Helen McShane
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H. McShane: Excuse the slightly croaky voice, I hope you can hear me okay.

I am Helen McShane and I am a clinician scientist working at the Jenner Institute which is based at the Old Road Campus on the Churchill site and I've been leading the TB vaccine programme here for the last ten years or so.

What I am going to do is talk you through a bit of the epidemiology of TB and why we need a new TB vaccine and the problems with the existing TB vaccine and then talk about the developments that are happening in the field in terms of trying to make a better vaccine both in terms of what everyone is doing and then focusing on what we've done here in Oxford and illustrate the pathway for the development of a new TB vaccine.

So this quote clearly was taken in the pre antibiotic era where you can see where the sanatoria came from. The enemies of consumption were sun and air and hence we ended up with many sanatoria where people sat in Switzerland and in the sunshine and supposedly that was what cured their TB although many people self cure their TB we know.

But the thing I like about this quote is "If you do have Tuberculosis do not give it to others by spitting. Even if you have not set a good example by refraining from a habit always dirty and often dangerous."

And the reason I like that quote is that I do a lot of work in Africa and I am often asked why I don't go to Russia and why I don't work in Russian prisons because there is lots of TB in Russian prisons too. There are lots of answers as to why I don't work in Russian prisons but the one that I particularly like is a colleague of mine who has done a lot of work in Russian prisons tells me that when the prisoners are sputum smear positive, this means they have the most infectious form of TB and are most likely to transmit it, they are kept in the sanatoria where the conditions are somewhat nicer than the general prison.

But when they lose their sputum positivity which typically happens two or three weeks into a six months treatment course, they then get moved back to the general bit of the prison where the conditions are just not quite as nice.

So there is a lot of saliva exchange that goes on between the prisoners in the sanatoria to maintain their sputum positivity so they can stay in the sanatoria as long as possible. I would suggest that we need far more than the vaccine in that particular situation.

That is one of the reasons why I don't work in Russian prisons.

Male What's the date of that quote do you know?

H. McShane: Turn of the last century. Early 1900's. It's fascinating, TB goes back to the Pharaohs actually, there is a fascinating amount to look up.

A little bit more history, Robert Koch as well as giving us Koch's postulates as to how to determine whether an infectious agent causes a disease, also identified the causative agent of tuberculosis, mycobacterium tuberculosis in about 1882.

Unfortunately this success in identifying this agent wasn't followed by success in developing a cure. He thought he had got a cure which he called the remedy which was what we would now think of as PPD. This was growing up stocks of TB and skimming off the soup at the top of it and injecting it into patients with TB, hoping that it would cure them.

Unfortunately it didn't and some of them it made rather sick and some of them I'm afraid it killed. So that was really the end of Koch's remedy.

But that legacy lives on in that eight years ago when we started our vaccine programme and we were the first, the vaccine that we've developed here in Oxford was the first new TB vaccine to go into clinical trials anywhere in the world since BCG had been developed. There was a huge concern within the field that we would induce just such a Koch reaction as it is now called if we vaccinated people who were infected with TB. There was a lot of concern and a lot of caution and I think the field has moved on since then but the legacy of this lasted a long time.

So fast forwarding 50 years where really we developed in the 1940's 1950's there were five pretty important antibiotics that were identified that clearly have anti mycobacterial activity and this was really when we started to be able to treat TB with things other than just sunshine and beds in Switzerland. One of the reasons to put up this slide is to point out that it's rather salutary to note that isoniazid and rifampicin which remain the cornerstone of our therapeutic repertoire today, were identified over 50 years ago and there isn't anything after that.

There are newer classes of antibiotics that are being tried, and we do use other antibiotics when we have to particularly in cases where we have drug resistant TB. There are two particularly concerning strains of drug resistant TB nowadays.

There is multi drug resistant TB where the organisms are resistant to both isoniazid and rifampicin and rather than having a six to nine month treatment course, if you have multi drug resistant TB you probably have a two year treatment course. There are obviously huge problems with that and indeed in Russia the problem has got so bad that people are going back to the pre antibiotic era and are doing phneumonectomies, removing lungs, doing a thing called plombage where they put essentially ping pong balls into the top of the lung to squash the lung because TB needs air to replicate. So we are going backwards rather than forwards here.

Then there is a thing called extensively drug resistant TB or XDRTB where the strains are not only resistant to isoniazid and rifampicin but they are also resistant to at least two classes of second line drugs and the WHO have described XDRTB as virtually untreatable. So there are some problems still to be solved here.

As I have said the typical TB regimen for someone who has drug sensitive TB is a six month treatment course. The problem is that people start to feel better when they have been taking their tablets for a month, so they stop taking their tablets and then the develop resistance and TB grows very, very slowly, it's replicating time is measured in hours, it's about 36 hours and that's why we need such a long treatment course. This is really where we ended up with DOTs, Directly Observed Therapy, where actually for six months people watched people taking their tablets because that is the only way to prevent the development of drug resistance.

So moving forward a bit further, TB today remains as big a problem as it ever has on a global scale. When I started working in this field ten years ago many lay people and friends said to me "Gosh, isn't TB eradicated? Haven't we got rid of that?" and interestingly people don't say that to

me now. I think it is because there has been over the last ten years a huge amount more awareness of TB with the Global Fund, with the Gates Foundation. Actually people who don't necessarily have a scientific or medical background know that TB is up there and is a big problem.

So nine million cases and 1.7 million deaths every year, I've discussed drug resistance which is a huge problem and really inhibits our ability to control this pathogen.

Global instance continues to rise. A part of that is fuelled by the HIV epidemic of course. The HIV epidemic and the geographical overlap between HIV and TB particularly in sub Saharan Africa has had a devastating impact particularly in that continent. People who are infected with HIV are more likely to get TB and people who are HIV infected who then get TB, their HIV disease gets faster as well. So there is a really devastating synergy between these pathogens. As if that weren't enough there is the burden of latent infection.

So one of the reasons why we could eradicate smallpox was there is no latent pool. Everyone who has got smallpox has disease whereas it is estimated that a third of the world's population, two billion people are latently infected with TB. Those people are at risk of reactivation of that latent infection or waking up of that dormant infection if they become immuno suppressed as they get older, may reasons for reactivation, but clearly in terms of eradication that makes it a real challenge when you are talking on that scale of infection.

So this is a figure taken from the WHO, these are 2006 figures which shows global incidence, so these are numbers of new cases per hundred thousand of the population per year. Red is the highest and you can see here sub Saharan Africa in particular, South Africa where I do a lot of my studies now, really bearing the brunt of the disease and clearly as I am sure many of you will have heard in the HIV talk, that's where the burden of HIV as well. But interestingly in terms of numbers, actually India, China, South East Asia is also a real problem because actually there are more people in those countries which means in terms of the prevalence actually the numbers of cases overall is greater in South East Asia.

This is illustrated here so you can see 1995, 1999, 2005, so how the absolute numbers of cases have changed. Clearly in established market economies the western world really is very flat. TB is going up very, very slowly in this country but the numbers are very small actually.

Eastern Europe, big rises partly due to break down in health care structures, partly due to HIV, there is a lot of drug resistance in Eastern Europe which is a worry. I think you can see here where you look at Africa, where there is low HIV prevalence and Africa where there is high HIV prevalence the impact that HIV prevalence has on the TB epidemic and actually you can see here that in terms of the numbers, South East Asia is top of the chart.

So this graph is to illustrate that XDRTB is everywhere. There was a very well publicised outbreak when the strain was first defined in KwaZulu Natal in South Africa where 48 out of the 49 people who contract that strain died. Most of them were HIV infected.

What happened at that time, because XDR is MDR plus so XDR is multi drug resistant TB that is also resistant to two classes of second line drugs. All the labs in the world that had identified MDR isolates went back to their MDR isolates and said "Well hang on a minute, are these actually XDR?" and many of them were. You can see the red DOTs mean that these are countries where XDR has been isolated. We've had a case in Oxford, we've had a case in Leicester, a case in Glasgow, it's everywhere. We live in a small world today. And I think the lack of red DOTs in Africa is not because there isn't any XDR in Africa, it's because the facilities to make this diagnosis don't exist in Africa. So don't be lulled into a false sense of security there.

So what do we do about this? Clearly TB is not going away. In 2006 the WHO put out this document, the Global Plan to Stop TB which was a very ambitious document put together with all the stakeholders, funders, the World Bank, the Global Fund all the people working in the field. It's a roadmap of where we need to get to and how we try and get there.

Some very ambitious targets taken from the millennium development goals, more than 70% of people with infections TB will be diagnosed, well that's not unreasonable. More than 85% of those will be cured, well actually that's not unreasonable either. This is where it gets tough, by 2015 which doesn't feel like a long way away anymore, the global prevalence of TB will be reduced to 50% of the 1990 levels, that's a tough challenge and by 2050 this will be off the WHO hit list, so the global instance will be less than one per million of the population. That is a very tough challenge.

What was important about this document was that for the first time there was explicit recognition by the WHO, by all the stakeholders that we weren't going to get there, we don't stand a cat in hell's chance of getting there with the current tools alone. DOTs alone, very useful though it is, so this is directly observed therapy short course, this is people watching people take their tablets, is not sufficient. We need to clearly implement DOTs as well as we can and DOTs plus for drug resistant strains and DOTs expansion to link into HIV treatment as well. But actually for the first time there was explicit recognition that we need new tools too. We need new drugs, we need new diagnostic tests and ultimately the only way to effectively control any infectious disease outbreak is to have a better vaccine.

And really the bottom line is the problem, the total cost of this plan was estimated to be $56 billion and there was a $31 billion funding gap and that was before the global financial crisis. This would all be fine if we thought we could fund it, but there is a lot of money still missing.

I work very closely with the groups in Oxford developing Malaria vaccines and developing HIV vaccines and clearly there are many similarities between these pathogens. But TB has a head start actually in that we already have a vaccine, BCG, which is the world's most widely used vaccine, it's been given to over two billion people throughout the world.

BCG is live attenuated mycobacterium bovis, this is a weakened form of the strain of mycobacteria that infects cattle primarily and it's the reason we pasteurise our milk. It's been around for a long time, it was first used in 1921 where interestingly it was given orally. Over many, many trials done with BCG over the years some of them work, some of them didn't and that's part of the problem.

There were two big trials done in the 1950's very well done, high quality randomised control trials, the best kind of clinical trial you can do. One was done in the UK and one was done in the US and these were both done in adolescent school children and placebo controlled very good trials and the UK trial worked. High level of efficacy BCG which is why in the UK we introduced BCG vaccination to adolescent school children and obviously that is something that has only recently changed. And the trial in the US didn't work so the public health agencies did what was logical in the UK we licence or introduce the vaccine into routine clinical use and in the US they didn't.

Taking a step back from those two trials and just looking more broadly at all the trials that have been done with BCG it's very clear that BGC, when it is given at birth as it is throughout the developing world is good at protecting against what we call disseminated disease. This is TB that has spread outside of the lungs to the rest of the body and particularly TB meningitis, so TB that's gone to the brain.

Interestingly BCG is pretty good at protecting against leprosy in areas of the world where leprosy is endemic as well. But what it doesn't do is protect against lung disease which is obviously where the burden of mortality and morbidity are from this disease and it also is no good at boosting.

So Lara Rodriguez at the London School did a fantastic study where she randomised over 200,000 children, adolescent school children in Brazil who had all had BCG at birth and she randomised them to either be boosted in adolescence or not and showed very clearly that giving another BCG doesn't make any difference. If BCG doesn't word giving it again doesn't make any difference. Interestingly it seemed to make leprosy better, so I think the message is if BCG works giving it again works better, but if it doesn't work then there is no point in giving it again.

So this is a figure taken from a paper a meta analysis trying to look at all the, so looking at all the, this is pulling out a number of clinical trials that have been done, looking at the efficacy of BCG and the top bar is control trials, i.e. what we consider better quality trials today and the bottom chart is observational trials. So just slightly less good trials in terms of scientific rigour but important nevertheless.

Nought here is the important line here so something that works, doesn't cross nought, all these trials where the confidence intervals cross nought really mean it didn't work and it's only these ones right up here were the vaccine worked. What hits you about this is the variability in this efficacy. Some of the trials it works some of the trials it doesn't work and it's the variability that is one of the keys to the problem with BCG. British school children there, that's that second trial so that was the big MRC trial done in the 50's here where the BCG worked.

It's very clear that the closer you live to the equator, the less likely BCG is to work, overall looking at all of that. Latitude is the strongest single thing that or variable that has an impact on efficacy.

So why doesn't BCG work? It ought to work, it's just a live attenuated bug that is of the same family and indeed very, very closely related to TB. Why doesn't it work?

It's important to thing about why BCG doesn't work because we don't want to develop a new vaccine and then find it doesn't work for exactly the same reasons.

There are lots of reasons that have been put forward over the years as to why BCG doesn't work. Different strains of BCG so it's very clear that there are many genetic differences between all the strains of BCG that are used throughout the world. BCG is not a single entity, it's not clonal, most people say if BCG were developed today it wouldn't be licensed because it wouldn't reach today's manufacturing standards and it is very clear there are genetic differences.

However what is much, much less clear is whether those genetic differences make any difference in terms of protective immunity, in terms of actually working. And there are quite a lot of animal studies looking at this and actually there isn't really any good evidence that the differences we see in the genetic sequence make any difference. It may have a small effect but I don't think that much.

Nutrition it's very clear that many areas of the world where TB is a problem are also areas of the world where there is huge global poverty and huge problems with malnutrition. However, some of the places where there is a lot of TB and Cape Town in South Africa where I work is an obvious example, actually there is poverty but not as much as elsewhere in Africa and yet there is a staggering amount of TB. Really nutrition, unless it is really extreme malnutrition doesn't really explain everything.

The best explanation that is supported by data is that exposure to environmental mycobacteria interfere with BCG. So environmental mycobacteria otherwise known as non tuberculous mycobacteria, these are bugs from the same family as TB that look very similar to TB to your immune system but don't cause disease unless you are profoundly immune suppressed. So most healthy people, we are all exposed to these bugs all the time, they live in the soil, they are present in the tap water and in most people they don't cause disease. To your immune system they look pretty similar to TB and they may interfere with BCG either by masking or by blocking so there are two hypotheses on this.

The masking idea and this is a busy slide, and this is work done by Hazel Dockrell at the London School and was absolutely seminal work, it was really, really brilliant work.

She took two cohorts of adolescents, one in the UK and one in Malawi. They hadn't had BCG and she looked at their baseline responses, their baseline immune responses to BCG or to TB, the bugs are very similar and what she found was that the kids in Malawi has high baseline levels of immunity, even though they had not had TB and they had not been vaccinated with BCG. And the kids in the UK had very, very low baseline levels.

They all then got vaccinated with BCG and what she found was the kids in the UK that have very low baseline levels had a good response to BCG. In contrast the kids in Malawi who had high baseline levels, they didn't change very much after BCG and in fact some of them went down. So the thought is that environmental mycobacteria give you some immunity that cross reacts and is similar to BCG induced immunity and BCG can't boost that anymore, so there is a ceiling effect there.

What we don't know is whether that immunity induced by environmental mycobacteria that we see so clearly in the Africans actually gives you any protection and it maybe that it does a bit.

The second thought and these two theories are not entirely separate, is a slightly more active idea, so it is that BCG is replicating mycobacteria, it's live and it replicates in your body and it has to replicate in order to work. If you have immunity that has been induced by those environmental mycobacteria that are in the soil then that immunity might stop BCG replicating and therefore might stop your BCG take if you like.

Really these two theories are not so different but it maybe that both are working in synergy to stop BCG working in areas of the world where there is high exposure to environmental mycobacteria. And we know that the closer you live to the equator the greater the burden of exposure to environmental mycobacteria.

Briefly some immunology. In order to make a better vaccine we also need to understand what we want a better vaccine to do. Really the immune system is quite clever; most people who are exposed to TB don't actually get TB. So of everyone who is exposed 70% of people completely clear of the bug without even becoming infected and that's obviously because of a very early, innate, immune response.

Of the 30% that don't clear it, most of them become infected and that's that latent infection I was talking about where it's dormant in your body and really takes something like HIV to wake up that dormant infection.

So most people become latently infected and stay latently infected so 90% of people who are infected, that bug goes to sleep and it's only in a very small percentage of people that people go on to develop active TB disease and clearly then they go on to die. And really if we could understand how the immune system is working to clear the bug in most people and how it is working to contain the bug in those people who become infected, that's what we want to try and copy with a vaccine.

So I don't know how many of you have a science or a medical background so excuse this gross oversimplification of the immune system, but the point of this slide is to say there are different types of immune system and not all vaccines are equal. There are antibodies which attack; broadly speaking, bugs outside of cells and those are induced by B cells. The point here is that all of the vaccines we use today induce antibodies.

So diphtheria, tetanus, polio, hepatitis B, protussus, the new vaccines coming along, haemophilus and HIB, they all work by antibodies. That's no good for TB, because TB hides inside cells. So antibodies aren't really very important in TB.

So we need to make a different kind of vaccine and that's the point, this is a different kind of vaccine and it's a new challenge and it's similar, we need a T cell inducing vaccine for HIV and for malaria too.

So we need to induce the T cell arm of the immune response. This is for bugs that hide inside cells so antibodies can't get to them, so you need your T cells to go and wake up those cells and then kill the bug inside them.

There are two difference kinds of T cells CD4 helper cells and CD 8 killer cells.

The other question is how do you make a vaccine? Broadly speaking again, you can either take the whole bug, so you can say "Okay we want a TB vaccine, let's take TB and make it weaker so we can give it to people."

Or you can take a bit of the bug, what's called a sub unit vaccine, one of the proteins. TB has about 4,000 proteins so you can pick one or two that you think might be important and make a vaccine that delivers those particular proteins to the immune system. So those are the kind of things you have to think about, you want to pick which kind of vaccine you want and how you want to get it into the immune system and what kind of immunity you want to induce.

So pulling all that together really everyone in the field thinks that BCG is with us to stay, at least for the short to medium term. That's because of that protection it confers against severe disease when it is given in infancy. And we need to induce a T cell immune response.

Broadly speaking you can either leave BCG given at birth and develop another vaccine to be given later as a booster, sub unit vaccine, perhaps four months later, perhaps ten years later or you can say "Let's just make BCG better, we can do clever genetic engineering nowadays, let's clone in some different things to BCG and make BCG better." Or you can put the two together and you can boost a better BCG.

Broadly speaking everyone in the field is pursuing one of these strategies.

The next couple of slides are just going to talk you through the vaccines that are now in development and this is with a real focus on vaccines that have made it as far as clinical trials. Ten years ago when I started work in this field there were no new TB vaccines in clinical trials despite the fact that BCG had started out in 1921. That was in marked contrast to Malaria and HIV where for both of those pathogens there are over 50 vaccines in clinical trials.

TB has caught up now and we have a number of vaccines that are going through and showing some promise in clinical trials.

This slide talks about the BCG replacement. This is saying let's make BCG itself better, let's not muck around with a second vaccine.

There are two recombinant BCGs, so BCGs that have different things cloned into them to make them better, the first one actually there were some issues, not with safety but with regulatory things and manufacturing things which meant that didn't get very far. The second one is in a phase one study in Berlin with Stefan Kaufmann at Max Planck. There are a couple of others that are coming through the pipeline another improved BCG and interestingly an attenuated strain of TB.

So this is someone who has taken TB and knocked out some genes that we think are important in virulence and we now think will be safe to give as a vaccine to people. Now clearly there are safety concerns there about giving a weakened strain of TB to people but I think with the right safety procedures in place that vaccine will go into the clinic probably in the next few years.

This slide talks through the main groups developing what I am calling booster vaccines or enhancer vaccines. These are vaccines designed not to replace BCG but to be given after BCG to make BCG better. MVA 85a is the vaccine we developed in Oxford here, it was the first of these new vaccines to go into clinical trials in 2002 and as I will tell you at the end we have just started a big efficacy trial in South African babies to see if this vaccine actually works.

LS402 this is a virus, so the same as MVA which is also a virus expressing some TB antigens which went into the clinic a few years later and is now in trials in adults in a couple of sites in Africa.

GSK are trying to develop a TB vaccine which is similar to RTSS their malaria vaccine and they had a few issues with stability but they are now doing some studies in South Africa as well.

Then the group in Copenhagen SSI are developing two protein vaccines, one which they call hybrid one and one which they call `[[hivac 0:27:59]]` four. The names are not important,

this is really just to illustrate that there is a pipeline now of new TB vaccines that are gradually coming into the clinic and for the first time there is real hope that we might actually end up with a better TB vaccine within our lifetime.

For the rest of the talk I am going to focus on MVA85a because it's the vaccine I know about because I lead the group here. But really not so much because of that but to illustrate the pathway for development of a TB vaccine. How you actually go from making a vaccine in the lab to trying it in the clinic to getting it into deployment.

MVA is a modified vaccinia anchora; this is a weakened form of the smallpox vaccine. We know it's safe because it was given at the tail end of the smallpox eradication campaign. What we have done is cloned a TB antigen, a very strong, immuno dominant antigen that we think is very important into MVA and that antigen is called 85a, so we end up with MVA 85a. The plan is that this is being developed as a booster vaccine so BCG will continue to be given and then you boost afterwards with MVA85a.

Before you go into clinical trials with any new vaccine you have to try out these vaccines in animal models, you have to show some safety and some efficacy in animal models. There are a number of different animal models that people use in TB, mice, guinea pigs, non human primates and cattle.

I'm just going to show you a couple of slides, one from a non human primate challenge so these are monkeys that, there are three groups, the first group didn't get anything, the second group just got BCG and the third group got BCG followed by MVA 85a. They were all challenged with TB, so all of these animals, after their vaccination were given TB and then at the end of the experiment they were all sacrificed. We looked at their chest X rays, we looked at their lung scores, their pathology scores, we did everything we could. The BM group, the BCG MVA group were better than the BCG group which were better than the saline group on every measure we looked at, chest X ray score, pathology score, I think you can look at those lungs and work out which set you would rather have. That was encouraging.

We then did a study in cows and cows are important because cows are not only an animal model but cows are a target species in their own right. DEFRA in this country spend at least ten times as much on bovine TB as they do on human TB and that is because actually in this country bovine TB is a much bigger problem. Bovine TB is also a huge problem in Africa and really the need for a better TB vaccine in cattle is just as great as the need for a new TB vaccine in humans. It's possible we could use the same vaccine.

Here are two vaccines that are being developed for human use primarily, ours MVA85a and another Adenovirus expressing 85a and you can see that in the BM group and the BA group, there was significantly more animals with no disease at all in these new groups than there were in BCG alone group. So again very small numbers, but we were encouraged by this.

That and a lot of other data gave us the confidence and our funders the confidence to take this vaccine through into clinical testing but because of the concern that I told you about at the beginning of the talk about inducing a Koch phenomenon so making people who were infected with TB sick, we had to do this pretty carefully.

What we did we considered a spectrum of mycobacterial load and we started with people who were what we called "As mycobacterially naïve as possible" these were people who were skin test negative, had not had BCG, had not had TB and had never set foot outside of the UK. They had had as minimal exposure to mycobacteria as we could find.

We then moved on to BCG vaccinated people and then moved on to deliberately vaccinate latently infected people in very controlled setting where we could then monitor very carefully whether there were any adverse events. We started for obvious ethical and safety reasons the trials in the UK and then moved to roll them out in my collaborator sites across Africa, primarily to start with in the Gambia and then South Africa.

This is a gantt chart which much beloved of industry which really just shows you the clinical trials we have done over the last seven years.

You can see that this is how we've worked down, we started in the UK in BCG naïve people, moved into BCG prime people, looked at latently infected people, we are currently vaccinating HIV infected people. In the Gambia we started in 2003 with some adults and then in 2006 started a big study in infants in the Gambia and then in South Africa in 2005 we started a big programme of research looking at many different ages, many different risk groups and then more recently we have just started a trial in Senegal as well in West Africa. Then right at the bottom there is the efficacy trial which I will talk about at the end which we have just started in South Africa.

These, with the exception of the efficacy trials, these were all phase one or phase 2a studies. They were safety studies and what you do with early clinical trials is do very small numbers of subjects and look very carefully at the safety before you can then go up in numbers and expand the trials. Safety was the primary readout in all of these trials.

Immunogenicity was also an important readout. So in these early studies with small numbers of people we take lots of blood at lots of time points and throw the book at it in terms of immunology. We do as much as we can in order to really try and understand what we are doing with this vaccine in terms of the immune response. In the most recent trials we are now looking for the first time at efficacy. Does it actually work?

To date we have completed seven clinical trials and we have seven more that are ongoing. We have vaccinated over 500 subjects including some latently infected people, including HIV infected people and including now quite a lot of children and infants and in fact of that number only 24 are children, so all the rest are infants under the age of one. All of those are in Africa.

Vaccine is universally well tolerated; we have had no serious, adverse events with this vaccine. It's given intradermally which is the same route of vaccination as BCG and therefore not surprisingly we see some local reactions as you would expect, it's given really just under the skin. And we see a few mild systemic side effects within the first 12 to 24 hours. A little bit of mialgia, feeling feverish although often we don't see fever, and just a bit of flu like illness common with, similar to typhoid or many other vaccines. Importantly none of the clinical trials have we seen any signs of immunopathology, we are not seeing so far any signs of those Koch reactions that the field was so concerned about.

A very little bit of immunology. I've told you that we need to look at T cells, how do we measure a T cell response? Well we do a thing called an ELISPOT where we have a 96 well plate, you put in your blood cells, take blood, separate your lymphocytes, put them on the plate and you put in your protein that is in the vaccine, so that's 85a. If your lymphocytes, if your blood sample from your person that you vaccinated recognises that protein, because they say "Ah we've seen it before" then that white blood cell wakes up and secretes a thing called a cytokine which is a chemical messenger which we can then detect.

We put a couple of antibodies on and you end up with a spot and this is an example here. We can count these spots and each spot represents one T cell that is specific for the antigen, the protein we are trying to induce an immune response to. So this is a relatively simple way of quantifying directly the immune response we are inducing with this vaccine. In the media control well you expect to see nothing.

You don't need to understand the details of that but just to tell you that is what we are measuring. So really the stronger, the higher up the Y axis we are the better. What we've done here, there were the early trials we did in the UK. We vaccinated people with BCG, we vaccinated people with MVA and we looked at people who had already had BCG and then gave them MVA. You can see that in BCG vaccinated people using that immune measure, we don't see very much actually. With MVA we see quite a good response but actually it doesn't last very long, four weeks later it's back to baseline.

In contrast, in the people who have already had BCG, when we give them this vaccine you can see we see significantly higher peak responses but perhaps more importantly, six months after vaccination they are still maintained at a significantly higher level. We want a vaccine to induce long lasting immunity.

This is the most complicated slide. If you just look at the pie charts on the bottom. Immunologists are very excited about things called polyfunctional T cells. Polyfunctional just means these T cells do more than one thing, they've got more functions than one.

We think that these poly functional T cells are important in protection against pathogens that hide inside cells. TB, HIV, Malaria.

If you look at the pies at the bottom, green means that these T cells are positive for only one of these functions, they are monofunctional. In contrast red means they are positive for all four that we looked at. So you can see that a baseline in BCG vaccinated people, the cells are all green, they are all only monofunctional. In contrast after vaccination we see a much more polyfunctional profile which we think is good, we don't know, but we think might be good.

Six months after vaccination some of them have gone back to being mono functional but you can see that quite a lot of them are still three plus or four plus. We think that's important but we don't know and we won't know for three years until we get the results of the efficacy trial.

So I said that we were vaccinating latently infected people and I said that there was concern within the field that we would induce some nasty reaction in people's lungs. What we did, as well as the normal safety things was we did a high resolution CT scan we did a CAT scan on these people's lungs before and after vaccination because we wanted to make sure that there wasn't any sub clinical immuno pathology. We wanted to make sure that there wasn't a little bit of inflammation that they didn't notice and they were still fine but might be a bigger problem when we rolled out these trials in Africa. And the CT scans didn't change before and after vaccination, there was no change. That was very encouraging.

We looked at inflammatory markers and the adverse event profile was exactly the same in this trial to all the previous studies and that was really important.

Actually what was equally important was the immunogenicity was the same as well. This vaccine stimulates just as good an immune response in those people who are latently infected as it does in people who are BCG vaccinated. That is important too if one third of the world's population are latently infected, we want the vaccine to work in that group.

Now we are vaccinating HIV infected people and it is obvious from the epidemiology that HIV is an important target group for a new TB vaccine. Probably after anti retrovirals a new TB vaccine is the second most important thing you could do for this population to improve the mortality and morbidity.

We've recruited people who are not on antiretrovirals who are at an early stage of their HIV disease because that's probably the easiest population to give a vaccine in. We are following that up for a year and one of the most important things in this trial is that we monitor their HIV disease and we make sure we are not making their HIV disease worse with this vaccine.

To date we are not, we are looking very closely at both their viral load and their CD4 count, the things we monitor in HIV disease and they are fine, completely fine. We also see it's immunogenic, but it is lower than in the HIV negative population, not surprisingly. So we need to think about whether we can make it better by increasing the dose or whether in fact it might be better to vaccinate people who are on antiretrovirals because they will have had an immune reconstitution and the vaccine might work better in that group.

Fast forwarding to South Africa, I have the great pleasure to work in South Africa and collaborate with a group at the University of Cape Town, here in Cape Town a South African TB vaccine initiative SATVI and their clinical field site which is in a place called Worcester which is about

120 km outside of Cape Town in the Boland Overberg region, over the mountain. It is a stunning place to work and the teams there are absolutely superb.

It's a very good place to do vaccine trials because it has absolutely staggering levels of disease, the Western Cape has the highest levels of TB anywhere in the world but it also actually has a great deal of infrastructure and has a lot more scientific and medical resources than many other areas in Africa. That means you can monitor these people properly, you can do good quality clinical trials. So actually it is a great place to work. It's also beautiful.

We started this programme in 2005, we did what is called an age de escalation so we started in adults, adolescents, children and then worked down in sequence into infants which is what we are now doing. That's out of date, we've completed that study, I'm sorry. And looking at what we call high risk people so TB infected adults, HIV infected adults and TB and HIV co-infected adults.

The bottom line, not to give you too much data is that the adverse event profile, the side effect profile is exactly the same in the African studies as it is in the UK ones and the immunogenicity is good as well which is encouraging.

Importantly these immune responses that we induce with this vaccine in the South African subjects last just like they do in the UK trials. So a year after vaccinating these South African adults the immune responses are significantly higher than baseline, just as they are in the UK trials.

In the Gambia we started in 2003 in adults and then in 2006 we decided to do a study looking at what we call EPI non interference. So if you give this vaccine to infants and infants are a target population for a new TB vaccine, then ideally you would give it at the same time as you give all the other infant vaccinations because then you get more people. It's not another visit, you've got the infrastructure there, it doesn't cost very much more and it's just logistically easier. But to do that it is important to show that the new vaccine you are adding doesn't interfere with the existing vaccines immunologically.

So we recruited over 200 infants into this study, we had three groups where they got EPI alone, they were randomised, EPI, EPI means Expanded Programme of Immunisation, these are the routine infant vaccinations and MVA or MVA alone. What we saw was that the safety profile was excellent, but what we saw was if you give MVA 85a at the same time as the EPI vaccines you get a lower immune response to MVA than you do if you don't give EPI at the same time. That's important actually.

Interestingly it didn't work the other way so MVA didn't have any impact at all on EPI vaccines but it is pretty clear that EPI does interfere with MVA. So we need to think about that and either we give them at a different time or we change the EPI schedule, but if this vaccine works then we will need to think about that more.

Just to sum up and pull this together clearly what I have shown you is a whistle stop tour of the last ten year's work. We know that this vaccine can improve BCG induced protection in all of the animal models and we know that it is safe and it stimulates a strong immune response in all of the clinical trials that we have done to date. TB infected people, HIV infected people, adolescents, children, and we know that it induces high levels of what we think is the right kind of immune response.

But the bottom line is does it work?

All that's fine, it's safe and it stimulates some pretty pictures and some nice immune responses but does it actually stop people getting TB?

That's the problem, is the huge challenge in evaluating the efficacy of a new TB vaccine. We don't have what we call an immunological corolla protection. If you want to make a vaccine against haemophilus you don't need to do an efficacy trial, you just make a vaccine that stimulates the right amount of antibodies and you know your vaccine will work.

We don't even know which measure of T cell immunity is important actually, let alone what the level is and there is no perfect animal model. The animal models are essential, you can't develop a vaccine in a lab and go straight into people but actually they all have flaws and many of them don't represent the human disease very well at all.

So what you are left with is efficacy trials where you actually look at the efficacy of a vaccine, whether it works, in huge numbers of people and long periods of follow up. There are three important target populations, infants, adolescents and HIV infected adults. This slide summarises the big trials we have just started in South Africa.

This is what we call a phase 2b efficacy trial, it's not a licensure trial, if this trial works and this vaccine works in this trial to reduce the incidence of TB we will have to do an even bigger trial, probably four or five times bigger than this in order to get this vaccine licensed and repeat the efficacy obviously. But it's a start and it will I hope give us proof of concept.

This trial will look at safety in bigger numbers, it will look at immunogenicity and it will look at efficacy for the first time.

We are storing blood on every infant that goes through this trial so that if we see efficacy we can go back to those blood samples and try and work out what immune response correlates with that efficacy so that we can make easier the next trials coming through. All of these babies will have BCG at birth within the first 24 hours in South Africa and then they will be randomised at four to five months to get either MVA 85a or a placebo vaccine and our sample size is nearly 1,400 per arm, so 2,784 babies in total. With accumulative TB incidence of 3% over two years that will give us 90% power, this is the statistical way of looking at it, to detect 60% improvement. So if this vaccine makes BCG 60% better then we will pick it up.

Well that's fine, but 60% is a bit of a bar. If we had a vaccine that was 40% better that would have a huge impact if we deployed it tomorrow. But if it was 40% that trial would be four times bigger and cost four times as much. So you can't get the funding to do it. This trial is going to take us three years to do; it will take us a year to recruit and two years to follow up and is costing between $13-14 million.

We've come a long way from Jenner, I work in the Jenner Institute, really the father of vaccinology. Jenner didn't have the European clinical trials directive and the endless bureaucracy and ever increasing bureaucracies that we have to deal with I'm not sure this was really fully informed consent when he was challenging Samuel Phipps, but clearly vaccinology has come a huge way since his time and I think ultimately the only way we can control the TB epidemic is with a better vaccine.

A huge number of people have been involved in this over the last ten years, my TB group in Oxford both past and this is my present group. SATVI the South African TB Vaccine initiative team in Cape Town who are superb collaborators, the MRC laboratories in the Gambia led by Martin `[[Oater 0:48:29]]` and Sheila `[[Dantek 0:48:30]]` with `[[?? 0:48:32]]` Senegal, again I really have the privilege to work with some fantastic people in Africa.

And to thank our funders, The Welcome Trust who have supported all of this programme and supported the early clinical trials in particular. We get some funding from the European Commission, The Oxford Emergent Tuberculosis Consortium, this is a newly formed joint venture between the University of Oxford and Emergent Bio Solutions which is a US based pharmaceutical company to take forward the development of this vaccine and Aeras Global TB Foundation which is a Gates funded foundation based in Rockville who are cofounding with the Welcome Trust that big efficacy trial I have just described to you.

And really I have to end by thanking the subjects. Clearly we can only do these trials because people take part and let their children take part and this is particularly relevant to me today, when I came here today I left my husband and our three children at the John Radcliffe enrolling my

children in Andy Pollard's swine flu vaccine trial. So I think I have to practice what I preach and I do understand what it is like to enrol your children in clinical trials.

Thank you.
