Manage TB

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Lecture – 60
Vaccine for TB-Session-01

Good morning, good afternoon, good evening depending on when you are tuning into this course. My name is Dr. M S Jawahar, I am a physician and an epidemiologist and I worked at the National Institute for Research in Tuberculosis which is part of the Indian Council of Medical Research and I have my primary area of interest has been in clinical trials for TB treatment.

As we come to the fag end of this course on managing TB we have gone through diagnosis we gone through treatment and we are in the module dealing with prevention and I am going to talk today about vaccines in tuberculosis.

My talk will be in two sessions, in the first session I am going to talk about the current status of vaccine that we have for tuberculosis bit as you know is only BCG and what we have achieved with this vaccine and in my second session am going to look at the future what is required and what are the new developments as far as vaccines and TB is concerned.

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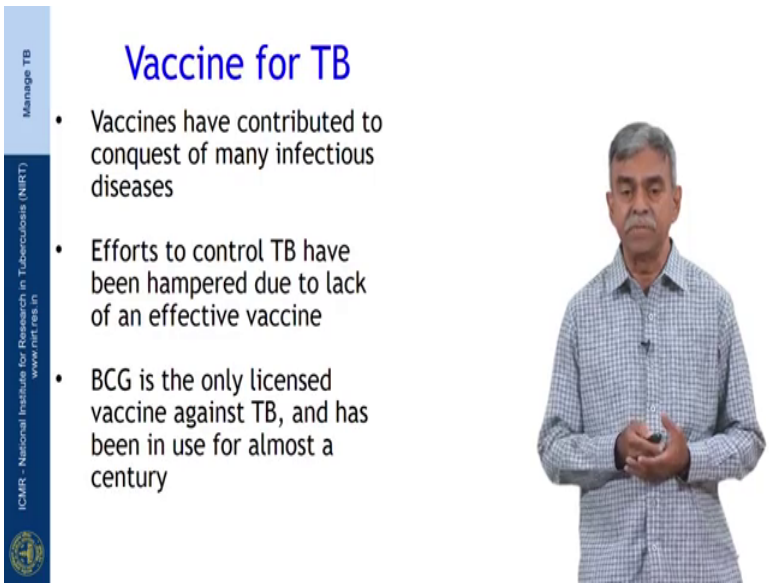

Now, vaccines have played a significant role and our efforts to contain infectious diseases. The classic example of course, is small pox which today is only diseases that has been eradicated from the globe by the use of a vaccine.

There are other examples Poliomyelitis or recent success by using vaccines, diphtheria, tetanus, pertussis, yellow fever, hepatitis, rubella there are many diseases. In fact, there are 26 vaccine preventable diseases and we have program of immunization with this vaccines which have played a significant role in controlling infectious disease across the world.

Now, therefore to control TB; however, have suffered a great sub bag because we do not have an effective vaccine against tuberculosis. BCG is the only licensed vaccine against TB and this has been in use for more than almost a century.

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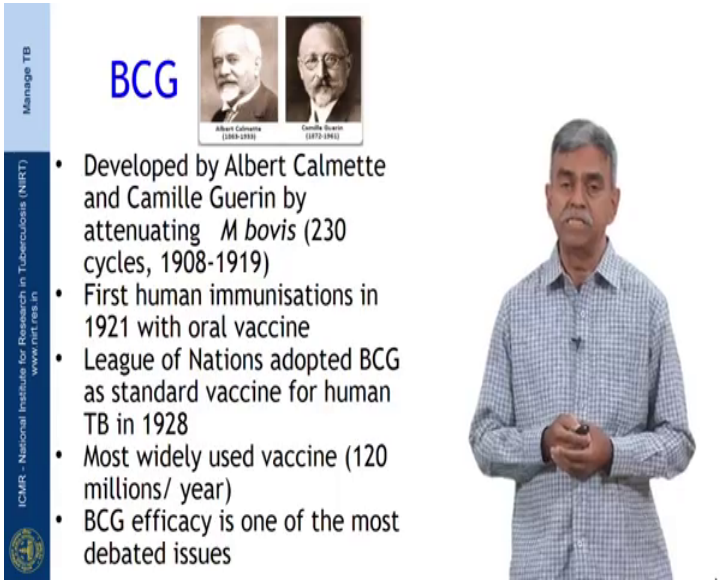

BCG was discovered by Albert Calmette and Camille Guerin, two French physicians. They developed this vaccine by attenuating microbacterial bovis over 230 cycles over 13 years. The first human immunization was done in 1921 as I said almost a century ago with a oral vaccine.

The League of Nations, the precursor of the United Nations adopted BCG as a standard vaccine for human TB as way back in 1928. It is a most widely used vaccine today with

120 million doses being used every year and it is also one of the safest of vaccines. However, efficacy of BCG has been a matter of great debate.

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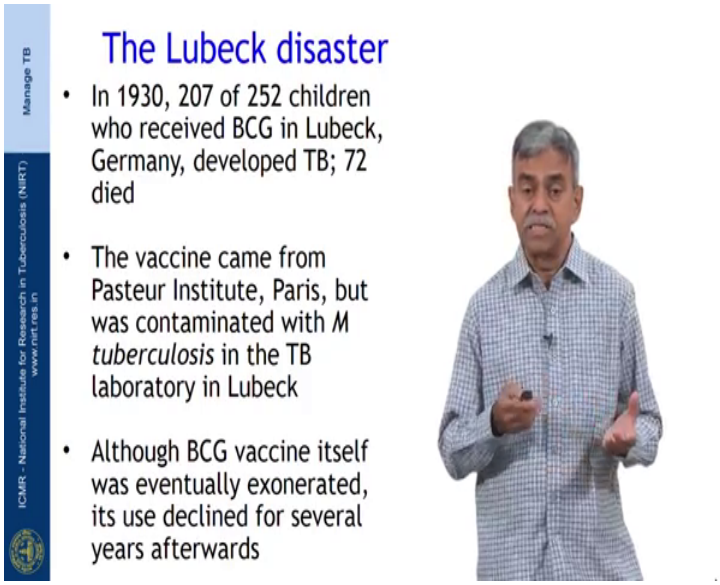

The development of BCG for a great said back in what is called the Lubeck disaster. In 1930, in a German town of Lubeck, 207 and 252 children who received BCG developed active TB and 72 died.

The vaccine came from the Pasteur institute in Paris, but was contaminated in the local TB laboratory in Lubeck. Even though BCG was subsequently exonerated it is application in the world suffered a great set back because of this disaster.

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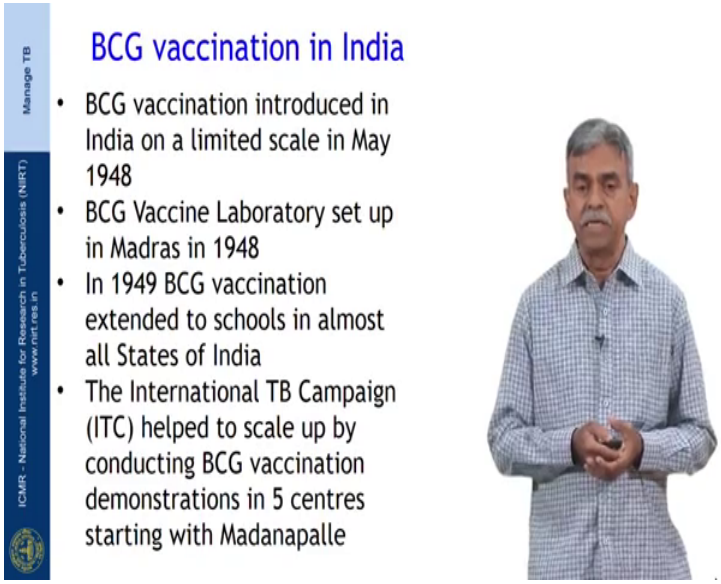

In India, BCG was first introduced in 1948 in a limited scale and in the same year a BCG vaccine laboratory was set up, in Gindi, in Madras, in Tamil Nadu, now Chennai. This was the only laboratory which was by using BCG vaccine for many many years and supplied vaccines not only in India, but many South Asian countries.

Unfortunately it was closed down a few years ago because of quality control issues. In 1949, BCG vaccination was extended to schools in most all the states of India and the international TB campaign or ITC helped to scale up the BCG vaccination campaign by demons by setting up demonstrations centers in five centers starting with Madanapalle in Andrapradesh.

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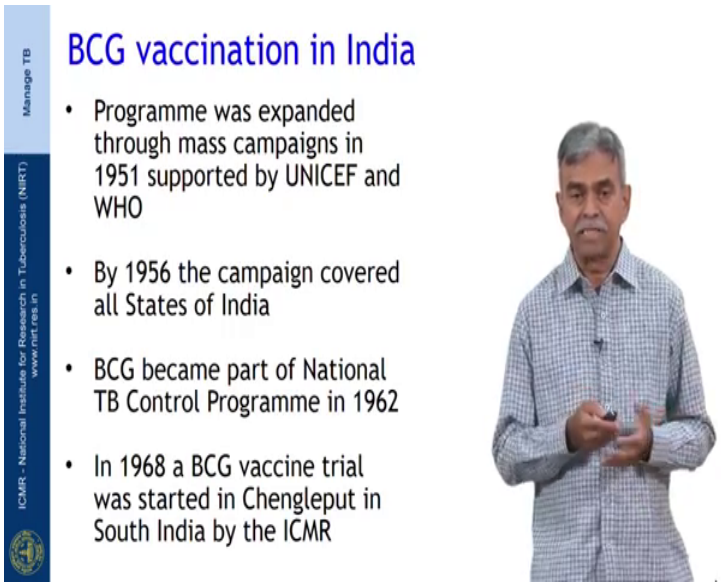

The program was expanded through mass campaigns in 1951 supported by the UNICEF and WHO, so it is a global campaign and by 1956 the campaign covered all the states of India.

So, we had BCG coverage almost for 60 years now and BCG became part of the national TB Control Programme in 1962 when the TB Control Programme was introduced, but it was only 1968 that that study was started to find out whether BCG works or not. This study was done by the ICMR in Chengleput in south in Tamil Nadu.

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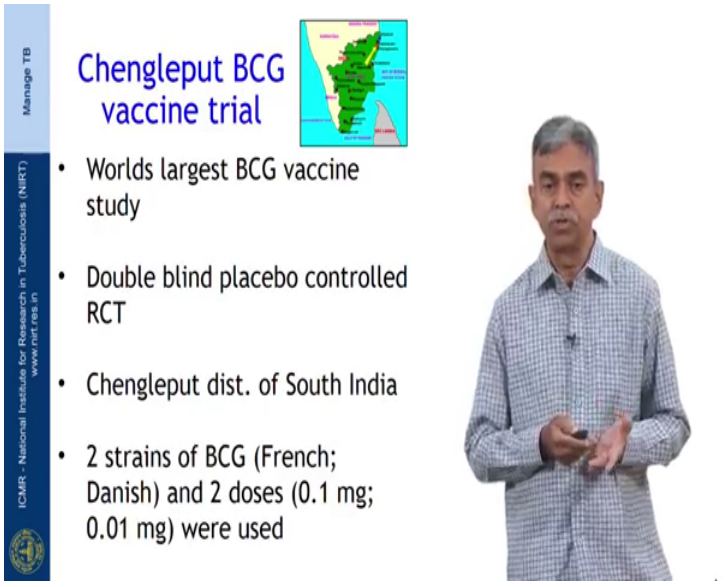

The BCG vaccine trial was a world's largest BCG vaccine study. It was a double blind placebo controlled randomized clinical trial, it was done in Chengleput in South India which is there situated on the Coromandel coast of Tamil Nadu, 2 strains of BCG were used were French strain and Danish strain and 2 doses of each were tested in this large trial 0.1 milligrams and 0.01 milligrams.

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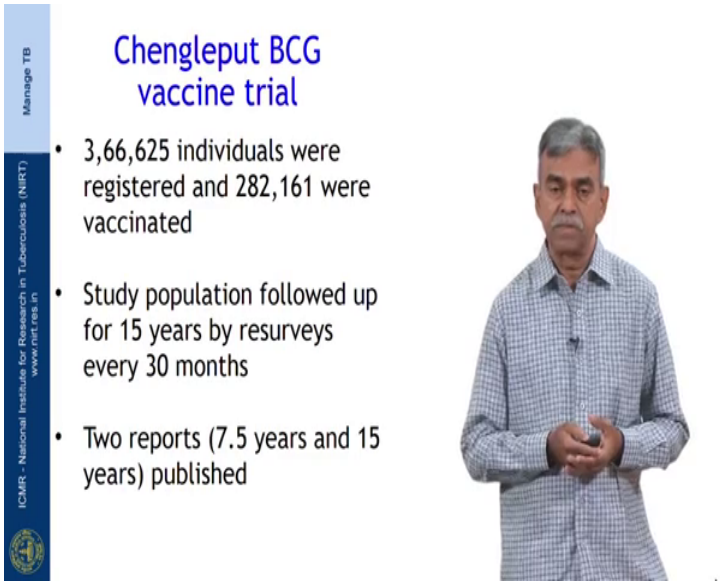

In this study a total of 366625 individuals were registered and 282161 and more were vaccinated. The study population was followed up for 15 years by resurveys every 30 months. There was no other study in the world which has such a large follow up of such a large population and two reports have been published one at 7 and half years and the second at 15 years.

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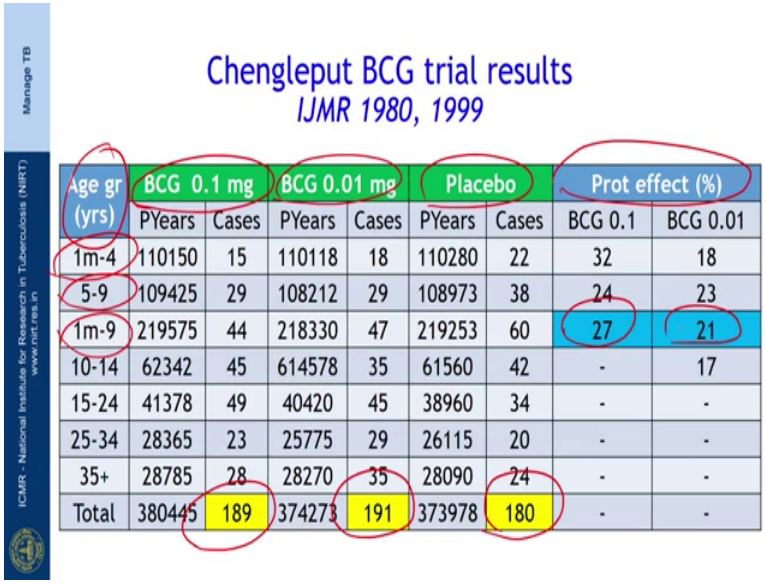

Chengleput BCG trial results
IJMR 1980, 1999

Age gr (yrs)	BCG 0.1 mg		BCG 0.01 mg		Placebo		Prot effect (%)	
	PYears	Cases	PYears	Cases	PYears	Cases	BCG 0.1	BCG 0.01
1m-4	110150	15	110118	18	110280	22	32	18
5-9	109425	29	108212	29	108973	38	24	23
1m-9	219575	44	218330	47	219253	60	27	21
10-14	62342	45	614578	35	61560	42	-	17
15-24	41378	49	40420	45	38960	34	-	-
25-34	28365	23	25775	29	26115	20	-	-
35+	28785	28	28270	35	28090	24	-	-
Total	380445	189	374273	191	373978	180	-	-

And this study this graph tells you the results of this study. This is the age group of the participants, this is the BCG high dose 0.1 milligrams, BCG low dose and Placebo and these columns tell you the protective effect of these vaccines. Overall it was found that among the patients among the people who received BCG high dose 189 persons developed TB. In the BCG low group 191 persons developed TB and among the placebo 180 person developed TB.

In other words there was no difference between people who received BCG and those who did not receive BCG. In fact, the people who have received BCG they have more BCG have cases both in the high group high dose group and in the low dose group. The protective effect therefore, was nil BCG did not protect against tuberculosis.

However, in children in the 1 to 4 age group and 5 to 9 age group and overall in children there was the modest protection of 27 percent in the high dose BCG and 21 percent in the low dose BCG. It must be said; however, that this study was designed only to detect pulmonary tuberculosis, it was not designed to pick up other forms of extra pulmonary tuberculosis.

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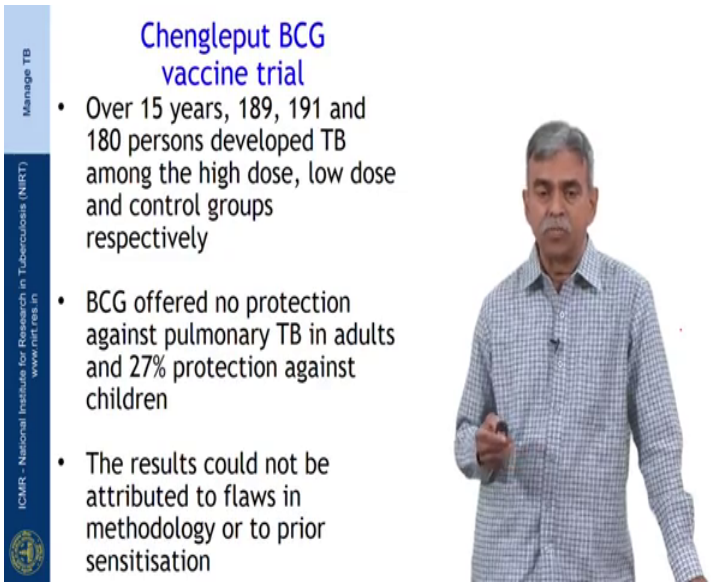

So, the Chengleput BCG vaccine trial showed that over a 15 year people here 189, 191 and 180 patients developed TB among the high dose, low dose and control groups respectively. BCG offered no protection against pulmonary TB in adults and a modest twenty 27 protection against children. The publication of this study elicited a global response and many studies were done to find out that why this vaccines failed in this large study.

So, many analysis were done and all these results showed that there is does that obtained in study was not due to flaws in the study methodology or to prior sensitization by non tuberculosis mycobacteria which is one of the reasons that has been advanced why this vaccine failed in Tamil Nadu.

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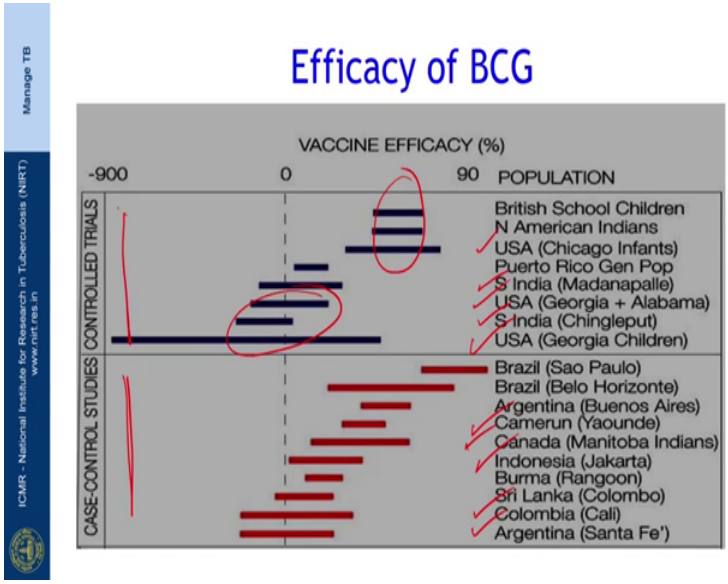

There also been many meta analysis and reviews of the efficacy and of BCG and this graph will tell you in control chemical trials and in case controlled studies the efficacy of BCG in control chemical trials the efficacy range about 80 percent to 0 percent.

British school children, North American Indians and infants in USA in Chicago had high protection more than 80 percent whereas, the South Indian Chengleput study also a study in Mandanapalle in South India and in children in the USA and Georgia showed no protection.

In contrast to controlled chemical trials case controlled studies have shown protection against discriminated forms of tuberculosis. So, large number of studies done in Brazil, in Argentina, in Camerun and Canada and Indonesia all these showed protection against disseminated tuberculosis, but in Argentina and Columbia there was no protection.

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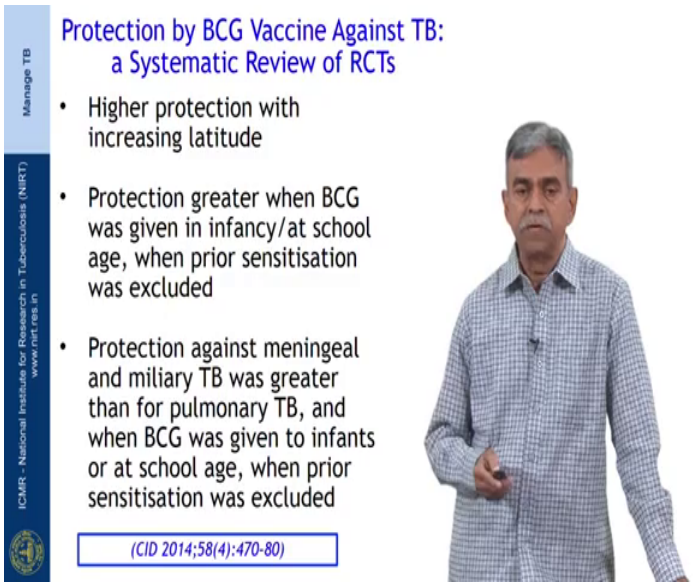

So, protection of BCG against TB there was systematic review which was very recently and this showed higher protection with increasing latitude protection was greater when BCG was given in a infancy at school age when prior sensitization was excluded and protection against meningeal and miliary TB was greater than for pulmonary TB and when BCG was given to infants of or at school age when prior sensitization was excluded.

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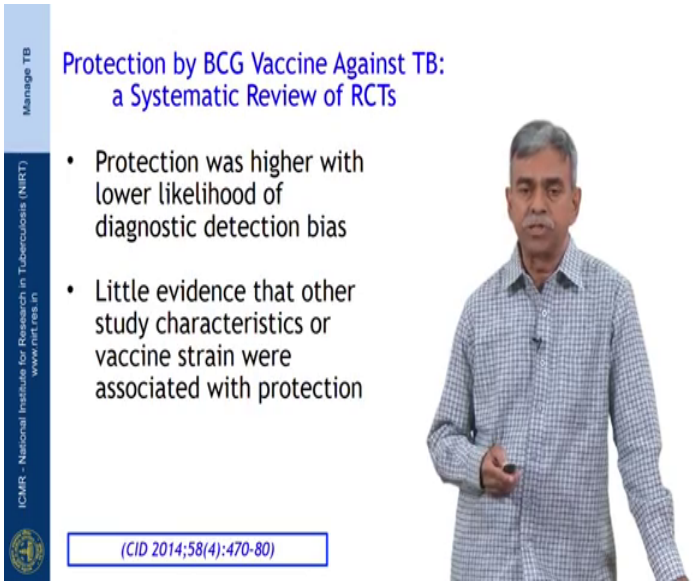

Protection was higher with lower likelihood of diagnostic detection bias. There was little evidence that the study characteristics or the vaccine strain was associated with protection.

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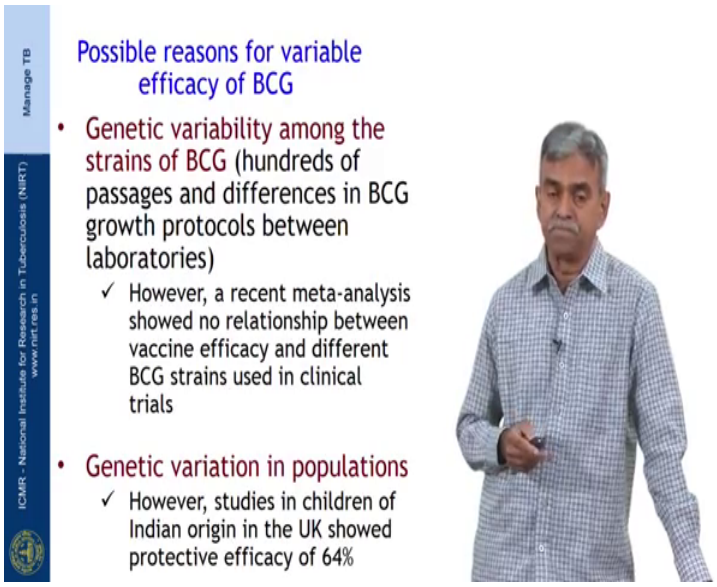

So, what are the possible reasons that the various efficacy of BCG? One could be the genetic variability among the strains of BCG. As you know BCG has been used now for almost a century. So, during this period there are number of vaccines stains in different parts of the world have been passage over many many cycles and it is likely that during this different passages likely mutations occur in the laboratories that is variation between strains between laboratories.

However, a recent meta analysis showed that that the relationship between vaccine efficacy and different BCG strains used in clinical trials there was no difference even in the Chengelput BCG vaccines trial they showed that there was a French strain and the Danish strain and there was no difference between in efficacy of these two strains.

And there could be genetic variations in the populations. This could be a reason why the BCG succeeded in certain populations and did not in others. Again however, it was shown that in studies in children of Indian origin in the UK had protection about 64 percent whereas in India the protection was much lower.

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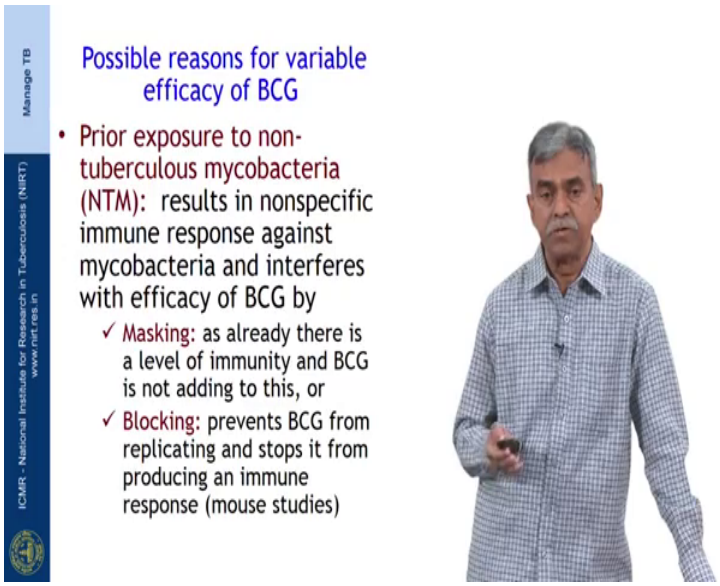

It is also possible that the prior exposure to non tuberculosis mycobacteria or NTM plays a role, this probably the most possible reason. Non tuberculosis mycobacteria in mycobacteria are ubiquitous in nature they are present in the soil they are present in water they are present everywhere and they induce a certain level of immune response in the population.

So, this nonspecific response to mycobacteria could affect BCG efficacy by either masking there is already there some amount of immunity the immunity produced by BCG in not adding to this or it could achieve the by blocking. It prevents BCG from replicating and stops it from producing an immune response. So, this is the reason that probably why BCG has failed in certain populations.

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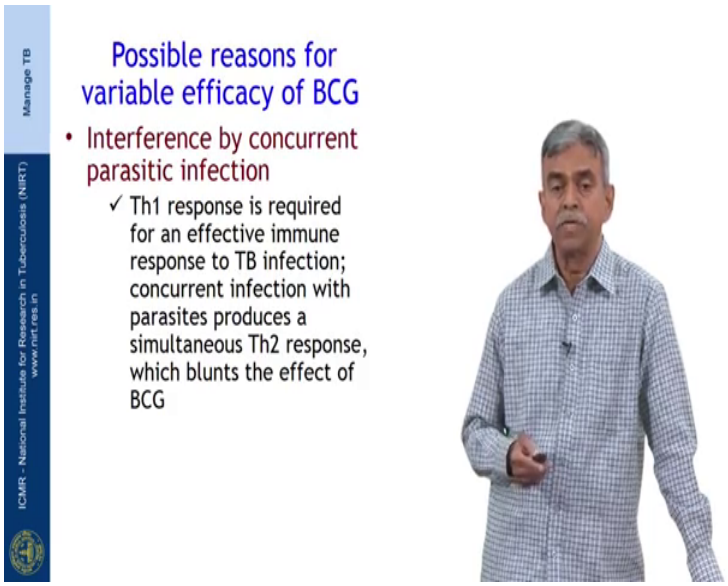

Another possible reason is interference with of by concurrent parasitic infections. In population were parasitic infection is common the response, the response is for effective immunity is due to the Th1 cells whereas, parasitic infection requires a response Th2 cells and this could interfere with efficacy of BCG vaccine.

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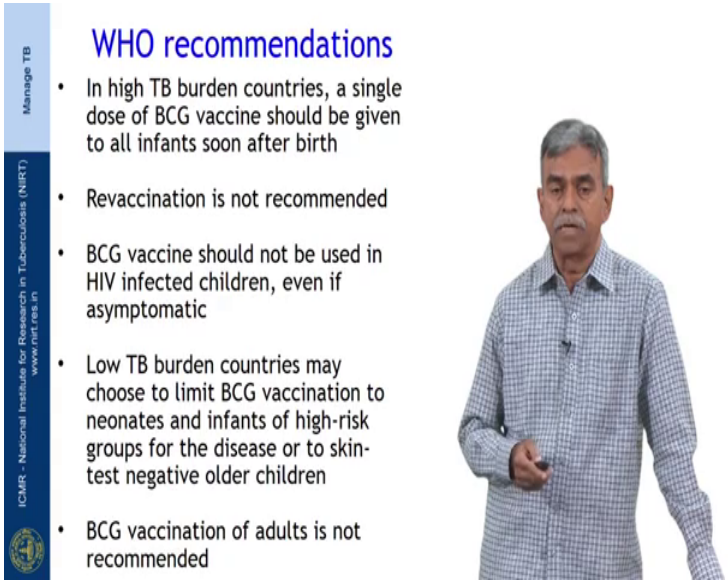

So, the WHO recommends that in high burden countries a single dose of BCG vaccination should be given to all infants soon after birth. Revaccination is not recommended. BCG vaccine should not be used in HIV infected children even if they are

asymptomatic and in low burden countries may they may choose to limit BCG vaccination to either neonates or infants of high risk groups or to children who test negative for tuberculin and BCG vaccination of adults is recommendable.

So, I am concluded session 1 and in session 2 will be talking about what are the newer vaccines that are available for tuberculosis.

Thank you.