


Manage TB
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Lecture - 61
Vaccine for TB Session 02

So, in this session on tuberculosis; Vaccine for Tuberculosis, we are going to look at what are the newer development as far as vaccines for TB is can is concerned.

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WHO Sustainable Development Goals
End TB Strategy

- Vision - a world of 'zero' deaths, disease and suffering due to TB
- 95% reduction in deaths, 90% reduction in incidence by 2035
compared to 2015

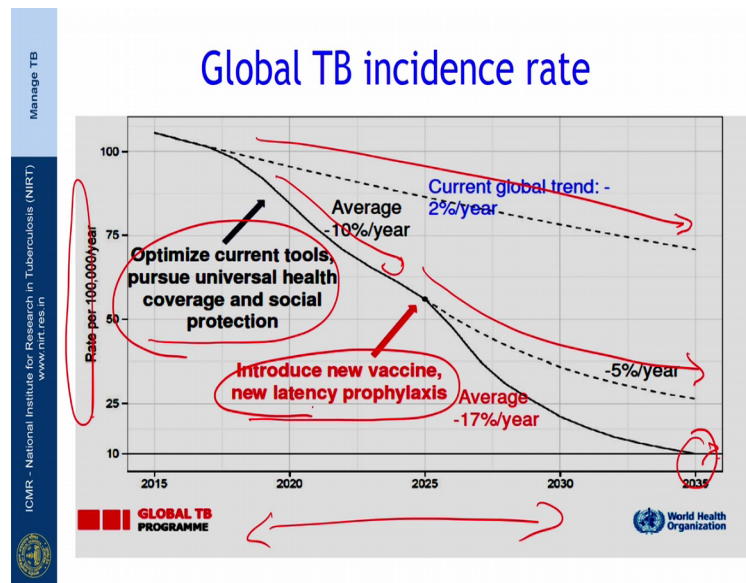
Indicators	Milestones		Targets	
	2020	2025	2030	2035
% reduction in no. of TB deaths	35	75	90	95
% reduction in TB incident rate	20	50	80	90

In the global efforts to control tuberculosis the WHO has enunciated certain strategies; we had the dot strategy in the 1990's followed by the stop TB strategy and currently we have the end TB strategy as part of the WHO sustainable development goals.

The end TB strategy envisages a world of 0 deaths disease and suffering due to TB and it aims at a 95 percent reduction in deaths, and 90 percent reduction in incidence of TB by the year 2035 compared to 2015. So, towards and then certain targets have been sent. So, if you want to achieve a percentage reduction in TB deaths of 95 percent by 2035 you need to reach targets of 35 75 and 90 over 2020, 2025, 2030.

Similarly, to reach a 90 percent reduction in TB deaths in TB incidence we need to have targets every 5 years. The Indian government has even a more ambitious strategy according the national strategic plan; we hope to achieve these targets by the year 2025 which is quite ambitious and therefore, special efforts are needed to achieve this target.

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So, this slide shows you the global TB incidence rates the x axis shows the rate of TB the 100000 population per year, the y axis is the time 2015 and 2035.

The current rate of decline of TB incidence is about 2 percent per year. Now this rate of decline is not enough for us to achieve a 90 percent reduction in TB incidence rates which is this line. At the most we will receive achieve about 25 percent reduction by the year 2035. Now by optimizing the current tools that we have that diagnosis, more efficient treatment by seeing the numeral health coverage and social protection we can increase this decline to 10 percent per year and even then by the year 2035 you are not going to achieve a 90 percent reduction you may reach about 75 percent reduction.

Now, if you want to achieve the 90 percent reduction in incidence rates by 2035 you need to need introduced new vaccines and you need to treat latent TB only if these are done there is any hope of achieving these targets that have been set by the set as the end TB strategy of the WHO. Now the aeras is a nonprofit organization the global TB vaccine initiative and this organization is helping to facilitate the development of new TB vaccines that are affordable and available to the poorest sections of society.

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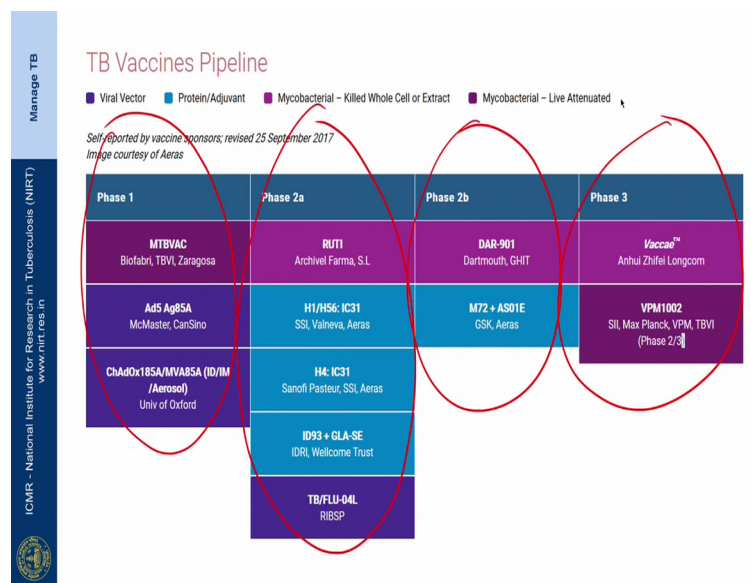
AERAS
GLOBAL TB VACCINE FOUNDATION

- A new model incorporating data from 183 countries shows that a 60% efficacious adolescent/ adult vaccine, delivered to 20% of target population, could avert 30-50 million new cases of TB by 2050
- A significantly improved infant vaccine could avert an additional 7-10 million new cases over the same period

Aeras says that a new model incorporating data from 183 countries shows that, a 60 percent efficacious adolescent or adult vaccine delivered to 20 percent of the target population could avert 30 to 50 million new TB cases by the year 2050.

And a significantly improved infant vaccine could avert an additional 7 to 10 million cases over the same period.

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So, this slide tells you the TB vaccine pipeline, the global TB vaccine pipeline we see that there are 3 vaccines in phase 1, 5 vaccines in phase 2 a, 2 vaccines in phase 2 b and

2 vaccines in phase 3. I will briefly go through the characteristics of these vaccines in my next few slides.

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Vaccine	Characteristics
MTBVAC	<ul style="list-style-type: none"> • Live attenuated Mtb strain with deleted phoP & fadD26 genes • Safety and biodistribution profiles similar to BCG; showed superior protection in preclinical studies. • Phase 2a studies expected in 2018
AdAg85A	<ul style="list-style-type: none"> • Recombinant adenovirus serotype 5 vaccine vector • Safe, immunogenic and enhanced protection against Mtb in murine, bovine and guinea pig models
Crucell Ad35/MVA85A	<ul style="list-style-type: none"> • Simian adenovirus-vectored vaccine expressing three Mtb antigens Ag85A, Ag85B and TB10.4 • Systemic and aerosol routes being explored

And in phase 1 we have 3 vaccines the MTBVAC these are live attenuated MTB strain with depleted phoP and fadD 26 genes, safety and by distribution profiles are similar to BCG and it shows superior protection in pinnacle studies; phase 2 a studies are expected in 2018.

The AdAg85A your recombinant adenovirus serotype 5 vaccine vector it is safe immunogenic and enhance protection against MTB in murine, bovine and guinea pig models. The Crucell AD85 the crucell 35 MVA 85 A is a simian adenovirus vectors vaccine expressing three MTB antigens antigen 85A, 85B and TB10.4 its being investigated in systemic and aerosol roots meaning that this is a vaccine that can be given by inhalation.

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Phase 2a trials...	
Vaccine	Characteristics
RUTI	<ul style="list-style-type: none">• Therapeutic vaccine• Non-live vaccine (fragmented, detoxified Mtb encapsulated in liposomes)• Following chemotherapy RUTI was effective in mice and guinea pigs• Well tolerated in Phase II studies. Phase III trial being planned in MDRTB patients
H1/H56+IC31	<ul style="list-style-type: none">• Protein subunit adjuvanted vaccine. Hybrid of ESAT6 & Ag85B with IC31• In Phase II studies in HIV positive adults it was safe and induced a specific and durable Th1 immune response
H4+IC31	<ul style="list-style-type: none">• BCG booster vaccine.• Protein subunit adjuvanted vaccine, contains Ag85B and TB10.4 in IC31

And the phase 2 a we have 5 vaccines the RUTI is a therapeutic vaccine it is a non live vaccine using fragmented detoxified MTB encapsulated in liposomes, following chemotherapy RUTI was effective in mice and guinea pigs its well tolerated in phase 2 studies, phase 3 trials are being planned in MDRTB patients the H 1 H 56, IC 31 and the HOIC 31 adjuvanted vaccines the H 1 H 56the protein subunit adjuvant or vaccine is a hybrid of ESAT 6 and antigen 85 B with adjuvant IC 31

In phase 2 studies in HIV positive adults it was safe and induced a specific and durable Th 1 immune response the H 4 IC 31 is a BCG booster vaccine and shows protection protein subunit adjuvanted vaccine contains AG 85 B and TB 10.4 in IC 31.

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Phase 2a trials	
Vaccine	Characteristics
ID93+GLA-SE	<ul style="list-style-type: none">4-antigen Mtb recombinant protein (Rv2608, Rv3619, Rv3620 and Rv1813) in a novel glucopyranosyl lipid adjuvant-stable emulsionPhase 2a study just completed for pulmonary TB in South AfricaPhase 2b being planned
TB/FLU-04L	<ul style="list-style-type: none">Mucosal prophylactic boost vaccineRecombinant influenza vaccine having influenza virus strain A/Puerto Rico/8/34 H1N1 and Mtb antigens Ag85A and ESAT6A Phase 2a trial is being done in latent TB

The ID 93 GLA-SE is a 4 antigen MTB recombinant protein containing Rv 2608, 3619, 3620 and 1813 in a novel glucopyranosyl lipid adjuvant stable emulsion.

Phase 2 a study just completed for pulmonary TB in South Africa and phase 2 b study is being planned the TB FLU-04 L is a mucosal prophylactic boost vaccine again can be given by a narration; it is the recombinant influenza vaccine having influenza virus strains H 1 N 1 and MTB antigen 85 A and ESAT 6 a phase 2 a trial is being done in latent TB.

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Phase 2b trials	
Vaccine	Characteristics
DAR 901	<ul style="list-style-type: none">Heat-inactivated Mobuense strain of MtbBooster vaccineBeing tested in BCG primed adolescents in Tanzania
M72+AS01	<ul style="list-style-type: none">Protein subunit containing Mtb antigens 32A & 39A in adjuvantClinically acceptable safety profile and highly immunogenic in Mtb-infected and uninfected adultsPhase 2b trials ongoing in TB+HIV infected adults

And the phase 2 b we have 2 vaccines the DAR 901, which is a heat inactivated mboense strain of MTB its again a booster vaccine is being tested in BCG primed adolescents in tanzania and the M 72 AS 01 vaccine which is a protein subunit containing MTB antigens 32 A and 39 A in adjuvant.

Clinically accepted safety profile has been shown and highly immunogenic in MTB infected uninfected adults phase 2 b trials are ongoing in HIV, TB infected adults.

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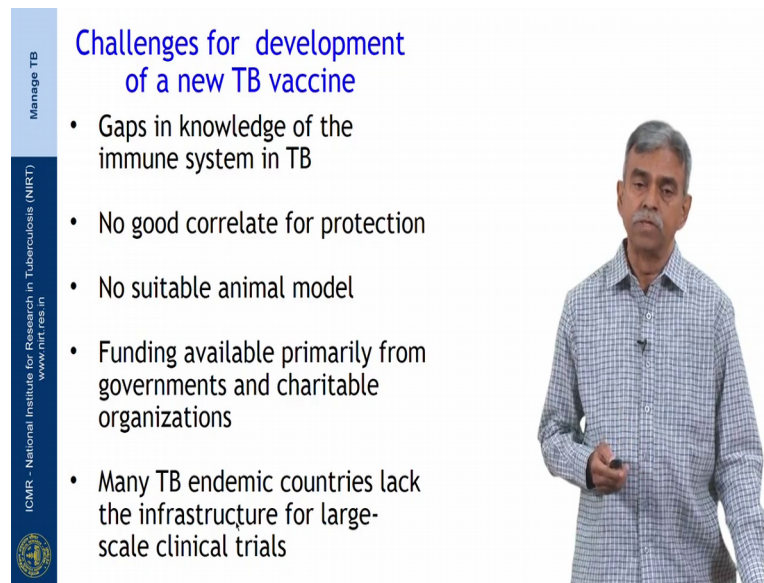
Phase 3 trial	
Vaccine	Characteristics
VPM 1002	<ul style="list-style-type: none"> • Live recombinant BCG strain carrying a gene of <i>Listeria monocytogenes</i> coding for the protein listeriolysin • In a Phase 2 study in comparison with BCG in newborn infants in South Africa it was safe and well tolerated • A phase 2/3 trial expected to start in India in 2018
M Vaccae	<ul style="list-style-type: none"> • Whole heat-killed bacteria. • Induced CD4⁺ T-cell-expressing IFN-γ and IL-10 responses in cultures from MV-treated mice • Safe and immunogenic in HIV positive adults • When added to chemotherapy of TB patients it showed improved sputum conversion and X-ray lesions • A phase III trial is ongoing in China in 10,000 participants

And in phase 3 which is the most advanced stages of clinical trials we have 2 vaccines the VPM 1002; it is a live recombinant BCG strain carrying a gene for listeria monocytogenes, coding for the protein the serialization.

In phase 2 studies in comparison BCG in newborn infants in South Africa it was shown to be safe and well tolerated and a phase 2 3 trial is expected to start in India in 2018 and M Vaccae is a whole heat-kill bacteria vaccine induces CD 4 T-cell expressing interferon gamma and iolite responses in cultures from MV treated mice is safe an immunogenic in HIV positive adults when added to chemotherapy of TB patients it should improve sputum conversion and X-ray lesions.

So, it is a therapeutic vaccine and a phase 2 trial is ongoing in China with more than 10000 participants.

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Challenges for development of a new TB vaccine

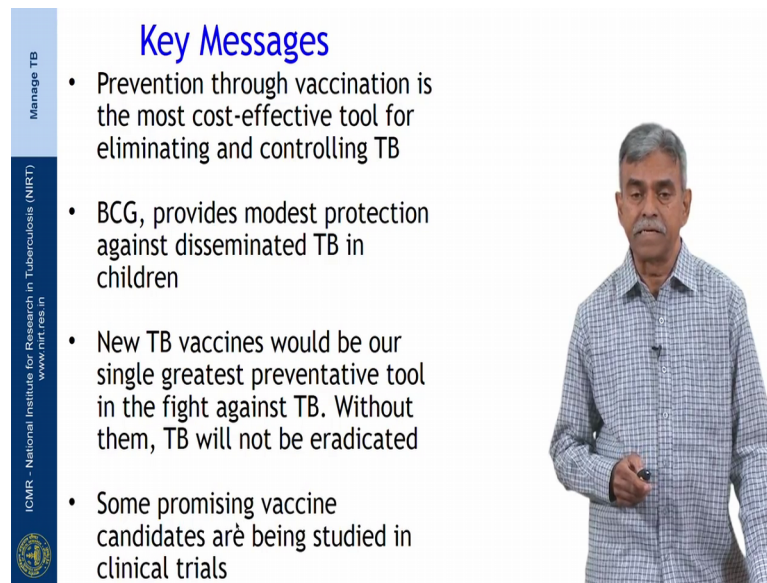
- Gaps in knowledge of the immune system in TB
- No good correlate for protection
- No suitable animal model
- Funding available primarily from governments and charitable organizations
- Many TB endemic countries lack the infrastructure for large-scale clinical trials



So, what are the challenges for developing of new TB vaccine? There are gaps in our knowledge from the immune response system in TB there is no good correlate for protection, we do not know what really constitutes protection and tuberculosis, there is no suitable animal model, funding is difficult only governments and charitable organizations are willing to fund for TB vaccines because there is no market for a TB drug or vaccine.

Industry is reluctant to fund TB vaccines and many TB endemic countries like the infrastructure to carry out large clinical trials that are necessary to or test out TB vaccines.

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Key Messages

- Prevention through vaccination is the most cost-effective tool for eliminating and controlling TB
- BCG, provides modest protection against disseminated TB in children
- New TB vaccines would be our single greatest preventative tool in the fight against TB. Without them, TB will not be eradicated
- Some promising vaccine candidates are being studied in clinical trials

So, the key messages in my lecture today that the prevention through vaccination is a most cost effective tool for eliminating and controlling tuberculosis. BCG provides only modest protection against disseminated TB in children. New TB vaccines would be our single greatest preventative tool in the fight against tuberculosis; without them there is no hope that TB will be eradicated. And some promising vaccine candidates are being studied in clinical trials.

Thank you.