New Tuberculosis Vaccines:
WHO IVR activities

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June 2019
Estimated 10 million new cases and 1.6 million deaths. Over 90% in LMICs

Approximately 1/3 world infected with *Mycobacterium tuberculosis*

First cause of mortality in HIV

First cause of mortality due to AMR pathogens

estimated third of all deaths due to AMR pathogens

558 000 cases of DR-TB, of which 82% had MDR-TB and 6% XDR-T

End TB Strategy assumes new tools including vaccines will be available.

2035, reducing 90% of TB cases (from 2015)
WHO IVR recent activities

New TB Vaccines PPC published (prevention of TB in adults, in children)

New PPC being finalized: TB vaccine for improvement of TB disease treatment outcomes

Follow-up on new TB vaccine promising results: M72/AS01E

Upcoming: participation to a Technical R&D Roadmap

Full Public Value Proposition evaluation
New TB vaccine PPC

Two strategic priorities
New TB Vaccines for Use in Adolescents and Adults: Preferred Characteristics

**INDICATION**
- Immunization for prevention of active pulmonary TB

**TARGET POPULATION**
- Adolescents and adults. Proof of concept should prompt pediatric studies.

**OUTCOME MEASURE AND EFFICACY**
- 50% or greater efficacy in preventing confirmed pulmonary TB
- Protect both subjects with and without latent *Mtb* infection
- Protective in different geographical regions and latitudes
New TB Vaccines for Use in Adolescents and Adults: Preferred Characteristics

SAFETY

• Safety and reactogenicity profile should be favourable, similar to other current WHO-recommended routine vaccines for use in adolescents and adults

• Mitigations to be considered given severity and major public health concern associated to TB

• Safety should be favourable in particular risk groups (especially individuals living with HIV/AIDS)
New TB Vaccines for Use in Neonates and Infants: Preferred Characteristics

INDICATION

• Prevention of TB, including severe, disseminated, meningitis and pulmonary TB, in infants and young children

OUTCOME MEASURE AND EFFICACY

• Superior efficacy as compared to BCG alone

SAFETY

• Improved safety as compared to current BCG
• Demonstrated safety in HIV infected babies
DURATION OF PROTECTION

- Demonstrated efficacy over 2 years min to support initial policy decision
- Ten or more years of protection should be conferred after primary immunization
- Long-term follow-up studies will inform the duration of protection (post licensure)

SCHEDULE

- A minimal number of doses and boosters required, no more than three doses for primary immunization. Long term follow-up studies, should determine the requirement for booster dose(s) – not more frequently than every 5-10 years

IMMUNOGENICITY

- Detailed characterization of immune responses
- Evaluation of association with protection; identification of a correlates of protection
- The conservation of biological specimen for future use upon advances in technology and knowledge is encouraged
New TB Vaccines:
Preferred Characteristics

PROGRAMMATIC SUITABILITY

• Innovation related to ease of administration and thermostability

VALUE PROPOSITION

• Evaluation of the vaccine impact on the TB epidemics in general, and on drug-resistant TB specifically, on co-morbidities (HIV), on health systems and the economy, is encouraged (role of modelling)

• The vaccine should be cost-effective and price should not be a barrier to access
Endpoints in TB Vaccine Trials:

Prevention of Mtb Infection (PoI - PPD skin test or IGRA conversion)

Demonstrating biological effect with smaller sample size, cost, short duration

Clinical significance? Prevention of disease not demonstrated

Risk of false negative result: a vaccine may be found not to prevent ‘immune take’ while successfully preventing progression to disease
Vaccines for improvement of TB treatment outcome

• Aim to reduce treatment failure (increase cure rates), reduce frequency of relapse, simplify and shorten treatment regimen

• Specific interest in drug-R TB

• M72 results arguing in favour of feasibility

• Opportunity to also reduce progression to TB in recently exposed contacts, in TB infection test converters

• WHO PPC document under finalization
Vaccines for improvement of TB treatment outcome: PPC

Recommended treatment as standards of care for initial proof of concept evaluation

Diagnosis and treatment initiation

- Sputum Screen, Mtb characterization if positive

**Intensive phase** | **Continuation phase** | **Follow up**

Possible vaccination timepoint for cure and PoR endpoints

Possible vaccination timepoint for PoR endpoint

- Proportion of cure

End of drug treatment

Sputum Screen, Mtb characterization if positive

End of follow-up

- Proportion of subjects free of recurrence after 12 months or more

Efficacy endpoints
Phase 2b Efficacy study of GSK’s Candidate TB Vaccine M72/AS01E in Adults with Latent TB Infection

Vaccine 2-dose IM $M72/AS01_E$ (fusion protein Mtb32A, Mtb39A)
Sponsor GSK (Aeras)
Population 3,500 IGRA+ adults
Endpoint Incident, confirmed pulmonary TB
Site/s South Africa, Kenya, Zambia

Favorable safety (some local and general reactogenicity)
VE over 2.3 years: 54% (90%CI 14-75%)
No indication of waning of protection (figure)
Data on additional 1 year FU awaited

Impact modelling estimates awaited
M72/AS01: WHO strategic vision

Progress the M72/AS01 candidate’s evaluation with a sense of urgency

April 5th WHO consultation:

- GSK is seeking a partner/s to take license of M72 from GSK to develop, license, manufacture, be liable for, and supply M72 for the developing world (GSK will maintain proprietary control for the non-developing world)
- Limited number of doses currently available. Process improvement needed for Phase 3 material
- No established consensus on pathway forward and investments
- Willingness from many stakeholders to contribute. Need to ensure country perspectives are taken into account, countries contribute to the research agenda and resources
- Major risk of undue delays. Need for coordination and advocacy.
Preferred scenario, for discussion

Assuming 3rd year data confirm the results of 2 years follow-up:

• progression to Phase 3 trial in a population of teenagers/young adults in settings with high incidence

• accelerated licensure with narrow indication (prevention of pulmonary TB in young adults in high endemic settings)

• parallel proof-of-concept evaluation for other indications (HIV+, pediatric, contacts, PoR) and schedule optimization

• post-licensure investigations, country-led
Next steps for WHO

• Consultation on **clinical development pathway** to lay the way forward for future studies, in the context of potential use cases, trial designs, timeline, risks and opportunities

• Co-convene with Wellcome Trust a Funders’ meeting to explore joint financing and innovative financial products to support development with and end to end perspective

• Development of a full **public health value assessment** for new TB vaccines

• Develop a **TB Vaccines R&D Technology Roadmap**

All activities to be conducted in close coordination with existing platforms (Global TB Vaccine Partnership)
Questions to PDVAC

Does PDVAC agree that the current level of evidence emerging from the Phase 2b M723/AS01E trial in Southern Africa justifies for WHO IVR to promote progression to Phase 3, based on the existing candidate product and schedule, with the intention to license the candidate vaccine for prevention of pulmonary tuberculosis in young adults in settings of high exposure?

Does PDVAC agree that finding the fastest feasible route to first licensure with subsequent expansion of indication constitutes an advisable product development strategy?