***Outline for China Paper***

***Mathematical modelling of future trends in TB epidemiology in China and the potential impact of TB vaccines in this population***

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***Timeline:*** See excel file

***Word count:*** 3000-4000 words

***Abstract (250 words)***

***Introduction (400-600words)***

* TB epidemiology in China (china biggest contributor to global burden, age distribution of cases).
* Ageing population and uncertainty around impact this will have on future TB epidemic. Although India projected to overtake China in terms of overall population in 2028, China will remain the greatest contributor to the global elderly population, with a projected 90.4million persons aged 80 or above in 2050 (UNDP 2012 revision). China’s median age is expected to rise from 35.4 years in 2013 to 46.3 years in 2050, with life expectancy at birth rising from 75.2 to 79.9 years in the equivalent period. (UNDP 2012 revision) Understanding the impact of ageing population on TB burden and transmission is an important unknown. Modelling is essential in planning implementation of control measures, so a model based on realistic predictions of future demographics and epidemiology will be highly valuable for effective decision making in TB control.
* Vaccine importance in future of global TB control (comparative intervention models) and size of China in the vaccine market - existing models taken a global view or considered SEAsia as a whole, and none have considered the impact of vaccination of the elderly – given the ageing population in China, need to consider the impact the demographic shift will have on the future TB burden, and also assess impact of different vaccine profiles for vaccination of ado/adults vs elderly on the burden in the elderly and the population as a whole.
* Importance of this research now to inform appropriate and efficient design of TB vaccine clinical development plans both by Chinese vaccine developers and international developers aiming to tackle to significant burden of disease in China.
* Aim: Understand the relative contribution of the elderly population to TB transmission in China, and estimate the impact of a new TB vaccines targeted at the elderly or at adolescents/adults in China, considering several scenarios of vaccination coverage and vaccine characteristics such as vaccine mode of action, efficacy and duration of protection.
* Objectives:

1. Create baseline model scenarios estimating relative potential contribution of the elderly to the on-going transmission of TB in China
2. Explore potential impact of novel TB vaccines delivered to elderly or adults, considering both pre- and post-exposure vaccines and varying efficacy, coverage and duration of protection.

***Materials and Methods (650-800 words)***

* *Data sources*: See excel sheet
* *Model:* Gwen’s model (deterministic, compartmental, age structured, difference equation, transmission model), with following adaptations:
  + TB control: one set of scenarios or a range of scenarios?
  + Vaccine strata: include TPP scenarios of different vaccine efficacies(40, 60, 80%), duration of protection (20yrs with waning for elderly, TBC for ado/adult), and mechanisms of action (pre vs post exposure).

**Materials and Methods**

**Data**

Demographic data, including age-stratified population estimates for 2010 and 2050, were taken from the UN population division 2012 revision (ref). TB incidence stratified by age was estimated by applying the WHO-reported China case notification rate to the age-wise notifications of all TB (smear positive, smear negative, and extra-pulmonary TB) in China.

Mortality by age was taken from WHO or estimated using WHO methods, as were treatment success levels ([22](#_ENREF_22)).

Prevalence of latent infection by age was taken from xxx.

**Model and analysis**

We used an age structured transmission model to estimate the TB burden in a base case and a range of alternative vaccination scenarios (Fig. xx, xxx in Appendix). The model was programmed in R ([35](#_ENREF_35)). This model was calibrated to the TB incidence in 2010 and population size in 2010 and 2050 in China via Sobol sequence sampling and Approximate Bayesian Computation. Natural history parameters were varied by age, with a set of parameters specific for each of children (0-14 years), adolescents and adults (15-64 years) and the elderly (65 years and above) (Table XXX). Interactions between different age strata were based on data on social mixing patterns in Southern China (Read et al 2014). Generating 1,000 calibrations allowed for the inclusion of the uncertainty in both natural history parameters and tuberculosis and demographic data. Estimates of projected TB burden between 2010 and 2050 were calculated assuming BCG coverage at current levels and under optimistic assumptions of improved TB control in China in order to be conservative about vaccine impact and to reflect ambitious WHO targets for improved TB control ([21](#_ENREF_21)) (Fig. xxx, Fig. xx in Appendix). The impact of introducing several potential TB vaccine profiles to different target populations was then considered in terms of cases and deaths averted. Vaccine introduction was implemented in 2025, and vaccine profiles differed by mechanism of action, duration of protection, and vaccine efficacy. We investigated twelve vaccine profiles with two mechanisms of action with protection if given pre-exposure or post-exposure, vaccine efficacies of 40%, 60% or 80% and duration of protection of 10 years or 20 years. Waning of protection also varied depending upon the target population, no waning in adolescent/adult populations, and waning by 50% after 10 years when delivered to adults aged 55-64years. The pre-exposure vaccine was assumed to prevent development of active disease only when delivered to never-infected individuals ([24](#_ENREF_24)), whereas the post-exposure vaccine is assumed to prevent development of active disease when given to populations never-infected, latently infected, or recovered from active disease. Vaccination was modelled as ‘take’ and duration of protection was exact. The two target populations were ‘adolescent/adults’ and ‘elderly’. The former involved vaccination of 10 year olds in schools with two doses six months apart and additional mass campaigns in two rounds to all aged eleven or older in 2025 and at a frequency corresponding to duration of protection. ‘Elderly’ vaccination involved steady-state continuous vaccination of adults aged 55 years old from 2025, plus a 3-year catch up campaign of 56-65 year olds during 2025-2027. Instant scale-up of vaccination was assumed, for coverage of 10%, 30%, 50% and 70% of the target population. It was assumed that catch-up campaign would achieve the same percentages of coverage, but evenly distributed over the 3 year campaign (e.g. 30% coverage assumes 10% per year for 3 years).

For each country, vaccine coverage was assumed similar to reported vaccine coverage ([39](#_ENREF_39)) or school attendance levels ([40](#_ENREF_40)).

**Uncertainty analysis**

Uncertainty in our estimates was generated by sampling from natural history parameter values for each fit from a gamma distribution generated from the 95% uncertainty range.

***Results (800-1100 words)***

*Baseline scenario*

* Number of TB cases (cumulative 2025-2050), 2050 incidence rate, % change 2025-2050
* Number of TB deaths (cumulative 2025-2050), 2050 incidence rate, % change 2025-2050
* Proportion of transmission due to the elderly
* Reactivation vs new disease, by age group

*Epidemiological Impact of TB vaccine for the elderly*

* For whole population: Number of TB cases and deaths (cumulative 2025-2050, 2050 incidence and mortality rate, % change in each: by vaccine mechanism (pre vs post), vaccine characteristics (VE, duration of protection), and vaccine coverage
* In the elderly: Number of TB cases and deaths (cumulative 2025-2050, 2050 incidence and mortality rate, % change in each: by vaccine mechanism (pre vs post), vaccine characteristics (VE, duration of protection), and vaccine coverage
* Expected results: Population ageing in China may lead to increased importance of the elderly in the TB epidemic. If so, TB vaccine targeting in the elderly may be an effective strategy to tackle TB given the anticipated future TB trends in China.

*Epidemiological Impact of TB vaccine for adolescents/adults*

* Number of TB cases and deaths (cumulative 2025-2050), 2050 incidence and mortality rate, % change in each: by vaccine mechanism (pre vs post), vaccine characteristics (VE, duration of protection), and vaccine coverage

***Discussion*** ***(900-1250 words)***

* Primary findings
* Epidemiological impact of population ageing on anticipated future trends, the contribution of the elderly to disease burden, and the contribution of new disease vs reactivation in the elderly
* Comparison of maximum possible impact (and smallest NNV) scenario for elderly and ado/adult – which would have greatest impact by 2050?
* Discussion of impact of the various TPPs explored in both age groups.
* Is there a profile that is high impact in both age groups?
* Comparison to what currently in pipeline
* Discuss applicability/generalisability to other countries
* Discuss how the outcome can fulfil blueprint critical activities and inform more efficient and appropriate vaccine clinical development and implementation.
* Limitations will include:
  + Heterogeneity of TB burden within China
  + Uncertainty caused by projecting demographics and TB control measures in to the future.
  + Comparisons in elderly vs adult are magnitude not exact numbers.
  + Vaccination strategy and coverage. Impact of time horizon.
  + Application of case notification rate for the country to age-wise incidence estimates – likely greater underestimation in children due to diagnostic difficulties
* Significance of research concluding statement

***Appendix***

* China and natural history parameters specifically by age, include discussion of immunesenescence in elderly and how think affects natural history
* Vaccine characteristics by pre- or post-exposure vaccine and with waning in elderly – including discussion of immune differences.
* Methods in full
* Model equations in full
* Calibration method

***Figures and Tables***

Figure 1 - Model structure

Figure 2 – Baseline calibration to incidence, mortality, demographics and prevalence of latency (2010-2050)

Figure 3 – Composite figure - impact of vaccine scenarios (VE, duration of protection, mechanism of action)

Table 1 – by vaccine scenario – TB incidence 2050, mortality 2050, TB incidence trend, TB mortality trend, cases averted up to 2050, deaths averted up to 2050, % reduction in incidence and mortality vs baseline, NNV per case averted, NNV per death averted.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Mode of Action** | **VE** | **Duration (years)** | **Waning efficacy (%, years after vaccination)** | **Age Vaccinated** | **Coverage (%)** | **TB incidence rate in 2050 (per 100,000pop/y)** | **TB mortality rate in 2050 (per 100,000pop/y)** | **% reduction in number of cases due to vaccination\*** | **% reduction in number of cases due to vaccination\*** | **NNV per case** | **NNV per death** |
| No vaccine | n/a | n/a | n/a | n/a | n/a |  |  | n/a |  |  |  |
| Pre-exposure | 40 | 10 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | 50%, 10y | Elderly | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 60 | 10 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | 50%, 10y | Elderly | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 80 | 10 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
|  | 20 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | 50%, 10y | Elderly | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| Post-exposure | 40 | 10 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | 50%, 10y | Elderly | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 60 | 10 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | 50%, 10y | Elderly | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 80 | 10 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | No | Ado/ Adult | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |
| 20 | 50%, 10y | Elderly | 10 |  |  |  |  |  |  |
| 30 |  |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
| 70 |  |  |  |  |  |  |

\*Reduction in absolute number comparing 2050 with vaccination to without vaccination