English Summary

Tuberculosis is a major public health problem, with particularly high morbidity and mortality among infants. The only licensed TB vaccine, BCG confers only partial protection against pulmonary disease, the most common and most transmissible form of the disease. Novel TB vaccines with better efficacy are urgently needed as part of the armoury of tools to eliminate TB by 2050. To properly design and implement these trials, several factors need to be borne in mind. These include, the most suited trial population, estimates of disease incidence, cohort retention and mortality. There are also diagnostic considerations, such as the utility of the chest radiograph and the possible role of the more prevalent non-tuberculous mycobacteria in confounding TB diagnosis. Finally, there are practical factors related to selection and development of research sites with the required trial infrastructure and expertise in high burden countries. This thesis explored the factors of design of new tuberculosis vaccine trials, diagnostic considerations and process of site development.

In **Chapter 1** the status of TB control and the need for new tools including a novel TB vaccine is examined. I explored the strengths and limitations of BCG vaccination, and reviewed the arguments around infant versus adult vaccination. In **Chapter 2**, we found a high culture confirmed TB incidence among infants (0.2/100 pyo) in Western Kenya showing recent on-going transmission. Definite TB was associated with infant HIV infection, higher Keith Edward Scores. Modeling study data of incidence and retention, we presented sample size estimates for future vaccine trials. In addition, cohort retention was positively associated with infant HIV infection and complete vaccination status at the four-month follow up visit. Thus, cohort characterization is useful in guiding future trial design and sample size estimates.

We examined post-neonatal mortality, its predictors, immediate and underlying causes of death in infants in **Chapter 3.** Post-neonatal mortality was high in 2009 to 2011 (58/1000 pyo) but lower than preceding years. Infant HIV status and being born in a health facility were positive (HR 10.3; 95% CI: 6.40, 16.7) and negative predictors (Hazard Ratio (HR) 0.54; 95% CI: 0.34, 0.84) respectively, of mortality at 12 months. Mothers delivering in a health facility may have different health consciousness, behaviour and access to health facilities that lead to longer term mortality benefits. Pneumonia and dehydration were the most frequently identified immediate causes of death. Since the study was conducted, pneumococcal and rotavirus vaccines were added to the national immunization schedule, therefore a decline in mortality is likely to be sustained. These gains are also positive for end-point detection in vaccine trials. In **Chapter 4** we examined the utility and inter-rater agreement of chest radiographs, a key diagnostic of composite TB endpoints in infant trials. Agreement on abnormalities consistent with TB was slight at best (k=0.14; (95%CI: 0.10 - 0.18) but was significantly better than agreement on any abnormality or normal radiographs. Hence the chest radiograph still has some utility as a diagnostic tool for vaccine trial endpoints despite its noted limitations. In **Chapter 5**, the clinical relevance, incidence and types of Non-Tuberculous Mycobacteria were described. NTM incidence was 5.7/1,000 person-years; 95% CI (3.5, 8.7). We found no association between TST positivity and NTM isolation OR 1.15 (0.41, 3.25). Isolation in all cases represented colonisation and not disease, based on the American Thoracic Society Criteria. Infants diagnosed with TB were more likely to have NTM isolation (odds ratio 11.5; 95% CI 3.25, 41.0). Therefore, NTMs are unlikely to

confound TB diagnosis in future trials. In **Chapter 6** the process of TB vaccine trial site set-up from 2007, infrastructure development and growth in expertise to conduct TB vaccine trials is described. Site development was gradual and incremental. Challenges encountered in each study were solved and turned into learning points, improving the implementation of future vaccine studies. Key lessons in site development include, the importance of conducting thorough epidemiological studies to provide context for clinical trials, including investigators in discussions of assays to be run on bio-banked samples. In context of the momentous breakthrough of an Ebola vaccine, I compare the TB vaccine development pipeline and suggest a shift to greater industry and government involvement, as well as greater global coordination of efforts by the WHO, will accelerate the development and approval of a novel TB vaccine. In **Chapter 7,** I reviewed trial and post-trial considerations in selecting the most appropriate target population for future TB vaccine trials. Trial related factors included the incidence of disease and the impact on trial sample sizes, complexity of vaccine design for a particular high risk group. Post-trial factors included the availability of vaccination platforms, the quantity and speed of impact on the TB epidemic, among others. I also reviewed the TB vaccine candidates targeting infants in phase I and II trials.

CONCLUSIONS

The high incidence of TB among infants makes them a suitable trial population. On the other hand, they hardly transmit disease and therefore vaccinating them will have a much slower impact on the TB epidemic, adults could be a more urgent priority. Nevertheless, developing vaccination platforms to reach adults will be costly and logistically challenging.

The chest radiograph is still an important diagnostic tool in infant TB vaccine trials. NTMs among presumptive TB patients are either colonizing organisms or super-imposed on pulmonary TB. The development of TB vaccine trial sites requires multi-national collaborations similar to what was observed during the Ebola outbreak of 2014-2016.

Recommendations

1. Selection of high risk populations will improve the speed and feasibility of TB vaccine trials. This may require inclusion of ignored sub-groups such as prisoners who suffer disproportionately high TB burden compared to the rest of the population.
2. Greater involvement of governments in both high and low burden countries will expedite the possibility of a new, more highly efficacious TB vaccine in our lifetimes.
3. Limited autopsies in infant trials may enhance our understanding of the disease process and increase trial end-point yield.