AERAS

Enriching Cohorts for Smaller, Quicker, More Efficient TB Vaccine Studies

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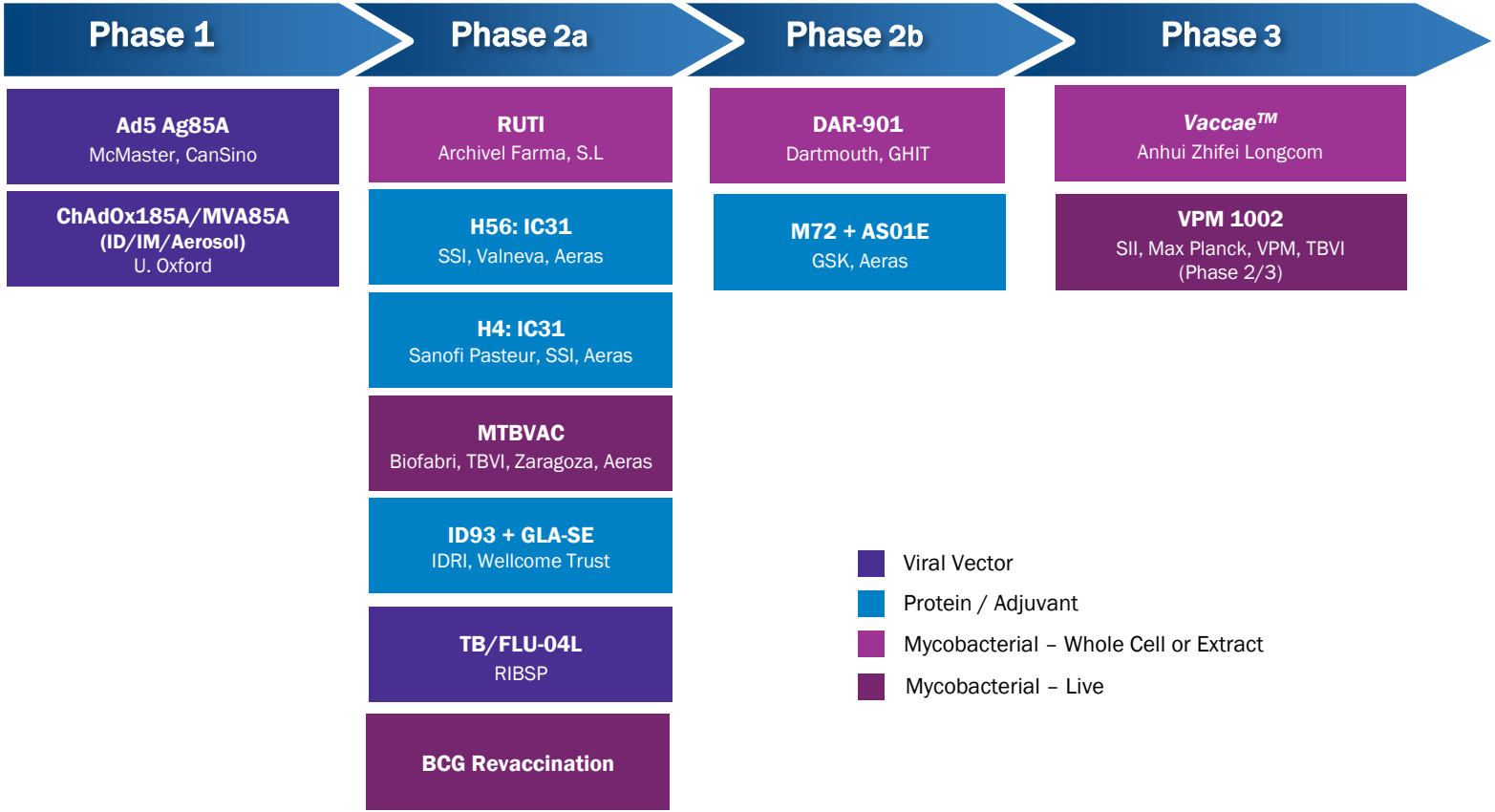
Introduction

- Optimal efficacy endpoint for TB vaccine studies is prevention of TB disease (POD)
  - POD efficacy studies require 1000s of participants and lengthy follow up to accrue disease endpoints
- No correlates of risk currently that can be used for selecting trial participants
- TB vaccines enter advanced clinical trials with safety and immunogenicity data but limited data supporting efficacy

Global Clinical Pipeline



Information on candidates in clinical development is self-reported by vaccine sponsors, coordinated by the Working Group on New TB Vaccines and updated September 2017

Target Populations

- Infants (healthy)
- Adolescents/Adults (healthy)
- TB patients

Premise

- Identify populations at higher risk of TB infection and/or disease than the general population
- These enriched populations will allow for smaller, quicker and more efficient studies
- Triaging tool for up/down candidate selection prior to conduct of large Phase 3 registration studies
  - Resource sparing

Identification of High Risk Groups – with focus on POD

- Populations identified by literature reviews and personal communications with key experts
- Using published data from these populations, evaluated their suitability for efficacy trials
- Prime considerations included:
  - Ease of recruitment
  - Potential for reduced sample sizes and/or quicker studies
  - Feasibility of study design/conduct

Potential High Risk Populations

Population	Estimated Increased Relative Risk TB Disease
Miners	~4-fold
HIV Infected Individuals	7 - 26-fold (much lower in ART era)
Diabetics	3-fold

Potential High Risk Populations

Population	Estimated Increased Relative Risk
Prisoners	3 - 151 for TB disease 5 – 84 for TB infection
LTBI+ with SOR for progression to disease	~7-fold in 18 months prior to TB disease
Prevention of Recurrence	2-8% per annum in the two years following treatment

Potential High Risk Populations

Population	Estimated Increased Relative Risk
House-hold contacts (HHCs)	2 - 50 for TB disease 2 - 83 for TB infection
Health-care workers (HCWs)	2 - 18 for TB disease 8 - 21 for TB infection

TB Disease in Health Care Workers (HCWs)

- Risk of increased transmission and disease in HCWs has been recognized for many years worldwide
- In low- and middle income countries annual incidence of TB disease in HCWs 0.5% to 14%[1]
- TB disease incidence higher than in the general population
  - incidence rate ratio (IRR) 1.4 to 20.0 (2 of 20 studies IRR of 0.7)[2]
  - Median estimated IRRs for high TB incidence countries 5.4[3]
- Clearly defined categories of HCWs have higher risk[2]
- Strong association between implementation of TB infection control programmes and reduced nosocomial transmission[1]

[1]McCarthy *et al*, 2015; [2]Joshi *et al,* 2006; [3]Baussano *et al,* 2011

Prevention of TB Disease in Health Care Workers

Variable	Naidoo *et al*[ref]	Phase 2b POD Trial in QFT+ Adults
TB disease incidence	1.1%/annum	0.55%/annum
Sample Size*	1754	3506
Duration	4 years	4 years

*Sample size - vaccine efficacy (70%), power (80%), type 1 error (10% 2-sided) will require 21 endpoints. Assume LTFU (15% over 2 years), length of follow-up (3 years).

Prevention of TB Disease in Household Contacts

- Previously been used to evaluate efficacy of BCG[1]
- Variable definition
  - individuals living in same household as adult/adolescent index case at least 3 months (for 7 days) prior to TB diagnosis; sharing meals; identifying common household head
- Establishing cohorts may be time-consuming and expensive *compared to* cohorts from general population

[1]Rosenthal *et al*, 1961

Prevention of TB Disease in HHCs - Considerations for Study Design

- Co-prevalent disease rates (definitions variable) are high
  - 1.4%[1]; 9.2%[2]; 4.2%[3] of recruited cohort have co-prevalent disease
  - 56%[1] and 67%[3] of TB cases co-prevalent
- Depending on setting, prevalence and incidence of HIV may be a significant issue
  - 17.9% prevalence and incidence 2.2/100py[1]
  - TB disease incidence by HIV status at baseline – HIV+ 5.4/100py; HIV- 0.7/100py[1]
  - 52% of incident cases HIV positive[2]

[1]Hill *et* al, 2008; [2]Van Schalkwyk *et al*, 2014; [3]Guwatudde *et al*, 2003

Conclusions

- Trials already being conducted in higher risk populations
  - An ongoing Phase 2b POD trial (TB-018; M72) utilizes a population at higher risk of disease than general population (IGRA+)
  - Prevention of recurrence trial (VPM1002) initiated in India

- Other populations at very high risk of infection and/or disease have been identified and should be considered for TB vaccine clinical trials

Thank You