

2nd Meeting of Stop TB Partnership Working Group on New Vaccines:
Task Force on Economics and Target Product Profiles

Meeting Report

October 5-6, 2009

Fondation Merieux, Center de Conférences "Les Pensières", Veyrier du Lac, France

1. TB Epidemiology, vaccine effectiveness, and cost-effectiveness

- HIV control is necessary to control TB in many high burden countries. Increased TB incidence in high HIV(+) areas is due to activation of latent TB as CD4 count falls as well as increased susceptibility to infection, but there is less transmission from HIV(+)'s to HIV(-) because rapid disease progression and earlier death means infective period is reduced from 2 years to 2 months (Corbett 2003).
- Latent TB infection (LTBI) is a major problem that must be treated along with active disease to reach elimination goal of 1 new case per million people by 2050; putting all HIV(+)'s on ARV treatment much earlier will effectively reduce HIV transmission by 95% by 2015 and eliminate HIV infection by 2050. This is expected to halve the incidence of HIV-related TB by 2015 and eliminate HIV-related TB by 2050 (Granich et al, *Lancet*, 2009, 373:48-57).
- Better health systems and reducing risk factors for TB (alcohol, smoking, GDP, BMI) is very important in the long term. While DOTS has averted millions of TB deaths in the world it may not be sufficient to reduce the burden of TB.
- Discussion on trends on HIV—Zimbabwe's prevalence of HIV and TB incidence is decreasing sharply, but not the case in Botswana and Malawi; could be related to higher level of education and understanding of public health. Wars, mobility (SA gold miners), rates of selling sex all impact HIV and therefore TB rates.
- Presentation on cost-effectiveness modeling and related issues in various papers (Rook et al 2009, Cohen et al 2008, Bhunu et al 2009 Abu-Raddad et al 2009), and recent analysis by Tseng *et al* looking at a replacement BCG vaccine with 70% efficacy with and without a boost at individual level. Found immediate cost savings with new BCG; vaccines targeting late/slow progression show cost savings later. Questions include: what costs are already sunk? Which are expected to be recouped through sales?
- Discussion on cost-savings from an individual vs. community standpoint (immediate savings or longer term). Also discussed what kind of vaccine is most needed: protection against infection vs. reactivation disease—BCG can provide some protection against early childhood infection and disease, but it is most important to prevent disease from reactivation of LTBI, which will also stop transmission. It seems clear that one size fits all will not work.
- ACTION: Consider including FIND in future TF discussions

2. Development and Regulatory Lessons from new Meningitis A conjugate vaccine

- MVP used a *push vaccine funding* development model; critical to start with what is affordable—negotiate vaccine manufacturing cost, purchasing price and use public funds upfront. Must be affordable in countries for sustainability: don't trust donors; men A target \$0.40/dose. Also emphasized local capacity building, using low income country contract research organizations.
- Lessons Learned: - use tough critics to make sure science is right, - "Don't let the perfect be the enemy of good," - go for "public health good," – need committed partners with face-to-face contact. Schmooze a lot to maintain good contacts, and expect the unexpected (DCGI decertification).
 - WHO pre-qualification necessary; critical to work with both WHO HQ and regional offices; SAGE recommended men A 1 year ago. EPI and GAVI support essential—introduction strategy = unambiguous, feasible, and familiar. Children are the customers.
 - Double estimated resources needed for regulatory.
 - Contract out dossier review to experts so repeating safety studies is unneeded.
 - Close local government involvement in Africa/India also extremely important.
- Discussion for TB: important to link TB vaccine to EPI. Recommend: School-based immunization programs as one of most effective, cheap ways to reach children beyond infancy
- One of the reasons for Universal Childhood Immunization's failures was that sustainability depends on local resources and must be defined as such. Different development techniques are needed according to local resources.
- Differences between Pneumo, TB, and Men A—Pneumo has large industrial market, and Men A had technology, processes and district micro-planning of health system infrastructure (from Measles control) already established. For TB, these are unknown.
- Timeframe for Men A development to introduction is 2001-2011, even *with* established epi, sites, processes, known correlates, no large-scale efficacy studies. TB time frame will be much longer.

3. Product development update - MVA85A

- Review of prime-boost strategy and candidates currently in clinical trials:
 - Aeras: 2 viral vectors- Adeno35 (phase II) and modified vaccinia with 85A (phase IIb); 2 recombinant proteins with adjuvants- GSK, Sanofi/SSI
 - Non-Aeras candidates: VPM-1002, SSI Hybrid I, RUTI (immunotherapy), *M. smegmatis*

- Presentation on MVA85A by Oxford-Emergent TB Consortium (OETC). Developed world partner is Emergent; developing world and clinical development partner is Aeras and its field site partners.
 - Phase IIb POC trial in infants currently enrolling in South Africa; HIV+s Phase IIb trial pending. Examining 2 new cell lines (immortalized duck retinal cell line and duck stem cell line) for manufacturing product for Phase III trials and market.
 - Future: Phase III studies and EMEA licensure. When is best time to go to FDA?
 - Phase III challenges: No correlates, clinical endpoints unclear (how will regulators react to ‘probable’ cases, not-culture confirmed), logistical issues, adolescent and HIV indication extensions
 - Discussion on correlates: in HIV(+)-s- CD4 count seen as good predictor of TB but not known if also true in HIV(-). MVA85A gives reasonable immunological response in HIV(+) but better in HIV(-). IFN- γ shown not to be an accurate correlate in other studies. Role of TH17 cells has not been investigated much to date
 - MVA gives less good response for primary immunization, but Oxford studies have shown a strong enhancing immune response regardless of timing post primary BCG immunization (1 month to 20 years). Studies have shown MVA vectors can be used more than once after 1-12 month interval. Role that environmental mycobacteria play in priming discussed; however they are not common in Cape Town.

4. Target Product Profiles (TPP) & Critical Path Analysis (CPA) Progress

- CPA identifies a timeline for critical and necessary steps and interlinks them through timeline to identify potential bottlenecks; helps streamline priorities for Gates Foundation (BMGF).
- For licensure, desirable to show better safety and efficacy than BCG but post-marketing or Phase IV studies needed to show rBCG safety in HIV(+) neonates important
 - Discussion about timeline if booster gets to market before rBCG—would need another Phase III showing rBCG efficacy/safety with booster. At what point do we need to start thinking about compatibility with EPI?
- TPP working definition: Succinct summary of developmental product’s most important characteristics with focus on those that can be clearly defined and are critical to success
 - Important to gather feedback on TPPs to ensure products fulfill end-user’s needs
 - For BMFG—need TPP’s to enhance oversight and portfolio management; also can help to bridge market and clinical research, get demand forecasting, etc.
- Discussion on reimbursement mechanisms- not clear if rBCG will need AMC if the price is close to current BCG, but a booster may cost much more (Men. A only \$0.40/dose which may contribute to why it wasn’t on the shortlist for AMC). TPP should be considered “agnostic to funding.”

- Discussion on TPP's in-scope: desire a new rBCG with improved duration and efficacy, likely given at <1 year-old. Boosters: every country now has BCGs in infants on board, so boosting can be anytime after BCG given at birth). Latency vaccine: antigens directed against immune responses thought to be related to controlling latent infection; trying both to prevent disease at 15+ years and also reactivation of LTBI.
 - How much of TB disease is reactivation? Suggested that half of TB disease in HIV(+) is reactivation, but very hard to differentiate new infection and reactivation of disease. Also latency vaccine may differ for BCG vaccinated and immunodeficiency.
 - Better diagnostics needed to identify latency for important future steps (i.e.: catch up immunization plan)

5. Market Research proposal

- Market research RFP sent out by Aeras, to be conducted by Baird's CMC—want to learn optimal market entry criteria based on product profile, price, and procurement strategy, also coverage forecasts, and perhaps availability of donor funds. Approach is to do 10 interviews (variety of people) in 6 countries.
- Discussion of country selection:
 - Examples under consideration: China, India, Vietnam, Kenya, South Africa, Brazil
 - Eastern Europe/Russia with high MDR and XDR incidence rates;
 - May want some countries with less global health interest such as the Gambia, Kenya. These are “more typical African” and are not conflict ridden but perhaps typically have lack of understanding re: health.
 - Peru? Used in a lot of recent studies, has widespread DOTS implementation with large MDR problem (may be due to good DOTS with retreatment strategy?). Political will present and many NGO's and academics involved in Peru today
 - Vietnam is probably most sophisticated country in SE Asia, perhaps Cambodia, Thailand would be better
- Discussion on Criteria for country selection:
 - Relative position of influence in network (i.e.: South Africa looked to as a leader); Prevalence of HIV and/or HIV-TB co-infection; MDR prevalence; Who manufactures and pays for BCG; Anticipation of future burden (say, 5 years); strength of EPI coverage and TB treatment and cure rates; diversity of economy/public-private markets
 - Is local manufacturing important (scenario of importing rBCG vs. local BCG)?

General Discussion from Day 1

- TPPs: should there be different TPP's for boost and latency vaccines? What about target populations? How does this affect indications in TPP's?
 - MVA may work as booster in those primed in other ways (environmental, exposure). Phase IIb proof of concept trial will tell more about efficacy; currently testing infants, which is easier because all infections are new.
 - Adolescents and young adults are where bulk of disease burden exists and should get vaccinated, with or without infection, so will need adolescent data for safety (with infection) and efficacy.
 - What changes will be made to TPP for different cohorts? I.e.: Adolescents with or without latent infection. Emergent does separate TPPs for separate indications, but could also do 1 TPP with multiple indications
 - For market research interviews, present different scenarios based on adolescent infection status and corresponding vaccine safety – TPPs and scenarios to test must be decided
- Men. A performed non-interference study for post EPI schedule (18-22 weeks). Non-interference study being done with MVA85A for TPP as well.

6. Communications and Advocacy

- A lot has been done to improve advocacy for TB: - document language (Berlin Decl, WHO, MDG), - new initiatives, - economic impact analysis in articles.
- But how to move decision-makers and increase support? - think/talk in billions, - sense of urgency, MDR, XDR, - simple messages that relate to own country's citizens, - media (no sensation)

- Discussion on other ideas: - ACTION to bridge all working groups to improve advocacy and communication, - need to find innovative, new models for investment and will get returns and profits, - profits reinvested in social change to convince people, - “TB anywhere is TB everywhere” to motivate by self-interest and fear, - speak more about tangible cost savings for other health interventions
 - Would be more cost effective for developed countries to redirect money from increased spending on TB control by screening immigrants to reducing TB incidence abroad
 - Leverage interest in TB-HIV co-infection. But would HIV stigma reflect negatively on TB? Change focus based on area, be aware of what you advocate where.
- TB advocacy for vaccines should be in addition to drugs and diagnostics (Abu-Raddad). Proposal to put into perspective the cost of TB to the world economy (300 billion U\$/year = 0,52 % of world GNI Ref. Economic Benefits of Tuberculosis Control (WHO June 2009, *Laxminarayan et al, idem World Bank august 2007*)).
- Use investments needed over **ten years** in vaccines, therapeutics and diagnostics, estimated at 20 billion U\$, small compared with the gains (0,5% of world wide GNI). Vaccines offer an excellent opportunity: relatively small investment needed (less than 4 billion over ten years to potentially deliver three types of vaccines: boost to BCG, replacement BCG and latency control, or 8 or more vaccines to be delivered). The TB vaccine community should elaborate further these financial arguments, in close collaboration with FIND and TB Alliance. Really 20 billion investment over 10 years is small cost compared to the human and economic gains.
- Could we leverage interest in H1N1? Both are respiratory and H1N1 shows how the fight against a sanitary threat can be organized world wide. Probably some lessons to be learned for TB.

7. Landscape revisited: Gaps and Plans Forward

- Mathematical models show that combinations of new drugs/diagnostics/vaccines most effective. But limited by data quality, realistic vs. optimistic, difficult to spread models over regions and not just country-based. ACTION- integrate economic CE data with phase III trials. Next meeting: invite industry experts on CE studies for vaccines, and also include CE studies with Phase III trials in future and in Critical Path.
- Prices and paying: 1. Pull mechanism (AMC), 2. Push mech (Mening A), 3. “pay for what you get” based on cost-benefit and ROI. Shouldn’t talk about pricing prematurely, must explore affordability, especially with constraints in next 5yrs (financial crisis)
- TPP revising: add flexibility for feedback and for interaction in package of products; TPP doesn’t give a big picture of implementation
- Advocacy—need to think about how to use the evidence we have and get people to listen, need different channels

8. Closing Comments and Next Meeting Agenda

- Refine TPP's
- CE Work: - match with TPP's, - some interest in bringing in FIND and Alan Brooks from MVI to discuss decision making framework, - what countries will be interested in CE and TPP?
- Further exploration of regulatory pathways and policy issues with Uli Fruth/WHO
- Market Research discussion to continue as research progresses
- Report to Core Group of Stop TB Working Group on New Vaccines
- Next meeting time and place to be decided later with Uli Fruth—Oxford as location?