TB Vaccine Scoping Study: Evidence and Methodology

Potential discussion points by topic area

This section contains many issues not all of which can be tackled. One purpose of discussion will be to put these issues in some priority ordering for future work.

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November 2008

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1. Epidemiology, socioeconomic impact of TB and cost-effectiveness of new TB vaccines

Surveillance: Sound cost-effectiveness analysis goes hand in hand with sound epidemiological analysis. However, tuberculosis surveillance is complicated by poor-quality data and potential bias in incidence estimates. Much of the data has not been gathered in controlled experiments and it is difficult to do inference from it. What are the advantages and disadvantages of various approaches to measuring tuberculosis incidence, prevalence and mortality? To what degree does the Working Group take such surveillance problems as given and work analysis according to these constraints? To what degree does the Working Group engage in discussions about the surveillance systems and the data generated from such systems with an eye to improving data available to its tasks? Who has ownership of data, and how can 'ownership' issues be prevented from slowing down the provision of evidence for vaccine cost effectiveness studies and launch strategies?

Cost effectiveness methodologies – quantity and distribution: There have been few cost effectiveness analyses of control strategies for TB, let alone of TB vaccines. One recent study, covering the years 1982-2002, counted a total 66 studies (including studies that covered more than one topic of evaluation). Of these only 28% were in developing countries. Very few related to vaccination strategies. Is there some sense in updating that study, given the surge in number of studies in the later period and therefore probable increase in quantity and coverage of such studies in the last 6 or so years?

Generating a range of cost effectiveness studies in developing countries is expensive and time-to-build is long. Should the Working Group take the level and range of cost effectiveness studies as given or should it instigate ways to expand the level and range of such studies? Evidence from other vaccine launches suggests that it is especially useful to design such studies around vaccine trial sites on the basis of a targeted early launch strategy that creates momentum for success. If so, what is the current distribution of such studies and what would be the priorities for the future distribution if such studies are to be used as part of an evidence base for vaccine launch? What would be priorities at different horizons? What is the optimal combination of cost effectiveness studies by region or country?

Common protocols: From past experience, it is also critically important to develop common protocols so that studies are comparable. Often studies are found at a later date to be non-comparable or not as comparable as they could have been with a bit more prior thought and coordination, and this weakens the ability to use such analysis for advocacy and to influence the policy decision process. Similarly, most studies use indicators of effectiveness specific to tuberculosis control, rather than generic measures, making it difficult to compare with the cost effectiveness of interventions for other diseases, with this further limiting the ability to use such evidence in the policy-making process. Should the Working Group be more involved in standardizing the protocols of such studies so at to make results more comparable (for example regarding hospitalization costs,

productivity impacts, treatment of exchange rates, appropriate sensitivity analysis, end points, etc.)?

Sensitivity analysis: How useful is the multivariate cost effectiveness sensitivity analysis of authors such as Zif et al?

Integrated strategies for prevention and control: TB vaccines are more cost effective when combined with other control strategies (see Figure 1.11 of Part 1 of the scoping study). What is the existing evidence for this? How can DOTS expansion complement the launch of a new vaccine or vaccines and vice versa? What are the implications at different horizons for infrastructure and costs?

In many of the analyses, the public markets for vaccines in poor countries are valued relative to costs (and efficacy) of non-vaccine options, and this is usually presumed to be the current state of play vis a vis DOTS. There *is* a presumption underlying some investment case figures (those of BVGH/BCGH) that there will be no new drugs between now and 2030. How should analysis be adapted to take account of new drugs being developed?

Health systems: There is wide variation in the selection and implementation of control strategies within and among countries; in particular DOTS programmes have mostly recruited patients who would have been detected and treated anyway in the public health systems, and DOTS has failed in some countries to reach deeply into the private sector, and in others to provide access to patients living in areas with inadequate health services. If vaccines are to optimally 'integrate', what are the implications for modeling vaccination strategies and cost effectiveness of new TB vaccines – especially boost and prime boost – of the health systems issues?

Multi-drug resistance: How important is multi-drug resistance as a driving force for uptake of vaccines? How is multi-drug resistance captured in models involving combinations of prevention and treatment measures?

HIV: HIV co-infection will reduce vaccine effectiveness in the very populations most at risk of TB. Does the Working Group need to know more about the long-term role of the HIV epidemic (for example impact on cost effectiveness in developing countries, on vaccine effectiveness, control programs, case detection), or does it take the work of others as given? What are the implications for product profiles and market sizing?

Pre- and postexposure vaccine strategies: What is the current consensus regarding pre- and postexposure vaccines? How important in determining product profile, market, etc., is the mechanism by which a preexposure vaccine works? There is a debate about the best strategy to improve immunisation against TB (pre- or postexposure, combination of vaccines and boost strategies). This shows up a little bit in the investment case literature. Are there nuances that that literature misses and ways that that literature could be improved by a more sophisticated approach to choice between strategies?

Duration of protection of new vaccines: How significant is the finding that duration of immunity has a much greater impact on cost effectiveness if it is greater than ten years, given that the product profiles often mentioned in willingness to pay questionnaires specify ten years? What are the implications for cost-effectiveness analysis of ten versus twenty versus life-long protection (mainly in terms of delivery costs and long-term consequences for the epidemiology of TB)?

Transmission dynamics: Ideally estimates of averted DALYs should incorporate any transmission effects of the disease, to support any predictions of how disease incidence may change in the future and therefore provide a more substantiated claim on the effectiveness of a new intervention. What is the state of such analysis in the case of TB?

Cohort studies: What is the situation regarding cohort studies for informing disease burden and existing vaccination and treatment coverage and impact?

Latency: What are the full complications and implications of the latent nature of TB for vaccine markets? The latent nature of TB means that it will take a long time to achieve a low rate of infection. Latent stage TB infection (LTBI) can be detected via a tuberculosis skin test (TST), and thence treated to decrease the chance of progression to active TB. However, the interpretation of TST can be complicated if a person has had a vaccine. How does this affect the decision of countries to use vaccines as part of a control strategy and hence cost effectiveness analysis of such strategies? For example, in countries where exposure to active TB is rare, treating latent TB is more likely to be the strategy of choice. How might this incentive change over time for countries that start off using vaccines?

Socio-cultural limitations: There are many socio-cultural factors associated with TB, which can have severe implications for accessibility and acceptability of treatment and prevention strategies. To what degree does the Working Group regard these as an area the Group should investigate, or should this be left to others? Such factors have a direct implication for the validity of any assumptions about coverage made in a standard cost-effectiveness analysis. Other costs include early exit from school by children on account of their parents' TB, the impact of social stigma, etc.

Other effects of a vaccine: When assessing a new vaccine candidate, how important is the interrelation with BCG and both direct and indirect effects of the new vaccine candidate? How significant are non-specific survival benefits from vaccination?

Active pulmonary TB: Active pulmonary TB is the leading cause of death in HIV/AIDS patients in the developing world and has spiraled in the last decade or so. What is the state of play of modeling and evidence on this? There was no inclusion of any modeling relating to this in the investment case analyses.

Horizon: Achieving a global incidence of active TB of less than 1 case per million population per year by 2050 will not be achieved (see Figure 1.5. of Part 1 of the scoping study); prevention and control will have to work for horizons of many decades. What are realistic success metrics for vaccines over such horizons presuming a vaccine is launched,

and presuming that vaccines are combined with other interventions? How do such horizons impact investment decisions / product profile decisions / the nature of follow-on generations of vaccines / sponsor funding, etc.?

Epidemiologically-driven targets: TB targets, as encapsulated in the MDGs, are not driven by an epidemiological framework. What would epidemiologically-driven TB targets look like, and what are the implications for vaccines? How can the Working Group influence an improved epidemiological basis for such targets?

2. Basic market and revenue frameworks

Current market and investment case analyses: How satisfactory are the global market and investment case analyses so far created? What is the balance between the need to generate absolute market numbers (the focus of current market and investment case analysis) and the need to improve the functioning of the market for vaccines and launch strategies?

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Public and private sectors: How is the division between public and private sectors best modelled? The treatments of this in the various market/investment cases so far have been relatively rudimentary. Should this division be based on country-level data pertaining to other vaccines or past vaccine launches? Does it depend on price? Is it useful having more granular details about this, or will the effort just complicate the process of deriving a market figure while adding little value? Conversely, is knowing the division useful for knowing how to adapt launch strategies?

High-income high-risk groups: We find repeatedly that the role of the high-income country and high-income high-risk groups still needs clarifying. Potentially, such markets could be important for tiered pricing strategies.

Middle-income and private sectors: What is the role of middle-income countries and the private sector in general?

Global MDR-TB and XDR-TB: Analysis of the impact of global MDR-TB and XDR-TB seems rudimentary in analysis of markets for vaccines. We know from data on the costs of treating MDR-TB and XDR-TB that such costs are high, and that in theory governments and individuals should therefore be prepared to pay to avoid MDR-TB and, even more so, XDR-TB. One of the market analyses (Applied Strategies) relies heavily on global XDR-TB to generate large revenue figures and NPVs from booster vaccine take-up (three times the NPV without global XDR-TB), but it is not clear how global XDR-TB fed through to dictate prices and country decision-making processes.

What is the scientific basis of any probability of MDR-TB/XDR-TB, and how should it be used in market analysis? Given such heavy weight placed on global XDR-TB to drive

large NPVs in some of the analysis, there seems little epidemiological and cost-effectiveness modelling of the impact of it.

Global XDR-TB does not have much impact on NPV of replacement vaccines, though it does for booster vaccines. Why?

Cases of large NPV: In some of the boost vaccine and global XDR-TB scenarios, NPVs are very large. Is this realistic? What happens if there are other interventions (drugs and diagnostics) 'competing' at the same time? If the NPVs are truly that large, why does private investment not flood in and drive NPVs down? If the problem is scientific uncertainty, and if the NPVs truly are that large, if a vaccine candidate gets through to stage III, should we not expect private investors to take it all the way to licensure? Is something missing in this reasoning?

Efficacy and duration of protection of BCG vaccine: Given that efficacy levels presumed in the various investment case materials are defined *relative to BCG vaccine* (and phrased that way in 'willingness to pay' questionnaires) how do we view these in the light of there being no consensus regarding the effectiveness or duration of protection of BCG vaccine, and the natural bias and the role of other factors in assessing those vaccinated and non-vaccinated individuals?

Strategic thinking: Because of the 'obsession' with numbers, much of the market analysis is remarkably devoid of strategic thinking. For example, over simple issues like: the levers that can be used to improve adoption of new technology; the relationship between efficacy and ease of uptake; catch-up strategies. Would it be too difficult to have investment reports adopting a more strategic approach?

3. Rate of adoption and mechanisms of uptake

Current analysis: Are the assumptions regarding rate of adoption accurate in any of the analyses? How might a methodology/system be created to gather and process the requisite information to improve the accuracy of this information?

Hep B as a template: Is Hepatitis B a good template for modelling rate of TB vaccine adoption, in particular of booster and prime-boost vaccines?

Replacement vaccine: What are the strengths and limitations in presuming that replacement vaccine will replace current BCG vaccine?

Efficacy and adoption curve: What specific role does efficacy play in dictating the shape of the adoption curve? In some of the analysis there is no connection between efficacy and rate of adoption.

China and India: What are sensible assumptions to make about speed of vaccine uptake in China and India, and at horizons of ten or twenty years? In none of the models is this particularly well defined, yet we know that the emerging and middle income markets in such countries will be important in ten to twenty years time, particularly with respect to global tiered pricing strategies. What are the sources of information? What are the policy processes?

Catch-up strategies: What are likely catch-up strategies, particularly of booster vaccines? The treatment of catch-up is treated inconsistently across the investment case literature, and at best there is (apparently) a limited catch-up phase modeled in many of these analyses. How will catch-up strategies likely vary across countries? How can this be worked into the policy-making literature? Catch-up is a way of generating lots of early sales and hence high NPV for every sale made. Price is also usually modelled as higher earlier, before competitive events lock in. Therefore catch-up strategies are likely to heavily impact the value of R&D investments.

EPI improvement initiatives: Can many recent ongoing initiatives to improve EPI performance (BMGF, WHO, PATH all have recent initiatives to improve EPI performance) be integrated into thinking about TB vaccine launch strategies, especially of booster vaccines?

Efficacies in product profiles: The product efficacies in the investment cases so far are fairly unsophisticated and it is not clear how they are derived as 'targets'. This is happily admitted in a literature that regards this as still to be formulated. What is the mechanism for integrating discussion about such efficacies into analysis of all other parts of the analysis (such as rate of uptake, pricing, and indeed R&D costs if higher R&D expenditure leads to higher expected efficacy)? How sensitive are all the demand figures to percent efficacy (including, for example, willingness to expand delivery mechanisms, especially amongst adult populations, and to change organizational practice)? There is no proper 'sensitivity' analysis done of this in any of the investment analyses.

Durability, price and demand: What is the impact of durability of response on price and demand? Again, none of the investment analysis has much to say about this. How do we capture the impact of the durability of response which is not captured in the efficacy measure? What is the evidence for the impact of rBCG vs prime-booster from a durability point of view?

Delivery systems and organizational change: What is the evidence of willingness to expand delivery mechanisms (especially amongst adult populations) and to change organizational practice (e.g. to provide vaccine to LTC and the homeless in the US, etc.) as a function of efficacy?

4. Pricing structures, tiered pricing, and willingness to pay

Current studies: What does the Working Group feel about the pricing structures used in the various TB market analyses?

Market research: What is the role of market research in setting prices? Most consultancy-based pricing seems presumed. Are there useful market research lessons from other products (both vaccine and non-vaccine)? What mechanisms should be put in place to derive pricing information in future, and updating it, and at what horizons (for example, the further from product launch, the more unreliable one would imagine the information would be)?

Private market pricing: In some of the investment analyses, private sector pricing is a small multiple of an already low price. Given the importance put on the private sector market, how should the division between public and private sector, including this division according to country, be accessed? How can the division be made more accurate? At the moment the treatment of this is very rudimentary in analysis.

Global XDR-TB: In seems that Global XDR-TB drives the biggest differences in levels of tiered pricing – but on what basis?

Low-income market prices: What are sensible low-income market prices? What about prices for China and India over likely horizons? Farlow figures show the power of poorer and middle income markets, even at lowish prices, to boost NPV if uptake is quicker. Mainly the issue is sheer quantity of sales and whether COGS can be low enough. Even just a $1-$2 mark-up has big impact if the number of doses is large and sold early enough (given the discounting of the value of sales). A $7 per-dose sale in 5 years is worth about $3 now at 15% real rate of discounting.

Challenges to tiered pricing: Clearly tiered pricing will not work with all vaccines, and it will be more difficult if the product used in rich markets deviates from that used in poor markets or if there is simply no demand in higher-income markets. What is the situation with TB vaccines? Compared to other vaccine cases, it seems that TB vaccines will more likely be universally applicable. The issue turns on efficacy considerations and ability to integrate with other control strategies in richer countries and not (as the case with pneumococcal) on issues such as the appropriate serotypes covered. On the surface it looks as if this is a case where one could emphasize a strategy of tiered pricing (and communicating this well in advance), and put huge emphasis on achieving 'affordable' production costs. Is this so?

If it is not the same product in all markets, what effort could be made to ensure that in advance the product is much more similar across markets, to avoid the problems seen in the case of pneumococcal, and such that tiered pricing can be used?

Rich-world vaccines: Rich-market sales are potentially (since it is not clear yet) key to positive NPV and to tiered pricing strategies. However, it is not clear how new TB

vaccines potentially fit into current prevention and treatment strategies according to efficacy in such high-income (and in the case of countries like the US, high-risk) settings. How are high-income countries to be treated in market analysis? How do we find out exactly what policy makers in those countries are likely to do according to product profile? How should the problem they face be better modelled?

Under what circumstance would the US and many EU countries that do not currently use BCG vaccine start to use new vaccines?

Production capacity and tiered pricing: What is the role of production cost decisions in achieving tiered pricing, including technology used in the US, such as the Aeras production facilities, and national manufacture in some of the most affected countries? Do other vaccine stories suggest lessons applicable to TB (Hep B, Meningitis, pneumococcal, HPV, etc.)?

Questionnaires: What sort of questions should questionnaires about pricing contain? Who should such questionnaires be directed to? What is the best timing for using such questionnaires? How should efficacy be communicated in such questionnaires?

Competition: What is the impact on 'willingness to pay' if there are competing (non-TB) vaccines and other control interventions?

5. Policy process methodology to improve accuracy of pricing and demand figure and speed of vaccine uptake

Booster v. replacement: Are booster vaccines more problematic for policymakers to deal with than replacement vaccines? If so, what are the likely specific challenges? The various investment case analyses count booster vaccine 'in' or 'out' but once 'in' do not treat them as particularly problematic.

Empirical evidence about decision making: What is the current level of use of models and empirical evidence of decision-making processes in informing market-building and procurement strategies? The Boston Consulting Group's and Applied Strategies' models do not have a clear underlying analytical structure for this component. Is it worthwhile improving this, or too expensive and out of the remit of a Working Group on economics?

Frameworks: Section 5 of the scoping study details a range of frameworks from the political science and public policy literature. Does any of this look promising?

Mapping vaccine adoption stories: Is it worth mapping out previous vaccine adoption stories for selected countries using any of these frameworks and creating country-specific models?

Criteria: Reviewing the criteria used by the consultancy models, what seem more or less reasonable? Do we stick with the current consultancy models and improve them, or are there other approaches to taking advice?

Vaccination and health policy literature: Are there any specific comments on any of the vaccination and health policy literature or the political science and public policy literature?

6. Cost issues

Attrition/success probabilities: Are the success probabilities used in investment cases plausible? Do 'current industry benchmarks' of success probabilities apply to the case of TB vaccine candidates? How do we make attrition/success probabilities for new vaccines more robust? What if we are being too optimistic?

Portfolio analysis: Some of the analysis uses portfolio analysis. This can look very sophisticated even if the underlying information is limited or even simply wrong. The best way to control for this is by having openness about the figures used in calculations and an ability to do sensitivity analysis (for example better stress-testing of probabilities). Who will do this portfolio analysis in the future? Should it be a consultancy company under instruction, or some other entity?

Optimal portfolio: What is the optimal candidate portfolio size? This seems to be a function of policy makers risk aversion about how high a probability of getting no vaccine they are prepared to tolerate, and the costs needed to achieve particular probabilities of getting 'at least one vaccine'. What is the portfolio formula for working this out?

Intuitively, as the pool of vaccine candidates increases in size, at first new additions to the pool have a big and initially growing positive impact on the probability of 'at least one success'. At some point however, the addition of new candidates to the pool, while increasing the percent chance of success, starts to do so at an ever-decreasing rate. Assuring 95% chance of 'at least one success' can be very expensive, since at that probability the act of raising the chance of 'at least one success' by a few more percent is getting ever harder (and more expensive) to do.

Portfolio impact: How do we turn portfolio measures into measures of impact? Can we, for example, model a link between a portfolio at a particular point in time to its expected impact, especially for candidates that have reached phase 3?

Average cost per new vaccine: For each percent chance *of at least one success*, a portfolio will produce a range of possible numbers of new vaccines. What will be the average number of successful products, and the average cost per successful product, for

any given probability of at least one successful product? What is the average cost per product based on the 95% reasoning?

Trials and phase III: How many products are logically possible in phase 3 anyway? What are the potential trial site bottlenecks? What is the optimal trial site sizing given the lumpy nature of trials?

Sponsor return: What do sponsors get as their payout (in terms of contract deals on quantities and prices in exchange for their investments)?

COGS: What is the importance of COGS, especially of booster vaccines? How might lower booster manufacturing costs stimulate uptake? And how does that feed in to NPV?

Competitive event: What is the social value of the 'competitive event'?

Plant size/capacity: What are the various plant size and capacity issues?

Investment externalities: The greater the investment and the earlier the success via drugs in tackling MDR-TB and XDR-TB, the lower will be the value of vaccine-based investments. At the same time, a combination of new pre- and postexposure vaccines could substantially reduce the risks of emergence of MDR-TB and XDR-TB reducing the market for drugs. Meanwhile, better diagnostics enable more precise targeting of booster vaccines, with impacts on booster vaccine sales (probably able to be lower) and prices (probably able to be higher). And better clinical biomarkers will shorten trial lengths, sizes and costs, and yet there will be poor incentive to develop and supply such biomarkers if they are costly to develop and if the benefits can't be internalized. What is the combination of negative and positive investment externalities across different possible areas of R&D? How does it impact investor incentives? How should any trade-offs be modelled?

7. AMC

The amount of R&D to pay for and the sizing exercise: In setting any prize-like mechanism to incentivise R&D, what amount of R&D would be targeted? What would be the methodology for setting the size for a TB vaccine? How would the following be factored in: Complexity of underlying science; R&D costs; epidemiological issues; already spent private and sponsor funding; production costs. Would an 'auction' be used as originally proposed, followed by a monitoring mechanism (to check firms are investing 'enough')?

Follow-on incentives: What dynamic follow-on incentives are envisaged that TB vaccine development will need? How will this be best managed?

PDP issues: How would this or any other mechanism interact with vaccine/drug/diagnostic PDPs, given that it is supposed to work by pulling in private finance?

Affordable prices: How is pressure kept up on product affordability, especially in the light of the recent pneumococcal experiences?

The pneumococcal lesson: The pneumococcal AMC case is providing a lesson; what are the salient features so far of that case? Given the heavy monitoring and evaluation being proposed (the recently-released report of the 'monitoring and evaluability study' is 110 pages long), this suggests that by the time TB becomes a potential target, a great deal more will be known and that there is therefore some sense in waiting.

Alternatives/complements: If an AMC is a prize-based R&D mechanism, what alternatives/complements are there in terms of procurement policy, other predictable funding streams, demand forecasting, delivery mechanisms, production capacity insurance, etc.? For example, how does tiered pricing fit in?

Funding available and tradeoffs: The current AMC counts on balance sheets earlier than originally thought. How does this affect the tradeoff of funding mechanisms? What is the probable budget constraint? How much funding is going to be available from governments probably?