COST-EFFECTIVENESS OF NOVEL VACCINES FOR TB CONTROL

Kevin Schwartzman

‘It’s just a matter of attitude. Daring to cross the desert.’

It’s Just a Matter of Attitude
Fito Paez

‘...my poor attempt to emptying the sea of blood, that is our century, with the tremulous cavity of the hand.’

End of Century
Jose Emilio Pacheco

The Thread
Pedro Pablo Oliva
Oil on canvas; 231 × 160 cm
INTRODUCTION
The development of novel TB vaccines offers the potential of a sentinel advance in TB control, of immense benefit to individual and societal health. Previous modeling studies have highlighted the marked impact that more effective vaccines may have, particularly in the context of increasing antibiotic resistance (1,2).

Yet development, clinical evaluation and implementation of new vaccines are complex, and very expensive in the short term. There is no question about the value and importance of the ultimate goal. Nonetheless, it is also relevant to consider the balance between the expense of a vaccine, its potential economic benefits, and its clinical impact, compared with other TB-related and health interventions. For example, the upstream costs of research and development (potentially $1 billion US or more) (3) must be balanced against those of other promising TB-related and health interventions. In this chapter, I will briefly review some key economic considerations, as TB vaccines move forward through development, and (it is hoped) introduction and then dissemination into public health practice.

GENERAL CONSIDERATIONS
The fundamental concern of economic evaluation, for health care interventions as for other commercial or societal investments, is that decision makers and payers are constrained by the availability of resources, relative to the vast array of options for using those resources. The term “resources” is often used to denote money, but can also refer to personnel, equipment, and supplies. However, attaching monetary value to these allows analysts and planners to express them in common units.

In the broadest sense, economic evaluations of health interventions can help guide decision makers and payers in allocating resources, so that priority goals can best be met. However, economic analyses can never be the sole justification for societal choices for resource allocation: the society’s values and priorities are fundamental. For example, a government’s decision between increasing funding for health
services and that for primary education cannot rest on economic considerations alone.

Closely related to the fundamental premise of scarce resources, relative to their potential uses, is the concept of opportunity costs. This simply means that resources devoted to a given use are no longer available for other uses. Again, opportunity costs may refer to money (e.g. government funds), but they may also refer to infrastructure (e.g. manufacturing capacity) or personnel (e.g. skilled public health nurses). Hence economic analyses always consider a choice between two or more alternatives, one of which may simply be current practice. It follows that the fewer resources needed to attain a given goal, the more remain available for other uses.

Decision makers will always favour the cheapest means to reach a given goal, if the outcomes of interest are equivalent. In the health care setting, the type of economic analysis that reflects this approach is cost-minimization analysis, where two or more interventions/programs with identical clinical or public health outcomes are compared, so as to identify the preferred (cheapest) strategy. In the TB vaccine context, a simple example would be a cost comparison of two different strategies for manufacturing and distributing the same vaccine.

A much more frequent situation arises when two or more interventions differ both in cost, and in their ability to achieve a desired clinical or public health effect (i.e. their effectiveness). Hence analysts and decision makers must account not only for cost differences between the relevant interventions, but also differences in their health benefits. The usual analytic approach is that of cost-effectiveness analysis. Effectiveness is compared using appropriate units of health gain: for example, years of life gained, or cases of TB prevented. A special type of cost-effectiveness analysis is cost-utility analysis, where health outcomes are expressed as quality (or disability)-weighted survival, e.g. quality-adjusted life years (QALYs), disability-adjusted life years (DALYs) (4). This allows analysts and decision makers to account for morbidity as well as mortality in quantitative terms.

The key output of any cost-effectiveness analysis is the incremental cost per gain in health, e.g. cost per QALY gained, when one program, strategy, or intervention is compared with another. As with other economic analyses, a cost-effectiveness analysis must always involve a comparison of at least two options; in the case of a novel TB vaccine, this might mean current BCG vaccination with or without the addition of a new booster. But it could also entail comparing costs and health gains associated with a new vaccine, with those associated with a new drug for treatment of latent TB infection, for example.
When health outcomes are expressed in generic terms (e.g. survival, quality-adjusted survival), it becomes possible to compare interventions targeting diverse health problems. This type of analysis is most relevant to higher-level decision makers and funders (e.g. national health ministers, international organizations, donor agencies), who must juggle competing health and other priorities.

Given the substantial investments of time, money and resources required to develop and implement new TB vaccination programs, it is evident that economic considerations are important for all stakeholders. Moreover, the specific costs that get included in an economic analysis will depend on which stakeholders’ perspectives are considered relevant to the analysis, i.e. the target audience. For example, parents’ travel costs and time missed from work to attend infant vaccination clinics may not be considered important by a health ministry, but may be vital to a broader societal understanding, and may in fact impose important barriers to successful vaccine uptake. Similarly, a for-profit company contemplating the initiation of a TB vaccine development program may face very different financial choices and considerations.

COSTING AND PERSPECTIVE

For an economic appraisal to be valid, cost estimates for the intervention of interest must be robust, realistic, and appropriate to the setting where the intervention will be deployed. This typically holds true for economic analyses of interventions involving existing drugs, technologies, or public health programs. For example, relevant costs may be obtained through “micro-costing” studies conducted in the context of clinical trials.

For new TB vaccines, robust cost estimates are much more difficult to generate. It may be possible to base forecasts about production, storage, distribution, and administration costs on data already gathered for the bacille Calmette-Guérin (BCG) vaccine or others, e.g. through the World Health Organization’s Expanded Program on Immunisation. However, new vaccines may rely on different production technologies, and may have different requirements for storage and/or distribution than do those currently available. Administration costs may reflect differing schedules, particularly if the new vaccine is not administered simultaneously with other routine vaccines. In that case, a new vaccine that requires one or more separate health care visits may imply more substantial personnel costs, as well as costs related to travel and time off work for vaccine recipients and/or family members.
Even more challenging is the approach to research and development costs, given the spectrum of candidate vaccines at varying points in the pre-clinical and clinical pipeline. It is clear that the single biggest component of development costs relates to the conduct of high-quality, large-scale clinical trials, which require multiple trial sites, large numbers of subjects, extended follow-up, and hence massive infrastructure and ongoing operations costs. Indeed, such trials can cost thousands of dollars per subject recruited. And there is no guarantee that a given vaccine will prove successful — meaning that from the most global perspective, the true “cost” of a vaccine that is ultimately proved successful will also have included the resources devoted to vaccines for which development was abandoned at earlier clinical or pre-clinical stages.

Similarly, from the broadest global societal perspective, all funds devoted to vaccine research and development are relevant to an economic analysis, regardless of the specific payer — since those funds are no longer available to global society for other uses. Along these lines, donor agencies must carefully weigh costs and potential health benefits of investments in TB vaccine development, as compared with other potential investments in control of TB or other health conditions.

On the other hand, from stakeholders with a more focused perspective, some development costs may not matter much. From the standpoint of a national health ministry, if vaccine development costs are covered by third party donors, and are not reflected in the vaccine purchase price, then those costs are not relevant to decision-making — only the costs of purchasing, storage, distribution and administration. Hence the perspective of any analysis involving TB vaccines is crucial: it must be explicitly stated, and must be relevant to the clinical and health policy question at hand.

**ASSESSING EFFECTIVENESS**

Fundamental to any economic analysis is a realistic assessment of the health benefits to be gained by the introduction of new TB vaccines, in the settings and population groups targeted. At present, there are very limited data available, as the first phase 2B clinical trials near completion. Emerging clinical trial data, as well as a better understanding of the immune mechanisms underpinning clinical activity, will be absolutely essential to robust cost-effectiveness analyses.
To date, economic analyses have examined different potential target groups for vaccination, using hypothetical efficacy scenarios — so as to predict what costs, savings, and health benefits might potentially be associated with eventual clinical use in various contexts. Of course, without clear evidence of clinical effectiveness and safety, there can be no economic justification for the introduction of a new vaccine. Key questions to be answered include mechanism and duration of action, e.g. pre-exposure vs. post-exposure vaccination.

Beyond this most basic challenge, there are other essential considerations in assessing the most relevant health benefits. The choice of endpoint is one key issue. Vaccine trials are designed to estimate efficacy — that is, the proportion of TB cases which may be prevented by the vaccine over a given time frame, when compared with either no vaccine or an existing one. Vaccine trials are not ordinarily designed to compare mortality between trial arms, given the vast sample size requirements. And quality-adjusted (or disability-adjusted) survival estimates require both mortality data and valid estimates of disability or health utility for TB-related health states. Yet for high level decisions about allocating funds to TB vaccines or to health programs targeting other diseases, it is precisely these generic outcomes that are most relevant. On the other hand, for TB control authorities, TB cases prevented may be the most important outcome to consider, when comparing TB vaccines with other specific TB-related interventions.

Another key point relates to the target group and setting. The potential benefits of TB vaccination will increase with the risk of becoming infected with MTB, the prevalence of HIV infection, and the prevalence of antibiotic resistance — to name a few key parameters. A vaccine that prevents TB disease in infancy and early childhood will have little impact on community transmission, while a vaccine that successfully prevents “typical” reactivation TB disease of adulthood may have a dramatic impact on transmission, and enhanced cost-effectiveness accordingly (5). For this reason, different approaches to estimating the downstream health impacts of a new vaccine may be required (e.g. dynamic vs. static simulation models), depending on the target group and the expected mechanism and duration of vaccine effect. For a discussion of dynamic vs. static simulation models for economic analyses of vaccine interventions, see for example reference (6).

More generally, the absence of solid clinical trial data necessarily implies that economic analysis of TB vaccine interventions must rely on models and forecasts. For this reason, both producers and consumers of these analyses must pay careful attention to the clinical and cost assumptions that underlie such models.
TIME FRAME

Another important consideration is timing. Like other preventive interventions, the development and uptake of one or more new vaccines involves considerable expenditures now and in the near future, with health benefits accruing later (as will associated savings, e.g. on medications and hospitalizations). From the perspective of society as a whole, as well as that of specific payers (e.g. donor agencies, health ministries), the timing of these health benefits and potential savings matters a great deal. The further into the future they occur, the less valuable any given health benefits or cost savings are, relative to the necessary investment now.

This concept is formally known as discounting. A detailed discussion is beyond the scope of this text, and can be found in reference (7), for example. It is separate from the issue of inflation, reflects societal time preferences, and is the reason investors expect a return on investment, over and above the inflation rate. Economic analyses use an exponential approach to discounting, where the present-day value of a future health benefit or cost saving X is:

$$X/(1 + r)^{year}$$

where r is the discount rate, and “year” refers to the number of years into the future when the event of interest occurs. United States and WHO authorities have recommended an annual discount rate of 3% (6, 8), although it is also recommended that analysts report sensitivity analyses (see below) using other potential values, e.g. 0%, 5%, 10%. With an annual discount rate of 3%, a TB case prevented 10 years from now is equivalent to 0.744 TB cases averted today. At the same discount rate, a TB case prevented 20 years from now is equivalent to 0.55 TB cases averted today. The same holds true for every dollar saved in the future, which is important when comparing potential future savings to outlays today. This reinforces the importance of carefully considering the onset and duration of vaccine action, and using these to choose an appropriate time horizon for any analysis. The sooner a given vaccine prevents TB cases, the more cost-effective it will be.
UNCERTAINTY IN COST-EFFECTIVENESS ANALYSES OF TB VACCINE INTERVENTIONS

At present, many key parameters needed for economic analyses of TB vaccine interventions are not yet known with certainty. Others (e.g. annual TB infection risk, HIV infection prevalence in various age groups, prevalence of anti-TB drug resistance) may be documented in specific settings, but will vary across settings and may also be expected to change over time.

For these reasons, any cost-effectiveness analysis addressing the potential costs and health gains from TB vaccines must carefully consider many key areas of uncertainty. This is usually accomplished by examining different scenarios for key parameters (e.g. TB infection risk, probability of reactivation, duration of vaccine action). From the modeling perspective, a systematic way to incorporate many such scenarios is to conduct extensive sensitivity analyses, where the values of one or more parameters are varied across a plausible range, and changes in predicted costs and health gains are tabulated. The appropriate range for such variation may be very wide, and simply represent the authors’ “best guess,” if no relevant data are available. In other instances, authors may cite a range of published values, and may use statistical pooling methods (e.g. meta-analysis) to come up with a base case value for a particular parameter of interest. More complex methods for probabilistic sensitivity analysis (e.g. Monte Carlo simulation) may be used to account for uncertainty surrounding a larger number of variables simultaneously.

The key point for analysts, decision makers, and other readers, is the extent to which the major conclusions or policy recommendations of the analysis vary with changes in relevant input parameters. For example, predicted survival gains from a TB vaccine might be very sensitive to the prevalence of HIV infection in the target population, but might vary little according to the annual risk of TB infection, if most active TB can be successfully diagnosed and treated in HIV-negative persons.
INITIAL RESULTS FROM COST-EFFECTIVENESS ANALYSES OF NEW TB VACCINES

Given the paucity of robust clinical data for new TB vaccines, there are very limited published data on their potential cost-effectiveness. A useful starting point is the analysis by Trunz, Fine and Dye (2006) which examined the cost-effectiveness of BCG vaccination with respect to childhood TB meningitis and miliary TB (9). This study reflected a new meta-analysis of existing reports of BCG vaccine efficacy; the authors estimated efficacy values of 73% and 77% for meningitis and miliary TB respectively. They then estimated that based on a vaccine unit dose cost of $2 - $3, BCG vaccination costs a mean of $206 per year of healthy life gained, compared to no vaccination.

If these estimates of efficacy and cost-effectiveness are indeed valid, the analysis suggests that a new vaccine targeting infants would have to be extremely efficacious, and/or cheaper than BCG, in order to be potentially cost-effective. In the case of vaccines designed to boost BCG-induced immunity, a new vaccine would have to demonstrate a substantial increase in protective efficacy over BCG alone, extended duration of protection, and/or a different target group or mechanism of action (e.g. prevention of later reactivation disease).

Berndt and colleagues estimated that a hypothetical TB vaccine with 60% efficacy would cost $31 per year of life saved, if the cost of the vaccine were $13 per person and it were administered to 200 million persons (10). However this analysis focused mainly on the economics of advance market commitments by donor agencies (particularly in the case of malaria), and no detail about mechanism of action, target group, or other key parameters was provided. Although not explicitly stated, such a vaccine would have to either supplement BCG in infants, or target a different age group, in order for these estimates to be relevant.

An earlier analysis by Bishai and Mercer likewise did not examine specific mechanisms of action, but considered a hypothetical vaccine with a 10-year duration of action and 75% efficacy, applied to different age groups in different countries (11). They estimated that such a vaccine could lead to global savings of $25 billion or more in medical expenditures.

Tseng and colleagues examined a hypothetical BCG replacement vaccine, from the perspective of Zambia, i.e. a setting with high TB incidence and HIV prevalence (12). They assumed that research and development costs would be reflected in the vaccine unit dose cost, although these development costs were
likely underestimated — as the total unit cost remained within the $2-$3 range suggested by Trunz et al. The analysis included societal costs accrued outside the health care system for TB disease. The authors concluded that from this broader perspective, the introduction of a novel BCG replacement vaccine with 70% protective efficacy would be associated with both cost savings and health gains, relative to the current BCG vaccination strategy (relative savings of $770,000 per 100,000 infants vaccinated, with prevention of 199 TB cases and 90 deaths per 100,000 vaccinated). It should be noted that the existing infant BCG vaccination was assumed to be 50% efficacious in preventing severe childhood TB, which is substantially lower than the estimates by Trunz et al. (9).

Most recently, Ditkowsky and Schwartzman used a similar modeling approach (13) to examine potential scenarios involving the MVA85A vaccine developed by McShane and colleagues (14, 15). They focused on its clinical use as a booster for BCG in South African infants, and incorporated preliminary estimates of clinical trial sample sizes and the attendant costs, according to different efficacy scenarios. They assumed that the costs of the efficacy trials needed for vaccine licensure would be reflected in the vaccine purchase price; this may in fact depend on the extent to which development costs are supported by donors versus commercial sponsors. The analysis again suggested that in a very high TB incidence setting, with frequent HIV coinfection, an infant vaccine which provides moderate protection beyond that afforded by BCG alone (e.g. a 40% relative additional reduction in severe childhood TB) is likely to be associated with societal cost savings in addition to the expected health gains.

**CONCLUSIONS**

For most candidate TB vaccines, development is still in pre-clinical or early clinical stages. As such, cost-effectiveness analyses have thus far been largely based on hypothetical scenarios; they suggest that new vaccines may be cost-effective or even cost-saving. However, these analyses are limited by substantial uncertainty about key parameters including efficacy and duration of action.

The most advanced candidate vaccines have reached the stage of extensive safety testing, and now efficacy trials. Indeed, in addition to initial efficacy data, emerging clinical trial experience will provide important information about the trial costs themselves, as well as potential costs of administration in the program setting — all highly relevant to more refined cost-effectiveness analyses.
Several initial cost-effectiveness analyses have focused on infant vaccination. These parallel a large-scale clinical trial in South Africa, which has examined the addition of an infant booster vaccine to BCG. However, as clinical trial initiatives turn to other age groups in high TB incidence settings, future cost-effectiveness analyses should address these target groups, e.g. young adults. Analysts will also do well to more consistently frame their cost-effectiveness estimates in terms of costs (or savings) associated with gains in healthy years of life, i.e. disability- or quality-adjusted life years, to enhance comparisons with interventions in other health areas.

In conducting and using future cost-effectiveness analyses of TB vaccines, both analysts and decision makers must carefully consider the most appropriate target groups and settings. They will need to incorporate the best possible clinical evidence for vaccine efficacy as well as other TB- and HIV-related parameters, and to consider the time frame and perspectives most relevant to the many public health and policy questions raised by the promise of new TB vaccines.

REFERENCES


