ECONOMIC APPRAISALS FOR PRODUCT DEVELOPMENT PARTNERSHIPS

Product Development Partnership Access Group
January 23-24, 2013
Population Council, New York, New York

1. INTRODUCTION

A two day meeting was hosted by the Population Council[1] and involved participants of 13 Product Development Partnerships (PDPs), the WHO, PAHO and USAID, as well as health economists and financing experts from partner organizations and academia. The meeting included presentations from leading economists, as well as case studies of how PDPs have commissioned, executed and applied economic and financing studies in their work.

The following document provides a brief summary of the issues considered and discussed by the participants at the meeting. The agenda complete presentations and list of participants are available on the website.

2. BACKGROUND

The robust PDP pipelines of health technologies offer the potential to improve global health. However, the rapid adoption and uptake of these products in the developing world will only happen in a timely and effective way, if PDPs can address the challenges to access. It has become increasingly clear over the last few years that it is essential for PDPs to have an in-depth understanding of the activities and processes needed for adoption and uptake off products in developing countries. In earlier meetings, the PDP Access Group had identified the issue of *economic and financial appraisal* as an area that needs to be better understood and discussed. The PDP Access Group therefore held its fourth technical meeting, with a focus on economic analysis from the PDP perspective, in New York in January 2013.

3. AIMS, OBJECTIVES, AND EXPECTED OUTCOMES

From a PDP perspective, access must deal with economics and financing in a variety of ways and at different points during the product development. Economic evaluations and financing studies will be needed to support: portfolio management, country policy decisions regarding choices of a single or series or bundle of interventions, development of introduction strategies, and evaluation of budgetary impact.

A wide range of methodologies, associated costs and time commitments exist, and there are many groups in both developed and developing countries that conduct cost effectiveness studies. There are different options for conducting these evaluations, which may also vary depending on whether the program is for on-going disease control, elimination or eradication. The efforts needed will also vary depending on the stakeholder perspective taken.

[1] The Population Council works on developing reproductive health products "from the bench to the bedroom" - researching, developing and delivering a comprehensive range of solutions for the range of issues related to reproductive health.

The aims of this PDP Access Group meeting were:

- To identify the types of economic valuations needed to support product development and global and country policy decision-makers
- To identify the key factors that drive health and economic impact of interventions and to pinpoint where better information or research would fill critical knowledge gaps to better inform decision makers

The objectives for the PDP Access Group meeting were:

- Understanding the key concepts, methodologies and tools available for economic appraisal
- Examining questions of how stakeholders (i.e. donors, normative agencies, country policy makers) apply various economic valuations, including cost effectiveness/ cost-benefit/ cost-utility/ analyses, along with considerations of affordability, acceptance, compliance, and logistics
- Exploring how PDPs can design and develop the most useful cost effectiveness studies to assist with decision-making that will lead to access.

Expected Outputs and Outcomes for the PDPs

- A better understanding of how to commission, implement, and apply economics and financing studies in a wide range of situations and for varying purposes,
- An understanding of the options for measuring cost effectiveness: what, how and when to use the different methodologies for cost effective analysis **(**CEA) at different stages in the development chain,
- A better understanding of the donors' perspective on how CEAs are used in decision-making,
- A deeper understanding of how country decision-makers use these analyses,
- A detailed report summarizing the workshop, conclusions and guidance for further work.

DAY 1 – January 23rd 2013

4. ECONOMIC APPRAISALS FOR PRODUCT DEVELOPMENT PARTNERSHIPS

Overview of PDP Access Group

Heather Kelly, the co-chair of the PDP Access Group, gave a brief introduction of the PDP Access Group history, structure and objectives.

The working definition of access that this group has agreed on was developed at the first PDP Access meeting in 2008 as follows:

> *"Access refers to coordinated sets of activities needed to ensure that the products developed will ultimately have an equitable public health impact". …."Achieving this impact requires that products are available, acceptable, affordable to end users and adopted into developing countries health systems"*[2]

The overall goal of the PDP Access Group is to enhance the effectiveness and efficiencies of PDPs in the area of access and to contribute to the knowledge base of PDP access work. While, the emphasis is on sharing knowledge, each PDP should be equipped to develop and implement the strategy that is best for them.

[2] *Brooks et al. 2010*

There are currently 16 members that represent 13 PDPs and not-for-profit product access organizations. The group works through two co-chairs and a part-time secretariat.

An Overview of Key Concepts, Methodologies, Tools

SESSION 1 – KEY CONCEPTS AND METHODOLOGIES

Donald Shepard, Brandeis University

Overview

This session gave a comprehensive overview of the concepts, techniques, and methods for economic appraisal, with some specific examples to help inform the PDP participants how to select the most appropriate methodologies.

The presentation discussed the descriptive tools that can be very helpful in building advocacy around the problem and intervention, including cost of illness and cost of an intervention or program. These descriptive tools essentially measure the amount of money/economic resources lost as a result of a disease or condition and serve three main purposes: the quantification of the economic importance of a disease in a country/region, the comparison of one disease or condition against another, and to act as a rough guide to whether the potential intervention would be economically worthwhile.

Examples of the cost of dengue in Malaysia and the cost per child of a 3–dose pentavalent vaccination programme were used to illustrate this methodology.

The comparative or analytical tools of cost minimization, modeling, cost-effectiveness, cost-utility, willingness to pay, and cost-benefit analysis, as well as the broader impacts on health systems were then discussed in detail with examples.

Discussion

An example given to illustrate the spin–offs and broader impact of an intervention on the health system was the positive impact of funding for HIV interventions on maternal health services in Rwanda. This was further highlighted through discussion of work done by Kremer and Miguel[3] on the evidence of the impact of school deworming programmes on children's health and school attendance, that justified subsidizing the treatment despite the fact that there was no evidence (in this case) of improved academic scores.

The issue of how to address and/or account for the apparently lower cost/benefit of interventions in poor countries was raised. Discussion focused on how cost benefit can be used within a country, but does not work across countries that have different levels of care and costs. Cost effectiveness (CE) was developed largely to address this; the cost per QALY/DALY gained is generally more favorable in less developed countries. This point was supported by the example of the approach by Sachiko Ozawa (presented at the GAVI Partners Forum, December 2012) that looked at the benefit and return of investments from GAVI, but ran into difficulties when used for cross country comparisons. WHO does encourage countries to use CEA, but there are some methodological issues in setting the thresholds for CE. If a country does not have its own CE threshold, the use of the WHO criteria (with certain limitations) is encouraged. WHO also encourages cost comparison across sectors, but does not advise comparing disease control programs (across diseases) because of the ethical considerations of placing a monetary value on life/value of life saved from one disease over another.

[3] Kremer and Miguel: Econometria 2004: 72 (1) pp 159-217

The increasing costs of an intervention in e.g elimination/eradication programmes as they progress is an issue that the malaria field will face in certain situations. It was recommended that the increased cost of the last mile in eradication/elimination programmes at country level could be justified by looking at the saved costs of projected years of prevention/treatment evaded by calculating – a 'life of the intervention' value. A methodology for estimating cost of the "last mile" is a major consideration for both polio and measles eradication programmes and is being investigated by the Kid Risk Group and colleagues in Boston [45].

For malaria, it is going to be difficult to capture the cost/benefits of elimination since prevention efforts need to be ongoing because of the risk of reintroduction. In many cases it may not be deemed economically viable until there is a (better) way of looking at the broader impact/benefits. This brought up the issue of whether there should be a push for elimination of malaria – and if yes, how to assess the long-term benefits.

Most PDPs are interested in understanding what kind of support to county level decision makers they could offer - especially with regard to analysis of benefits of combinations/sequencing of interventions. It was suggested that modeling could be a very useful area for PDPs to share knowledge/analyses with each other and the country level partners.

In the panel discussion on: *"Which techniques are most appropriate for product introduction and what are challenges of application in low-resource settings?"* Tom McLean made the following points from the IVCC perspective:

- *'Cost of intervention is not necessarily the price of the health commodity – the real costs of vector control are not in the sticker price but are the delivery costs.*
- *So far, the PDP's best approach is cost minimization – but there is no data yet for cost effectiveness, although they would dearly like to get there.*
- *Modeling attempts largely do not take into account weakness of data for particular countries - there is a great need for improved techniques for measuring denominator savings.*
- *Looking ahead to moving from cost-minimization, aggregation of cost effectiveness over the lifetime of a product will be a very important consideration.'*

Debbie Atherly, a health economist from PATH, addressed this question from a vaccine perspective.

- *'Cost utility and cost benefit analyses have been problematic methodologically, politically, and in terms of equity in the international public health sphere.*
- *For vaccines work, cost of illness and cost effectiveness has been most useful.*
- *Perspective is vital, particularly for cost-effectiveness analysis. What question are you trying to answer?*
- *The front-end work can be more important than the analysis - an example to illustrate this was a very high level study of the global cost effectiveness of GAVI across countries as part of the "global investment case".'*

In these discussions it was not clear how to relate these issues back to the neglected disease environment, where willingness to pay is not an issue as these are diseases of poverty and the disenfranchised.

[4] Tebbens et al Vaccine 2011: 29 pp 334-343

[5] Thompson and Tebbens : Economic evaluation of benefits and costs of disease elimination and eradication initiatives From "Disease Eradication in the 21st Century: Implications for Global Health," edited by S. L. Cochi and W. R. Dowdle. Strüngmann Forum Report, vol. 7, J. Lupp, series ed. Cambridge, MA: MIT Press. ISBN 978-0-262-01673-

SESSION 2 – WHAT TO DO WHEN

1. Determining Which Type of Economic Analysis to Use at What Phase of the Product Development Life-cycle

Paul Wilson, Columbia University

Overview

This session considered the hierarchy of questions about economic evaluation and explored the following options and examples:

- What decision do you want to inform or influence – the purpose of the economic evaluation?
- Which tool is valuable and appropriate for different decision–making needs?
  When considering cost of illness/economic impact, the quality of a lot of this work in the field is questionable. There is also the concern that building a case on economic impact carries the threat of losing the case on economic impact - *"If you use economic analysis to build your case, are you willing to lose the case?"*
- The timing and feasibility of evaluation. What is the right time, relative to stage of product development and project data of introduction, to influence key decisions?
  The PDP discussion paper by Andrew Jones[6] gives a high level outline of which tools are appropriate at the different stages of product development.

Examples were cited of the difficulties encountered in a malaria economic impact study and an early IAVI demand study that were carried out too early, and uncertainties were such that it was not possible to prepare groundwork for adoption. Two useful studies in terms of timing and cost effectiveness were given: 1) an IAVI impact study and 2) work on HPV CEA in East Africa. The analysis of an HPV vaccine in East Africa - where the price of the vaccine was not yet determined in the relevant settings - was quite sophisticated. It looked at a combination of interventions (screening, immunization), attempted to quantify and produce cost-effectiveness estimates and came up with an intricate approach for cost effectiveness that could inform discussions on price.

It was pointed out that, for example in Africa, if there is no effective intervention in place, any intervention will help, and so will be cost-effective. Budget impact and affordability analysis can be more useful than cost effectiveness in these situations.

This led to a discussion on the idea of an *intervention package*– e.g. HPV vaccine and cervical cancer screening for daughters and mothers - that would be most cost effective and have a cost benefit in terms of not only as prevention of HPV infection in adolescent girls, but of getting these populations into the health system.

Credibility in commissioning studies and what role the PDP should play, both from the PDP perspective(when there is only one right answer) and the alternatives to PDPs carrying out or commissioning this kind of work were explored.

2. Cost Effectiveness Analysis for Different Product Categories

Angeline Nanni, Aeras

Overview

[6] http://pdpaccess.org/downloads/projects/full-papers/PDP%20Economics%20and%20Financing%20Paper.pdf

The importance CEA to policy makers was highlighted and the example of a consultation with a range of country-level policy makers was given. Even if there was no money in their budget, all of them asked for CEA data first, and then if WHO had sanctioned the product/intervention. The message was clear: if you don't have CEA data, country level policymakers are not as willing to talk with you about adoption of an intervention. If you do have the CE data to present, they are willing to talk but without assurances they will be able to adopt the product. In essence, policy makers needed to know that there is CEA data, but CE was not a key influencer for product adoption decisions.

A common dilemma for the PDPs is what to do when a cost-effectiveness analysis for a product that does not yet exist is needed and that product is still 10 years away from licensure and with no Target Product Profile (TPP) to build analysis around.

To address this challenge, the example of a potential TB vaccine was used. As no economic analysis of TB vaccines has been done in the last 10 years, Aeras organized a consultation with experts and stakeholders. Outcomes from the consultation suggested a research plan to address building the economic case for investment in TB vaccines in line with the 'Strategic Access Framework'. The plan is to conduct 3 types of CEA at varying stages of product development; first when 1) no product yet, 2) no defined demand, 3) no pricing and 4) uncertainty of the target population, the analysis: will be at global level (not at regional or country level at this point); will look at infant, adolescent, and adult vaccination; will use a set of hypothetical product profiles; and will set the groundwork for future advocacy, public policy and investment decisions that can be built upon over years, but is grounded in solid data that is available today. Second, assess cost-effectiveness data on a very specific product for a specific population, and third, by phase III trials, Aeras will move into 'Operational Access' to assess the cost-effectiveness of the vaccine at country level including price of the vaccine and cost of delivery to inform country readiness.

Discussion

A 'strategic access' approach, conducted early in the product development life-cycle, attempts to look at the cost effectiveness of *investment* first, answering the questions, *'.. is this an area partners should invest in? Using estimates based on the best possible available data but with clear limitations?* 'The answer is not clear but there is value in demonstrating *a cost-effective investment* vs. *investment in a product that is cost-effective*.

From experience in both MDC and LDCs, Government uptake is often dependent on financial vs. economic considerations. The questions asked are "*how much does it cost*" and then "*can I afford it*", rather than a comparison with another intervention.

The groups were reminded that the primary need is to find out if the product is *effective* before finding out if it is *cost effective*. This is important to understand in this staging in analysis.

SESSION 3 – USE OF ECONOMIC ANALYSIS: CASE STUDIES & STAKEHOLDER PERSPECTIVES

A. CASE STUDIES

1. Economic Study Conducted as Part of Advocacy for MenA Vaccine

Anais Colombini, Agence de Medecine Preventive

Overview

The presentation gave a microeconomic perspective of the cost of meningitis to the population in Burkina Faso, in the context of establishing the investment case for introduction of the MenAfric® vaccine. The presentation looked at the context, study design and rationale, the results and conclusions, and how these have been used for both advocacy and improved surveillance and response systems.

Conclusions and Policy Implications:

- The total cost of surveillance and response of meningitis and the epidemic to Burkina Faso in 2006-200? (US$9.4 million); the cost to the public health system (US$7.106 million – 2% of national health expenditure); and the cost to households (US$90 per case – 25% of GDP per capita).
- Despite public policy, many households paid for curative treatment.
- In reactive immunization campaigns in which an epidemic threshold is reached before starting vaccination, the costs are very high.
- Overall meningitis results in high human and economic costs.
- Improved meningitis preventative strategies should reduce costs for households and the health system.
- These results were used by the GAVI board in their decision on the package to fund and in advocacy at World Health Assembly, etc.
- This kind of study can be used for advocacy to funders and decision makers, as well as at national level to improve health policy and intervention strategies.

2. Cost-effectiveness of Insecticide-Treated Wall Nets (ITWL)

Donald Shepard, Brandeis University

Overview

This study estimated the cost effectiveness of Insecticide-Treated Wall Liner (ITWL) plus Insecticide Treated Net (ITN)[7] vs. ITN alone and identified key policy questions for research and scale up.

The effectiveness of the ITWL intervention had been determined by Gimnig[8] and extended 'survival time' before infection with malaria, giving an overall adjusted protective efficacy of 38%. The study showed that 63 clinical cases are averted per 100 children/year.

The product is relatively expensive at $64.23 per person, but becomes relatively more cost effective as duration of the product intervention extends. The main conclusions from the study were:

- If ITWL provides protection for at least 2.2 years, it is highly cost-effective.
- If substantial "moral hazard"[9] occurs where recipients of ITWL reduced use of ITN, net benefits would be reduced and perhaps eliminated.
- Long-term projected results: 13.3 cumulative discounted life years gained (DLYG) over 4 years.

[7] ITN – insecticide treated bed net

[8] Gimnig JE 2011 Am.J. Trop. Med. Hyg. 85 S199

[9] **moral hazard** is a situation where a party will have a tendency to take risks because the costs that could incur will not be felt by the party taking the risk. In other words, it is a tendency to be more willing to take a risk, knowing that the potential costs or burdens of taking such risk will be borne, in whole or in part, by others. A moral hazard may occur where the actions of one party may change to the detriment of another

- Prospective trials comparing ITWL to IRS and longer term follow up are key for informed policy (a 3-year study in Tanzania is being planned now including comparison with Indoor Residual Spraying).

Discussion

The problem of "moral hazard" initiated an interesting discussion, as this is an issue that the TB world has to deal with, regarding policy and the reality on the ground. It should also be noted that in the study presented above, both the interventions were provided free in a scaled roll out. So how would out of pocket expenditure affect the impact of these interventions?

This also led to discussion on the current (and future) issue of how to deal with the fact that country decision-makers are increasingly choosing packages or bundles with multiple interventions rather than single interventions to address a public health need– e.g. the case of a malaria vaccine or HIV prevention - and how policy makers will have to take decisions on trade-offs of interventions or a package of interventions.

It is clear that there is a major gap in modeling of combined interventions and this should be a priority for future work.

3. Malaria Prevention and ITN Distribution Systems: Role of Economic Evaluation in Determining How the Product Will Reach Consumers

Joshua Yukich, Tulane University

Overview

This presentation looked at the various models proposed and used for delivery of ITNs, and discussed the questions arising from the different approaches and economic appraisal studies.

One study looked at the scale-up and delivery of different models across African countries. The results indicated that ITN distribution was slightly more cost effective than Indoor Residual Spraying (IRS) and a shift to Long Lasting Insecticidal Nets (LLINs) would then be substantially more cost effective. However, the results also generated another series of questions to be examined e.g.: scale-up, acceptability, uptake, cost-recovery, economies of scale in delivery, re-treatment strategies, etc.

Further analysis indicated that the distribution strategy generally mattered little in terms of differences in cost-effectiveness – as long as there was no cost to the consumer. Even nominal fees limited uptake, despite willingness to pay studies on malaria prevention.

Repeated local mass delivery campaigns result in coverage fluctuations, but there is no knowledge/data as to what epidemiological impact these fluctuations may have.

As discussed earlier in the day, CE often provides justification rather than rationale for decision-making.

Conclusions

- Economic evaluation should consider the methods that are going to be used to reach 'consumers' i.e. delivery.
- This in some instances can even feed back into product development.
- Life time and durability of capital goods (under field conditions) are key drivers of cost and CE.
- Program managers do consider these kinds of results for decision making, though CE often is used as a justification rather than a component of rational decision making.

B. STAKEHOLDER PERSPECTIVES

Donor Perspective

Priya Sharma, Centre for Accelerating Innovation and Impact, USAID

From a USAID perspective, there is a need to start thinking about access strategies early on in the product development phase and to gather existing data for scale-up. The onus is for donors to push for relevant economic analyses data earlier and more often, to facilitate planning for introduction and access. CE is important (at lowest price possible) as it can help set parameters for the TPP and in costing and price negotiations for procurement later on. With the scarcity of resources, USAID increasingly needs cost-effectiveness analyses to guide product selection and data on what is the highest price at which a product will still be cost-effective.

In terms of country –level decision making, it is crucial to have the donor country office buy in.

Country Perspective: Use of Economic Analyses for In-Country Decision Making

Mercy Mvundura, PATH

Although developing countries are increasingly becoming aware of the importance of economic analyses, most evaluations are driven by other institutions, rather than the country itself. Currently, the use of economic evaluations for decision–making by country policy-makers is limited (as compared to developing countries).

Three examples of the kind of work PATH has done to inform country-decision making were presented and discussed as follows:

1. *Delivery costs for vaccines and the need to understand costs of the vaccine supply chain.*
   Most countries do not know how much it costs to move vaccines from the national store through the health system. Studies can help countries understand what is needed to prepare and improve supply chain performance and plan for the introduction of new vaccines.
2. *The cost to governments of four different cervical cancer screening methods.*
   This work provided information on screening methods that provided best value for money in developing country settings and also provided data for scale-up.
3. *Economic burden study for introduction of a new vaccine (rotavirus in Rwanda).*
   This looked at different perspectives (including government) of the value of vaccination of children and provided data for advocacy for continued funding of the vaccination program. The data can feed into cost-effectiveness analyses but factors limiting use in country-level policymaking were also discussed. These included: the limited understanding of an economic analysis - framework, methods and interpretation (data is often not understood); lack of capacity to conduct/lead evaluations; limited investment in resources to support evaluation; limited engagement and ownership – trying to accomplish quick results by minimizing government involvement.

The ways in which PDPs and other stakeholders can increase buy-in and better understanding of the use of economic analysis by Ministries of Health were also explored and the Importance of PDPs providing country-level capacity building support to help use/understand these tools was emphasized in the discussion.

Regional Perspective from the Americas

Alexandre Lemgruber, PAHO

The growing interest in Health Technology Assessment (HTA) and economic evaluation (EE) for decision-making and processes and legislation in the Americas region was comprehensively presented. Some specific illustrative examples from countries were given as follows: Brazil, which classifies drugs by comparative efficacy (additional benefit derived from the treatment) and cost minimization and has a new commission – CONITEC – which regulates incorporation of new health technologies in public health system; Mexico has developed guidelines for economic evaluation and hosts CENETEC – a WHO collaborating center for health technologies.

One of greatest achievements of PAHO and member states in past years is the agreement and resolution on HTA and the decision-making process. Countries agreed on 6 essential elements for the region. The resolution urges member states to encourage the establishment of decision-making processes for HTA and EE. The challenge now is the implementation of the resolution.

The objectives and early activities of RedETSA, a new network formed to deal with HTA (with PAHO as the secretariat) were described, as it will focus on priority setting and mapping the situation of HTA and EE in the region.

The ProVac Initiative (funded through a Bill and Melinda Gates Foundation grant) has the goal of strengthening national technical capacity to make evidence–based decisions regarding the introduction of new vaccines. The Initiative currently focuses on the introduction of four vaccines: Rotavirus, Pneumococcal conjugate, HPV, Influenza and will in the future look at dengue, IPV and HepA.

The challenges that the region now faces include: lack of availability of relevant information on EE; the need for an effective way of sharing HTA and EE reports and models; the transferability of EE and HTA and interaction between regulatory authorities and HTA bodies.

WHO Perspective on the Use of Economic Analysis for Vaccines and Immunization Programs

Raymond Hutubessy, Initiative on vaccine research/Immunization, Vaccines and Biologicals, WHO

This presentation highlighted: which tools are relevant and when to use them; going beyond traditional CEA –the broader value of vaccines, WHO's normative role to increase transparency and country ownership of economic analysis, and WHO's role in building technical capacity in LMICs.

A literature review carried out by WHO on the introduction of the HPV vaccine into LMICs highlighted the lack of detailed national delivery cost information. In order to address national program affordability and sustainability, this information is crucial, also for resource mobilization. It was also noted that in LICs, the HPV vaccine price is less important than the delivery costs – but in High Income Countries (HIC) the opposite will be true, whilst in MICs both scenarios exist, so CEA will be important.

Approaches looking at the broader value of vaccines were discussed and illustrated with a WHO framework that has been developed. A broader perspective of the value of vaccines takes into account outcome-related productivity gains, behavior-related productivity gains, ecological externalities, community externalities, macroeconomic/change in GDP.

Discussion

In the discussion, the need for multiple tools for economic analysis was emphasized, as there are different questions being asked and different perspectives -"*if you put 10 different economists in a room you will have 10 different opinions*"- so CEA is not so much a hard science. There is a need to really understand the issues that need to be demonstrated with the tools.

However in the TB field, there is an effort not to have publications that draw different conclusions, so some core models can be developed that can be applied to answer many different questions (e.g. model of TB transmission can be used in different analyses). Transparency is crucial in model development and people need to understand the model that is proposed to them.

The issue of who funds and conducts the economic analysis in PAHO countries was raised, but there was no clear answer. Some countries expect the companies to carry out the studies but there is also clearly a need to build capacity in country to assess the CEA. A report from Center for Global Development on priority setting for investment in health[10] was referred to, where a recommendation was to build a global/regional facility to do economic evaluation alongside building capacity locally.

In answer to a question about whether to continue doing CE studies later in the development of a product, it was recommended to keep the CE information up to date as the situation is constantly changing. With time the CE data will become more robust and more useful.

SESSION 4 – UPDATES & DISCUSSIONS FROM RECENT MEETINGS

This session started with an update from a series of recent meetings and discussions that have taken place that looked at the broader impact of vaccines, as well as the reality and challenges in evaluating and using the results of economic analysis in low-resource settings.

1. Update from Recent Meetings on the Broader Impact of Vaccinations and Economic Analysis

Raymond Hutubessy

Overview

To date, health economic evaluations of childhood vaccines have only captured the health and short-term benefits.[11] There is increasing interest in ways of measuring broader and longer-term impact of health interventions and most of the recent work in this area has focused on vaccines. Dr Hutubussey summarized the discussions from recent GAVI consultations on 'the value of vaccines in health and economic development' at the GAVI Alliance Partners Forum (December 2012) and a workshop on the value of vaccines that aimed to:

- Achieve consensus on ways to explore the broader development, social and economic impact of vaccines
- Identify existing studies, data sources or work to be leveraged to evaluate the broader impact of vaccines
- Provide recommendations on the short, medium and long-term work plan, including methodological issue to address.

WHO has been looking at different conceptual frameworks on the broader economic value of vaccines (e.g from Barnighausen, Deogaonkar and Ozawa) and will review these with economists outside the health sector at an upcoming meeting. The Framework categories broadly include:

- Health-related benefits

[10] http://www.cgdev.org/files/1426241_file_priority_setting_brief_web.pdf
[11] Deogaonkar et al 21012 MBC Public Health 12:878 doi:10.1186/1471-2458-12-878

- Productivity related benefits
- Community externalities
- Broader indicators (changes in household behaviors, public sector budget impact, short and long-term macroeconomic impact).

In preparation for the next consultation, good practice in this area that addresses the target audience, transparency, evidence–based, feasibility and methodology have been outlined and a questionnaire to rate strength of evidence prepared for the expert consultation.

Short, medium and long-term research priorities to understand the value of reaching Fully Immunized Child goals were identified at the GAVI consultation. Future studies should focus on primary data collection, country-level evaluation, prospective data collection alongside Randomised Controlled Trials (RCTs) or surveillance systems. *(textbox with the research priorities?)*

Discussion

There was no clear answer to what should PDPs be doing regarding the GAVI meeting recommendations , apart from the acknowledgement that looking at the broader impact is not a substitute for traditional economic analysis but an adjunct.

2. Challenges in Translating Results of Economic Evaluations

David Dowdy, Johns Hopkins Bloomberg School of Public Health

Overview

This presentation considered the challenges of translating results of economic evaluation, from the perspectives of the various stakeholders. This was illustrated with the example of the population health impact and cost effectiveness of TB diagnosis with Xpert MTB/RIF[12] and explored translation of economic evaluation results into appropriate decision-making. Results showed 'reasonable value' based on standard benchmarks of cost- effectiveness, with the qualification of the substantial nature of the costs.

Bearing in mind the three main challenges to address: 1) making the outcome meaningful, 2) generalizing the outcome to other settings, and (3) planning for the future, how does this translate to decision-making?

1. Is the cost per DALY averted the desired outcome? This is not meaningful to most decision-makers, so need to consider population impact, cost-effectiveness, and affordability relative to other available options. Different types of economic evaluations will matter to different consumers. Clarify priorities ahead of time and economists can lay out potential options for model structure – ensure discussion *before* and *after* to ensure relevance of the analysis
2. Locally relevant results matter, but so do results that are generalizable. Different input parameters will matter to different people and in different contexts (e.g. in the area of TB, HIV is important in Africa while MDR-TB is important in India and China etc.). Ideally, economists and decision -makers would discuss model inputs before and after the analysis is done.
3. Planning for the future: very few evaluations explicitly incorporate changes in economics over time – impact is projected over many years but assuming that costs remain relatively stables – but this is not the case. Decision-makers can explain how they are planning for the future and what scenarios would be most relevant to them.

[12] Menzies et al 20102 PLOS *medicine* 9 (11) e10001347

In summary 'One size does not fit all' – goals of decision-makers will vary and evolve over time – useful partnership between economists and decision-makers is ongoing and long-term. It is also important to discuss the logistics of how this can happen.

Discussion

The GeneXpert paper has been cited a lot, but does that mean the data is useful? The response was that this was difficult to assess as success depends on the perspective. The following examples where CE evidence had worked were given:

- The 1993 World Development Report generated huge interest in countries for more cost-effectiveness evidence of existing interventions for cost allocation.
- The Copenhagen Consensus set out priorities among a series of proposals for confronting ten great global challenges based on cost benefit and cost effectiveness[13] and
- The work by Martha Gold (1996) on a US-based panel on cost-effectiveness analysis for health and medicine which utilized elements of standardization to work, standard discount rate of 3% and a reference case of status quo.

Discussion on whether donors and journals should require adherence to standards of review of methodology similar to ethics/human subjects review and registration of clinical trials was not conclusive. Although it was agreed that highlighting critically important (minimum set) criteria for studies that researchers will know must be included would be useful – another view given was that the context and country setting has to be taken into account and as economic analysis is constantly evolving, standardization of approaches would essentially stop the constructive evolution.

3. Vaccine Economic in Low and Middle Income Settings

Dagna Consenla, Johns Hopkins Bloomberg School of Public Health

Overview

This presentation started by reminding us of what it is that makes developing countries unique in terms of demographics, decisions about healthcare spending in the context of the health budget and wider development goals. The reasons for recent major growth in economic evaluations in low and middle-income countries were discussed; the fact that specific types of evaluations have experienced more growth than others (e.g. cost utility analysis) was highlighted. Recent systematic reviews have looked at evidence from a broad economic perspective, with a focus on low-and middle-income countries. For example, the systematic review of cost effectiveness and economic benefits of vaccines in low- and middle-income countries by Ozawa *et al*. was discussed in detail.

This paper reviewed economic benefits of adult and childhood vaccines in developing countries and from 108 papers from 51 countries covering 23 vaccines. It found that although most studies were for LMIC only 36 were actually from LMIC. Rotavirus vaccine was the most frequently evaluated vaccine, followed by Hib and HPV. Overall, it was concluded that more attention should be paid to measuring societal benefits of vaccines and more information on costs, treatment savings, and benefits and outcomes is needed.

Discussion

The Cochrane collaboration has had tremendous impact on assessing effectiveness for the ITN field, that used to have the same concerns regarding methodological constraints as the vaccine community. There is no equivalent in vaccine studies to the Cochrane Framework that defines methodology for studies and meta-analysis. This kind of approach to vaccine reviews would be very

[13] The Copenhagen Consensus 2008

helpful as there are certain methodological constraints (e.g. lack of transparency, different methodologies, different questions/designs… etc.), which a level of standardization and quality criteria would address.

The challenges of indirect cost calculations in developing countries were raised and it was recommended that cost-effectiveness data should be reported with and without indirect costs.

SESSION 5 – CASE STUDIES FROM PDPs

In this last session five case studies from some of the PDPs were presented and discussed.

1. A Case Study from Family Planning

Martha Brady, Population Council

Overview

The Population Council conducts biomedical, social science, and public health research in the fields of contraception, reproductive health, and HIV. The Council's PDP component is focused on reproductive health products. An overview of the diversity of women and their unmet contraceptive needs was provided. A range of contraceptive products is required to meet the diverse reproductive health needs of women globally. Increasing the number and types of contraceptive products, increases overall uptake. In terms of economic arguments, there is good evidence of the association between family planning and maternal, infant, and child health, economic development, and poverty reduction. For every US$1 spent on contraception, US$1.40 is saved on maternal and newborn healthcare costs.

The critical path from product development to introduction should include attention to the "end user"; thus research on user perspectives' should be embedded into product development. The Population Council's 'bench to bedroom' research, couples biomedical with social science agendas.

Developing countries want to know if the product will be acceptable to users and feasible to deliver in their country programs before it is approved for wide scale use. Pilot demonstration projects with the new technology are often requested. Product introduction needs to demonstrate system capacity, affordability, acceptability to women and service providers; uptake can be achieved and sustained, as well as longer-term impact and how the product fits into the overall method mix in a given country.

Lessons from reproductive health include:

Clinical efficacy vs. typical use effectiveness in real life conditions not the same

- Risk perception influences whether and how well women will use various products Adoption takes time. Diffusion of innovation indicates that the speed of uptake of a new product or innovation depends on how much behavior change is required for adoption, the type of service delivery, the price, and marketing investments.

2. TB Alliance –Cost effectiveness Analysis of REMox Regimen

Elizabeth Gardiner/William Wells, TB Alliance

Overview

WHO has explicitly stated that it will use CEA as part of its decision-making for new TB drugs. To meet this requirement, but also to get a better understanding of the potential value of new TB regimens, the TB Alliance is working with a consortium to look at the cost effectiveness of REMox, which would shorten treatment from six to four months. The consortium consists of the LSHTM (the Principal investigator), AIGHD[14] and JHSPH and brings together expertise in economic evaluation, modeling epidemiology, technical assistance to national TB programmes and presentation of CEA to national and global stakeholders. The study was initiated at the end of 2012 and results should be available in Q3-Q4 2013.

The study will measure provider and patient costs in four countries: Brazil, South Africa, Tanzania and Bangladesh. It will use a two-stage methodology: 1) model a cohort of TB patient through to cure, recovery, or death and 2) a transmission model of indirect impact. The decision tree, which adds costs to each branch and estimates number of deaths averted (each branch of the tree must have costs and probability of outcomes) is very complex and a large number of parameters are needed for these models.

The challenges of the CEA that are already emerging were discussed and include the problems with a conservative model (i.e., good evidence is never available for all parameters, in which case the model must revert to the most conservative estimates), the subjectivity of some decisions made during the modeling, and the fact that cost effectiveness may not be the most important determinant for adoption decision-making. This last point was illustrated by the examples of: 1) Anti Retroviral Treatment (ART), which is not cost effective, but activists and patients demand it and 2) the fact that current TB treatment is extremely cost-effective, but we need to demand a better standard of care even if it is less cost-effective.

Given the example of ART as a product that is not cost-effective but is necessary - does this mean we should be looking for a better or different definition for cost-effectiveness? There is a tension between cost effectiveness and effectiveness, and it is important to consider how to package and publicize cost-effectiveness evidence.

3. HIV Vaccines: Exploring the Potential Cost-benefit

Jennie Aylward, International AIDS Vaccine Initiative

Overview

IAVI is working with the Futures Institute on impact modeling of an HIV vaccine, which will help IAVI in making the case for investment.

The model estimates the impact of an HIV vaccine under three scenarios depending on assumed efficacy and population coverage. Impact modeling indicates that an HIV vaccine could avert between 5.2 million and 10.7 million HIV infections. This effectiveness assessment was helpful but IAVI wanted to look at cost effectiveness as well. It is challenging to estimate cost effectiveness when there is no product, but knowing the cost of keeping a patient on ART, two scenarios were explored:

1. Targeting the general population and assuming a vaccine efficacy of 70% - a vaccine costing as much as $189/person vaccinated would be *cost saving* (equal to savings of not providing treatment)
2. A vaccine of $332 would be highly *cost-effective* by WHO standards (3x less than GNI per capita when sub-Saharan Africa GNI per capita is used).

[14] Amsterdam Institute for Global health and development

The limitations of this approach were highlighted e.g.: the analysis is quickly out of date, many assumptions around incidence, population trends in the epidemic change, vaccination effectiveness is necessary; vaccine efficacy in all geographies and across all modes of transmission is in question (e.g. those that work at mucosal level would likely not be effective for IDUs), and the fact that the real cost of vaccine cannot be arrived at by using proxies.

The benefits of this early work include the fact that potential investors appreciate the analysis and that working with the Futures Institute has been successful. In addition, cross-fertilization of work across clients has been beneficial. IAVI is also working with UNAIDS and the CDC so the assumptions in approaches are the same across the work of different normative stakeholders.

4. Economics of TB Vaccines

Angeline Nanni, Aeras

Overview

TB can be considered somewhat neglected as it is not as well funded as HIV or malaria and needs increased donor investment in R&D, so the economic analysis is important for the case for investment.

Aeras is at an early stage in its thinking and is just putting together its access strategy, but would have like to have conducted some cost effectiveness analysis earlier to help inform R&D investment decisions.

Aeras convened 30 experts in TB epidemiology and economics to advise them on the research agenda. The expert group suggested three levels of cost-effective analyses: the first CEA is for the donor investment case, the second study when there is a profile of a vaccine candidate, will focus on donors and financing support for countries, and the third CEA will be for country decision–makers and will include the vaccine product and the delivery costs.

In terms of what would be good to do in the future, it is clear there is a need to move away from looking at preventive vaccines in a silo. Vaccines will not prevent the need for drugs and treatments, so immunization must work in tandem with other interventions.

How can cost-effectiveness analysis be conducted that combines the health impact of preventative vaccines, control strategies, diagnostics, etc. such that country decision makers do not have to choose between investing in control vs. prevention? One is not meant to replace the other, ultimately we want total impact.

IOM has been working on smart tool for decision makers, which will be available to LMIC, LICs and HICs to help them better understand and prioritize their decisions around health interventions. The breadth and depth of data required may be a barrier to use in LMIC and LIC countries though. Cost effectiveness is just one of the 50+ variables that go into decision-making and the tool makes comparisons across diseases and interventions. The tool is still in *beta* version, and it is hoped introduction to public health community will happen within the next year, much of the cost effectiveness data that PDPs are working on could help to inform this tool.

As well as the economic analysis, investors/donors want a market analysis and cost effectiveness analysis to help inform them about pricing, population impact…. etc.

5. MVI Case Study: Cost of Illness Projects

Farzana Muhib, MVI

Overview

Malaria treatment constitutes a large share of overall health expenditures in endemic countries (e.g. 18% in Rwanda and 25% in Kenya). Many studies focus solely on treatment costs and there is little data on indirect costs and household expenditures.

The objectives of this study were to estimate costs of both uncomplicated and severe malaria borne by health systems and households in Burkina Faso, Nigeria, Ghana, and Uganda. The sites were selected based on the existence of vaccine trials, disease burden, country economic profile and malaria context.

Study results have yielded data on current costs of illness from these four sub-Saharan African countries. Direct costs from: public and private, rural and urban, primary care and tertiary facilities, as well as indirect cost estimates for productivity loss are available. The study has also established relationships with local institutions and researchers and local ownership and capacity building.

Some lessons learnt from the process on country level capacity and buy- in were discussed. There were issues arising from the fact that despite development of a common protocol - the variable definitions were not clear to all investigators and this complicated synthesis and comparability across countries. In future, the development of a common database will be important.

The study had difficulty comparing data to WHO CHOICE. In future it is important that data collected can be compared to the WHO CHOICE data and other cost of illness studies.

In the conclusions, the importance of collecting prospective data that captures key changes in the health system (e.g. national insurance schemes, AMFm etc.) in developing country settings was highlighted. As new interventions are introduced, it is also important to understand the potential impact on treatment costs.

5. DISCUSSION AND KEY ISSUES

Discussion arising from the case studies and previous presentations centered round the following key issues:

1. The Relevance of Cost Effectiveness Data for Decision - Making

- The question of what if the product/intervention is not cost effective, but there are other elements that cannot be valued has to be carefully framed towards the particular investor or stakeholder. The question and answer will not be the same to an international donor as to a country-level stakeholder. Separate conversations at multiple levels will need to take place and in the case of investment for donors, CE is one piece of a bigger picture that also begs the question “whose cost-effectiveness?”. The example of GeneXpert in India was given, which though it was found to be cost–effective, would completely deplete the country’s TB budget.
- In arguing for more efficacious but more expensive treatment, some interesting CE studies take into account cost to manage side effects from more cost-effective drugs. It is clear that the usefulness of CE studies depends on the client.

- Ultimately, a *whole package of value-for-money* argument is needed. CEA helps identify what the drivers are, which can be addressed by the global community.
- In the case of the Neglected Tropical Diseases, countries are not interested in investing and WHO is interested in the tool, not the cost. The donors are financing the development of the product, but not the procurement of it. Donors want to know how to best introduce a product in a certain environment for a given purpose – they are looking for cost effectiveness of a *strategy.*

2. Cost effectiveness Evaluation of the PDP Model as a Whole

- Beyond the cost-effectiveness of drug issues, is the question of CE of the PDP model as a whole. The paper by Moran *et al* [15]evaluated the role of PDPs and concluded that PDPs have been extremely effective in increasing the pipelines. However it could be interesting to look the additional benefit and incremental value that PDPs add over Pharma in product development and make the costs of developing drugs through PDPs transparent. It would be interesting to look at strategies to ensure that R&D carried out in the public interest is at cost of production plus small sustainable margin.

3. Country Stakeholder/End User Engagement with Models

- At country level, there are challenges in using even simple models (e.g. in Excel), thus it is important in the planning of a tool that it can, and is, used and not just on a website. It is also important that the assumptions in a model are transparent, and users and decision-makers need understand the variables that go into the models, the assumptions that are made, and how to deal with data that is not available. It was pointed out that 99% of models are propriety - and that the PDP models be openly available.
- David Dowdy is working on a user-friendly model for the TB Alliance, which will be openly available. The goal of this is to distill a more complicated model down to a user-friendly model for end users, who can enter select values (online tool in development).
- The PAHO PROVAC model is about building capacity – working on development of an integrated model, as well as training people to understand inputs and results generated.
- The Futures Institute has the IAVI model on their website and other tools are starting to be made available on line.
- In order for tools to be used successfully there must be training and continued support on why and when to use models. Funding for retraining is critical as well since there are so many turnovers in these institutions.

4. Implementation Funders' Forum - How to Ensure PDPs are Better Represented at Existing Fora

[15] Moran et al 2010. International health 2 pp 114-122

- As there is no Implementation Funders' Forum similar to the PDP Funders' Forum, is there some value in asking the PDP Funders, WHO and countries to come together and let PDPs know what their plans are and what they will be looking for in terms of economic analysis? Although there was some support for exploring this, it needs more discussion on the possible process.

5. Who is asking for Cost-effectiveness Data?

- Countries are very reluctant to share cost effectiveness data across borders. If Governments are not asking for CE data it does not mean they do not need the data, but that they may not know the questions to ask. Countries want assistance understanding merits (not necessarily CE) of using different first-line therapies. For the Ministry of Health (MoH) it is not a cost-effectiveness question but rather an implementation question – what is the cost of the strategy to introduce the product?
- For the FIND Sleeping Sickness diagnostic, many partners (e.g. donors, WHO) are asking for CE data but the most cost effective strategy is really what they want.
- In the case of reproductive health products, countries and donors ask for implementation strategies.
- It would be useful to have a short-run analysis that looks at implementation of existing products and longer term analysis to estimate what the case would be when a new product is introduced. Product introduction completely depends on the health system and there is a big difference between preventive and treatment products.

6. Ideas and Questions for Modeling Capacity

- Models do not necessarily take into account partial efficacy (of vaccines). It is important to evaluate with MoHs to what extent products will still have an impact with partial efficacy. IAVI and the Futures Group are doing work on partial efficacy models for HIV vaccines.
- Participants were interested in how to articulate the case for investing in extremely expensive R&D for vaccines vs. investing money in scaling up existing tools to get cases close to zero over time. There is reluctance among donors to fund second generation tools, so making the case for this is important.
- Valuation models rather than CE can demonstrate/make the case for one tool over another and the value of developing the product vs developing another one.
- It will be important to evolve thinking about 'packages of interventions' – a preventive tool or treatment can add additional benefit rather than selecting one over the other – so show global benefit of a new product as an addition to a package of interventions. E.g. Mass Drug Administration for Lymphatic Filariasis is not achieving elimination alone in some settings, so there is a need to be able to calculate additional benefit achieved from adding vector control.
- How could the incremental value of funding be looked at – what value donors can add on top of pharma funding – e.g. increase the speed of success, give leverage to push down price of product… etc.? Understanding this can help to make the case for public sector investment in R&D.

FUTURE WORK

- Modeling combined interventions is a major gap and a priority for future work. Moving towards packages of interventions including diagnostics, drugs, vaccines, insecticides, etc. will be important. When looking at costs and using tools, supply and delivery costs, cost savings from side effects and the cost of delivering multiple interventions need to be factored in.

- A Cochrane collaboration approach to vaccine reviews would be very helpful as there are certain methodological constraints, (lack of transparency, different methodologies, different questions/designs, etc.) which a level of standardization and quality criteria would address.

- Convening countries (through WHO) and donors (through the PDP funders group) to understand their plans and needs with regards to Cost Effective Analysis.