Box A  Cost-effectiveness analysis and economic production

Cost-effectiveness analysis (CEA) developed partly in reaction to ethical concerns about the implications of cost-benefit analysis (CBA). CBA values health improvements in money terms. If it is applied properly, it gives higher weight to health gains in people who earn more. CEA values each unit of health improvement equally regardless of the income of the recipient. Accordingly, production gains resulting from health interventions have not generally been included in CEA, although this is not by any means a universal practice.\textsuperscript{w1} We exclude them in this series for ethical reasons, arguing that health professionals and planners should seek to improve population health to the greatest extent possible for the available resources.\textsuperscript{w2} Questions of the impact of health actions on national income require interaction with other sectors of the economy. However, it is important to acknowledge that CEA provides only one, though important, part of the information set required to decide how best to allocate resources. In this series of papers, economic production concerns are most relevant to HIV/AIDS, where it has been argued that lack of action could even lead to the complete breakdown of societies.\textsuperscript{w3} This is discussed further in that paper.\textsuperscript{w4}

Box B: Economies of scope

We illustrate how shared costs or economies of scope were incorporated using the number of outpatient visits for each of the three antenatal (ANC) interventions from Box 1 as shown below.

<table>
<thead>
<tr>
<th>No.</th>
<th>Intervention</th>
<th>Description</th>
<th>Number of visits</th>
<th>Regimen as applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tetanus toxoid</td>
<td>Two tetanus toxoid immunizations</td>
<td>2</td>
<td>Two tetanus toxoid immunizations</td>
</tr>
<tr>
<td>2</td>
<td>Screening for pre-eclampsia</td>
<td>Blood pressure measurement for all pregnant women and urine examination for proteinuria and pre-referral care of pre-eclampsia and eclampsia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Screening &amp; treatment of asymptomatic bacteriuria</td>
<td>Screening of urine of all pregnant women at antenatal visits and treatment of identified cases with amoxicillin.</td>
<td>1</td>
<td>Amoxicillin 500 mg TID orally for 3 days.</td>
</tr>
</tbody>
</table>

The total number of visits for when all three interventions are undertaken simultaneously should not be a simple addition of the number of visits required by each individual intervention, i.e. $2 + 3 + 1 = 6$ outpatient visits. On the other hand, it is likely that only 3 visits are required to undertake the necessary activities. That is, in visit one, the first tetanus toxoid would be administered along with 1 blood pressure measurement to screen...
for pre-eclampsia. In the second visit, the second tetanus toxoid dose and another blood pressure measurement would be administered. In the third visit, the third blood pressure measurement along with the urine screening test for proteinuria and asymptomatic bacteriuria would be performed. Other cost items, such as those described in the regimen column are assumed to be independent. In this series, careful attention was paid to the identification of possible economies of scope as demonstrated here when combining individual interventions.

**Box C: Measuring the health impact of interventions undertaken simultaneously**

To illustrate how the health impact of interventions undertaken simultaneously is measured we use the example of the three ANC interventions from Box 1. The effectiveness of each individual intervention in terms of reducing cause-specific neonatal outcomes (the maternal health impact is excluded for the purpose of this example) is shown below. These estimates were determined from a systematic review of the literature in conjunction with expert opinion.\(^5\)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Neonatal outcome</th>
<th>Risk reduction on neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus toxoid</td>
<td>Deaths from tetanus</td>
<td>90%</td>
</tr>
<tr>
<td>Screening for pre-eclampsia</td>
<td>Deaths due to prematurity</td>
<td>15%</td>
</tr>
<tr>
<td>Screening &amp; treatment of asymptomatic</td>
<td>Deaths due to prematurity</td>
<td>10%</td>
</tr>
<tr>
<td>bacteriuria</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If we assume that the death rate from neonatal tetanus and prematurity is 4 per 1,000 and 11 per 1,000 live births respectively, and no current coverage exists for the above interventions, the cause-specific death rate and number of neonatal deaths averted per 1,000 live births with implementation of each of the individual interventions at 50% coverage can be estimated as shown in the table below using the following equation:

\[
\lambda_I = \lambda_N \times (1 - c \cdot e)
\]

where \(\lambda_I\) = hazard rate with intervention (e.g. death rate)
\(\lambda_N\) = hazard rate without intervention
\(c\) = coverage of the intervention
\(e\) = effectiveness of the intervention.
As both screening for pre-eclampsia and asymptomatic bacteruria impact on the same outcome (deaths from pre-maturity), however, we do not simply add the total number of neonatal deaths averted by each intervention to determine the joint impact of the three interventions, i.e. 1.8 + 0.82 + 0.55 = 3.17 deaths averted per 1,000 births. Evidence on the joint effects of other types of interventions\(^6\) suggests that where the interventions address the same outcome, the joint impact is best estimated by multiplying the individual relative risks. This is also consistent with other published modelling studies\(^7\). This is represented by the following equation and is shown in the table below for the current example.

\[
\lambda_I = \lambda_N * (1-c_1*e_1) * (1-c_2*e_2) * \ldots * (1-c_n*e_n)
\]

where \(\lambda_I\) = hazard rate with intervention (e.g. death rate)
\(\lambda_N\) = hazard rate without intervention
\(c\) = coverage of the intervention
\(e\) = effectiveness of the intervention.
the subscripts on c and e represent the number of the intervention.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cause-specific death rate with intervention</th>
<th>Number of neonatal deaths averted with intervention per 1,000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus toxoid</td>
<td>(4 \times (1-0.5^{*}0.9) = 2.2)</td>
<td>4 - 2.2 = 1.8</td>
</tr>
<tr>
<td>Screening for pre-eclampsia</td>
<td>(11 \times (1-0.5^{*}0.15) = 10.18)</td>
<td>11 - 10.18 = 0.82</td>
</tr>
<tr>
<td>Screening &amp; treatment of asymptomatic bacteruria</td>
<td>(11 \times (1-0.5^{*}0.1) = 10.45)</td>
<td>11 - 10.45 = 0.55</td>
</tr>
</tbody>
</table>

The joint impact of all three interventions is then determined by adding the number of deaths averted by cause, i.e. 1.8 + 1.33 = 3.13 deaths averted per 1,000 births. The approach described here is used for all combinations in this series unless there is evidence to suggest otherwise. This is consistent with the approach described above.

**Box D: DALYs and QALYs**

The Disability adjusted life year (DALY) is a summary measure of population health combing information on mortality and non-fatal health outcomes into a single measure.
It represents the population loss of years of full health due to disease and its consequences. Because it is the only summary measure for which consistent estimates are available across all parts of the world, it is a useful starting point for assessing the impact of interventions. Quality adjusted life years (QALYs) emerged from the health economics literature which needed to summarize the overall effects of interventions on health, accounting for changes in mortality and morbidity.

For cost-effectiveness analysis (as opposed to burden of disease calculations) the mechanics of estimating DALYs averted and QALYs gained are virtually identical. DALYs require subtracting the years of premature mortality without an intervention from the estimated years with it - the years of life gained. This is the same as the QALY calculation - years of life lived with the intervention minus years of life lived in its absence. Both measures weight each year gained somewhere between zero (death or equivalent) and one (full health) depending on severity.

The approaches differ only in the weighting system and the resulting interpretation. Respondents to questions designed to elicit weights for QALYs are asked to express their personal preferences for a state of health, and the individual preferences are summed and averaged to obtain an overall weight. Because one of the methods of eliciting these weights is said to be consistent with economic welfare theory, these weights have been called utilities. Respondents to questions for DALYs are asked to determine how bad a given state of health is in terms of what preference society should give to preventing or improving it. They are called disability weights.

People who prefer DALYs make no claim that the weights represent individual valuations of the welfare derived from different states, the claim made for QALYs. The weights for DALYs are said to represent the extent to which health is compromised by different outcomes. We prefer the DALY interpretation, though as argued above, the mechanics of calculating the two measures is the same. Another practical issue is that QALY weights have not generally been calculated from the responses of participants across a wide range of countries, something we need for our analysis.

DALYs accruing in the future to an intervention today are traditionally discounted at 3%. Age weighting is also used giving higher weight to DALYs averted during adulthood - ages 15-64. Because of these practices are somewhat controversial, all papers in this series use a 0% discount rate and no age weighting in the sensitivity analysis.

**Box E: Determining the null scenario**

The null scenario is derived by back-calculating the impact of current coverage of interventions. For a single intervention using the formula:

$$\lambda_N = \lambda_C / (1 - \text{c.e})$$

where $$\lambda_N = \text{null hazard rate (e.g. death rate)}$$

$$\lambda_C = \text{current hazard rate}$$
c = current coverage of intervention
e = effectiveness of the intervention.

As described in Box C, where interventions address the same outcome, the multiplicative form of the interaction is appropriate:

$$\lambda_N = \frac{\lambda_C}{(1-c_1.e_1) \times (1-c_2.e_2) \times \ldots \times (1-c_n.e_n)}$$

where the subscripts on c and e represent the number of the intervention.

We illustrate this back-calculation procedure using estimates of current coverage and effectiveness shown below for our three ANC interventions from Box 1.

<table>
<thead>
<tr>
<th>No.</th>
<th>Intervention</th>
<th>Current coverage</th>
<th>Risk reduction on neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tetanus toxoid</td>
<td>51%</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>Screening for pre-eclampsia</td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>Screening &amp; treatment of asymptomatic bacteruria</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Using the equations described above we determine the null scenario death rates due to neonatal tetanus and prematurity as shown in the table below.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Current cause-specific death rate per 1,000 births</th>
<th>Null cause-specific death rate per 1,000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus toxoid</td>
<td>Deaths from neonatal tetanus: 2.16</td>
<td>2.16 / (1-0.51*0.9) = 4</td>
</tr>
<tr>
<td>Screening for pre-eclampsia + Screening &amp; treatment of asymptomatic bacteruria</td>
<td>Deaths from prematurity: 10.22</td>
<td>10.22 / ((1-0.38<em>0.15)</em>(1-0.15*0.1)) = 11</td>
</tr>
</tbody>
</table>

The null scenario death rates are then used as the baseline to determine the health impact of interventions (Box C).

**Box F: Determining and interpreting the expansion path (or efficiency frontier)**

We illustrate using the earlier example of the 3 antenatal (ANC) interventions. The costs and effects of the 7 intervention scenarios (at a coverage level of 95%*) described in Box 1 relative to the do-nothing scenario are firstly determined as shown below.
The ratio of the costs and effects relative to the do-nothing scenario we label the average cost-effectiveness ratio (ACER). The first point on the expansion path is determined by choosing the scenario with the lowest ACER – in this example, tetanus toxoid with an ACER of IS$22 per DALY averted. To determine the next point on the expansion path we then determine the costs and effects of the remaining scenarios relative to the tetanus toxoid scenario, including only those interventions that give us additional health benefit, i.e. those with a positive incremental effect.

The ratio of the incremental cost to incremental health benefit compared to the previous step is the incremental cost-effectiveness ratio (ICER). The next point on the expansion path is the scenario with the lowest ICER – in this example, the combination of all three interventions with an ICER of IS$30 per DALY averted. Sufficient cost reductions result from combining the three interventions to make it cost-effective than all combinations of two. This process is repeated until no scenario provides additional health benefit.

The cost-effectiveness results can also be illustrated graphically as shown below with the solid blue line indicating the expansion path.
The overall interpretation is that from a scenario of doing nothing, and on the basis of cost-effectiveness alone, a decision maker would first purchase tetanus toxoid. If additional resources become available, screening for pre-eclampsia together with screening and treatment of asymptomatic bacteriuria would be added. It would only make sense to move to combination 5 if funds were not sufficient to move to 7, and there were no prospects of obtaining those funds. All scenarios that do not lie on the expansion path (indicated by the square boxes) are considered “dominated” i.e. they are less cost-effective than the scenarios on the path.

*For the purposes of this example. In the individual papers the costs and effects of the different scenarios are determine at all three coverage levels.

**Box G: Probabilistic uncertainty analysis**

Stochastic uncertainty analysis allows each parameter to vary between specified upper and lower limits of plausibility. A probability distribution is specified for each parameter, and costs and effects are computed randomly choosing one value of each parameter from its distribution. Computer programmes exist for repeating this many thousands of times, and the variation in cost-effectiveness ratios associated with the overall uncertainty in parameters can be estimated.

The assumption, however, is that parameters are not correlated with each other within or across interventions. We cannot assume this when we analyse combinations of interventions. For example, one draw might select a high price of labour. This high price must be used for all interventions using labour - e.g. the draw for those interventions is not random but perfectly correlated with the draw for the first intervention. If
distribution costs are high for one drug, they are probably high for all drugs.

The same is true for effectiveness but even more complicated is the fact that some parameters determining costs might be correlated with some that determine effectiveness. The currently available stochastic uncertainty tools allow a high price for a drug to be drawn from the specified limits of plausibility, but assume this is independent from the assumed level of adherence on the effectiveness side. This will not be the case where high prices reduce purchases, so reduce adherence to long term therapies. We are currently working on a tool to build in all possible correlations, but we are unaware of a tool that does this at the present time.\textsuperscript{w8,w9}

<table>
<thead>
<tr>
<th>Box H: Cut-points for cost-effectiveness</th>
</tr>
</thead>
</table>

In theory, cut-points emerge from the process of using cost-effective information to set priorities. The interventions are chosen in order of cost-effectiveness until all resources are used. The costs per DALY or QALY gained of the last intervention funded is, by definition, the cost-effective cut-point. In practice, information on the cost-effectiveness of all possible interventions is never available and relatively arbitrary cut-points are been used. The first global comparison of a large number of interventions in 1993 decided that interventions costing less than US$25 per DALY averted were extremely cost-effective, while those costing over $1000 were cost-ineffective.\textsuperscript{w10} No rationale was provided. The Australian and British governments have implicit cut-points for accepting medicines or technologies for public subsidy or provision of approximately 1 times GDP per capita and 1.8 time GDP per capita in turn, and one times GDP per capita is sometimes used in cost-effectiveness studies.\textsuperscript{w11} Recently it has been argued that societies are willing to pay much more than this to improve health\textsuperscript{w12} and, partly for this reason, background work for the Commission on Macroeconomics and Health suggested that interventions costing less than three times GDP per capita to avert each DALY were cost-effective.\textsuperscript{20} We have adapted these suggestions by categorizing interventions as highly cost-effective if they averted each DALY at a cost of less than the GDP per capita, and cost-effective at a cost between one and three times GDP per capita.

Cut points for the two regions were, in international dollars:

<table>
<thead>
<tr>
<th></th>
<th>AfE</th>
<th>SearD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-effective if less than</td>
<td>$4,728</td>
<td>$4,347</td>
</tr>
<tr>
<td>Highly cost-effective if less than</td>
<td>$1,576</td>
<td>$1,449</td>
</tr>
</tbody>
</table>

Reference List


Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003; 327:586.


