perspective paper

CHRONIC DISEASE

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A commentary on

Jha P, Nugent R, Verguet S, Bloom D, Hum R

"Chronic Disease Prevention and Control"

by

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1.0 Introduction

Jha and colleagues introduce the case for increased funding of five health interventions to control chronic disease in low and middle income countries: a 33% tax on tobacco; acute management of heart attacks with low cost drugs; prevention of heart attacks and stroke through salt reduction by a mix of voluntary manufacturing changes, behaviour change using mass media and other awareness raising campaigns; prevention of hepatitis B through immunisation; and secondary prevention of heart attacks and stroke through a combination of 3-4 drugs in a 'generic risk' pill[1]. The benefit/cost ratios range, in order, from 40:1 to 4:1.

The determination of priorities begins with a focus on the current and expected future burden of disease, as measured by deaths, avoidable mortality, and cost of illness. The 'very approximate' (*p5*, Jha et al 2012) discounted cost-benefit ratios are based on comparing a monetised value of a disability adjusted life year (DALY) with intervention cost. Evidence on interventions draws largely from the second Disease Control Priorities Project (DCP 2) (Jamison et al 2006), Copenhagen Consensus 2008 paper on disease control (Jamison et al 2008) and selected other literature with a reflection that the investments proposed reflect views of other similar exercises. The five CB ratios are subject sensitivity analyses of single and combined changes in the following assumptions; changing the discount rate from 3% to 5%, increasing all costs by 300%, and increasing the value of a DALY from $1000 to $5000.

The cost-benefit ratios are supplemented, to indicate a move to an 'idealised' version, that 'accounts' for the value of financial protection and 'nonfinancial' costs (e.g. transaction, organisational and administrative effort to implement the intervention). The 'accounting' is a categorisation that relies on: a) a literature review

[1] E.g. use of aspirin, a statin and an antihypertensive drug (Jamison et al 2008)

of various aspects of health system capacity and; b) a review of the (limited) evidence on costs and effects of the Chronic Care Model and its very limited adapted application to low resource settings. This, at least partly, influences the qualitative ratings based on the 'speculative' judgement of financial protection and 'nonfinancial' costs by the authors (*p32*). All interventions are argued to offer high financial protection with only the impact of 'capacity' differentiating the proposed interventions; tobacco taxation is considered to have low capacity requirements, a salt reduction programme to have medium capacity requirements and the others to have high capacity requirements.

The paper ends by calling for an increased role for donor assistance in controlling chronic diseases despite a concern that this 'may not be politically feasible in the short or even medium term' (*p53*). This role is charged to 'conduct research which makes the marginal costs of these affordable' (*p54*) and includes both more research and development of relevant health technologies as well as implementation research to close the gap between knowledge and action.

There is a real challenge in drawing together a justified list of priorities for funding in an area which is recognised as being both short of evidence in terms of geographical coverage and range of interventions evaluated (Suhkre et al 2012) and hampered by poor quality studies (Mulligan et al 2006). The paper by Jha and colleagues is therefore a valiant effort to put forward the case for investment in an area of human life that has a worrying future health and economic impact.

This perspective paper considers whether the best interventions for investing in the in the improvement of chronic disease are presented in the challenge paper. It considers: the influence analysis of burden of illness analysis might have had and should have; the construction and testing of BC ratios for the five interventions selected; and the approach taken to reflecting uncertainty. The paper ends by suggesting alternative interventions for the expert panel to consider.

2.0 The influence of burden of illness

The paper appears to reflect the premise that the decision problem should be framed in terms of the burden of disease and, having accounted for the size of burden, focus on the set of cost-effective interventions to reduce the burden (p30). However, focussing initially on disease burden is not the most appropriate approach for decision problem aimed at select interventions that will have most impact given resources. Counting the size of the epidemiologic or economic problem may indicate problems for which there are no solutions and could lead to distorted priorities as more cost-beneficial interventions might never even be considered (Williams 1999, Wiseman and Mooney 1998).

Beginning with benefit-cost ratios first is more appropriate as it is a solution focussed approach. It allows a fuller range of potential interventions to be considered regardless of the focus of disease. It is possible that the most cost beneficial intervention would also address the disease of highest burden, but not necessarily.

Having taken issue with an initial focus on disease burden, there appears to be a slight disconnect in the paper. Evidence presented points to mental health conditions having the highest economic burden under the cost-of-illness method and the second largest using the value of lost output method. However, no interventions are proposed for addressing this burden. By implication the authors may either have considered evidence on benefit cost for all mental health interventions to be less than 4:1 for or alternatively have adopted a very restricted definition of burden of disease or possibly applied a burden of disease approach inconsistently. I consider these options below.

The possibility that the benefit cost ratios for all mental health interventions are less than 4:1 is a moot point as the authors provide no evidence to support or refute this position. Evidence from DCP2 (Jamison et al 2006, p40) suggests mental health related interventions in the area of alcohol abuse lie cost around $600-800/DALY averted and that treatment for depression by drugs with episodic or maintenance psychosocial treatment) is roughly $900-3000/DALY averted. The detailed DCP2 chapter by Hymen et al (2006) suggested that treatment of depression with episodic treatment using older tricyclic antidepressants ranged (by World Bank region) between $478-1,288/DALY averted. More recent evidence suggests that several mental health interventions could be provided for under $1000/DALY averted in both sub-Saharan Africa and South East Asia. These include a bundle aimed at alcohol reduction (including tax increase, reduced access and tax enforcement), episodic treatment of depression with newer antidepressants (selective serotonin reuptake inhibitors) and treatment of epilepsy with older anti-epileptics at 80% coverage (Chisholm et al 2012).

Evidence presented in Jamison et al (2006, p41) further suggests that interventions to improve mental health compare well with some of the five interventions recommended. For example, legislation with public education to reduce salt content was shown to have a cost/DALY averted of around $2,000 and secondary treatment of AMI and stroke with a polypill to be around $700/DALY averted. It is plausible therefore, that benefit cost ratios of 4:1 or greater for mental health interventions may exist and be on a par with several of the interventions proposed.

Perhaps interventions to improve mental health are absent because the impact on mortality is comparatively low. There is a notable absence of cause of death attributed directly to mental health in Table 1 and a statement (p7) that “we focus chiefly here on changes in mortality ….. simply because it is far less likely to be misclassified than are the more subjective measures of disability”. Valuation of health benefits in the benefit cost ratio therefore only appear to account for disability averted when it is tied to cases of premature mortality. This suggests first that the burden and impact of disease is massively underestimated as highly morbid low mortality chronic diseases will be missing from any estimate of burden. Indeed Bloom et al (2011) conclude that cardiovascular disease and mental health conditions are the dominant contributors to the global economic burden of non-communicable diseases. Secondly, it implies a further restriction imposed by the particular burden of disease approach adopted – a removal of the possibility that cost-effective interventions aimed at alleviating conditions with lower mortality rates can be recommended. For a proposal focussed on best buys for reducing chronic

disease, this seems somewhat limited. It is a further reason why the investment proposals presented by Jha and colleagues are unlikely to reflect the best possible investment possibilities for reducing chronic disease.

With respect to the consistency, it is not clear how estimates of burden are used in practice to narrow down the most appropriate interventions. For example, a burden of illness approach based on mortality rates in Table 1 would suggest that ischemic and hypertensive heart disease should be the focus of all interventions. However, this is not the case as the selection of interventions is aimed at alleviating 3.2 million deaths from heart disease and stroke and 0.8 million deaths from cancer[2]. Use of avoidable mortality might explain the discrepancy but these data are not provided by disease and the influence of this approach is therefore unclear. Another explanation might be that burden of disease has not been the lens through which cost-effective interventions are selected. However, if this were the case, it doesn't explain why so much information on burden of disease is presented without reference to the impact of health interventions or why some potentially cost-effective treatments of chronic diseases appear to be missing. If this reason is correct however, it would seem more important to provide an explanation justifying the exclusion of 'near miss' interventions in terms of benefit cost ratios or the other criteria used by the authors.

2.0 Construction and sensitivity of the BC ratios;

'Indicative' BC ratios are presented in Table 7 of the challenge paper with details of calculation presented in the text and sensitivity analysis in the Appendix. Reflecting past research on immunisation for hepatitis B (Brenzel et al 2006; Sanderson 2005) I opted to replicate and reconsider one of the options, using the approach presented in the paper. Column 2 of Table 1 shows the replication. This indicates a 7:1 ratio which, through the rounding in Table 7 and further recalculation to reflect the rounding was increased by the authors to 10:1 (Verguet, personal communication). The replication therefore satisfactorily reflects the assumptions of the challenge paper.

The assumptions specific to the hepatitis B vaccination option were that:
a) cost per vaccinated child was $3.6, reflecting a study of India's national hepatitis B vaccination programme[3];
b) all benefits would occur 40 years after immunisation;
c) of the 600,000 annual deaths from hepatitis B reported by WHO, a quarter were considered avoidable by increasing global vaccination rates from 75% to 100%.

While vaccine effectiveness was referred to as 75 and 95%, the increase from 75-100% coverage appears to implicitly assume 100% effectiveness as all 150,000 deaths were considered avertable. All other assumptions (e.g. value of a DALY

[2] Given a rather unrealistic assumption that mortality gains from tobacco tax are split equally between cancer and heart disease.

[3] Not in references or obvious from a quick search on google. Perhaps it is a different reference or unpublished?

averted, discount rate, DALYs lost per death) were constant across investment options.

In reviewing the benefit cost calculations three questions arose; why were particular data and assumptions adopted?; how valuable was the sensitivity analysis in exploring these issues?; and what is the potential impact of adopting different assumptions?. Little justification was provided for the HBV-specific parameter values. As the sensitivity analysis only evaluated generic assumptions across all options, no sensitivity analysis considered the impact of option-specific assumptions. Therefore little consideration was given to the possibility that the BC ratios might change in relation to each other. If one (or more) intervention could move significantly closer to another, differences between options diminish and this could be of decisional importance. As it is relatively easy to choose alternative assumptions to effect change in these BC ratios, the reasoning for choosing alternative values is important. Therefore this quick reanalysis reflects sources the authors have cited, and applies health sector specific evidence to well versed economic arguments (i.e. rising marginal cost to achieve maximum coverage) to support four cumulative analyses:

For achieving more favourable BC ratios

1. Used mean cost from Brenzel et al (2006) referenced in challenge paper (range $2.02-$2.37) and inflated to the publication year for Indian cost data used in base case. New cost was $2.7 per vaccinated child.
2. No amendment made for avoidable mortality as assumptions already appeared favourable (future burden likely to decline given increasing hep B vaccination rates and assumption of 100% efficacy)
3. Used a slightly older coverage rate of 64% vaccine coverage from Duclos et al (2009). While out of date, the % will reflect the position for some countries.
4. Assumed benefits occurred in 30 rather than 40 years.

For achieving less favourable BC ratios

1. Doubled cost of achieving last 10%-point increase in coverage to achieve 100%[4] from $3.6 to $7.2 per child vaccinated for (the effective average cost increased to $5.04 from 75-100% coverage)
2. Used assumptions on avoidable mortality from Brenzel et al (2006)
3. Assumed increase of 3% in global coverage rates since 2010.
4. Assumed benefits occurred in 50 rather than 40 years.

Results for the final cumulative step are given in Table 1. The more favourable assumptions move the BC ratio from 7:1 to 9:1 and 13:1. The less favourable assumptions move the BC ratio from 7:1 to 5:1 to 4:1, 4:1 and finally to 3:1, which is on a par with the generic risk pill. Further investigation of the impact of alternative option-specific assumptions for the four other interventions may reveal a credible alternative positioning of BC ratios, both in absolute and relative terms.

3.0 Treatment of uncertainty

The challenge paper refers to uncertainty[5] in a number of ways: the size and shape of the future tobacco hazards (*p14*); more misclassification of morbidity compared with

[4] Johns and Baltussen (2004) showed that marginal costs rose by 70-100% roughly double for achieving the last 10% coverage of a hygiene outreach programme

[5] This should be distinguished from variation for which further information could not increase precision as heterogeneity in patient (e.g. age, severity of disease, health outcomes) or health system (e.g.

mortality statistics; methodological uncertainty about completeness of data (*p30*), age weighting and discount rates (*p27*); in effective interventions to prevent elevated blood pressure, blood lipids, and diabetes (*p43*); and adherence to the polypill (*p44*). To reflect this, the BC estimates are referred to as 'indicative' and parameters to being a 'ballpark idea' (e.g. of the economic cost at the macro level (p14)). In each case further information on these issues would reduce uncertainty and provide more precise estimates.

The challenge paper concludes that, given the "often broad ranges in CE ratios, and hence in BC ratios, it makes little sense to conclude with precise estimates or with attempts to quantify statistical uncertainty around the point estimates" (p30). While there may be little possibility, given the uncertainties noted, of providing precise estimates, the conclusion that quantification of uncertainty should therefore be avoided is a little hasty. Indeed, its avoidance may result in inappropriate recommendations.

Briggs (1995) showed clearly that knowing the precision of an incremental cost-effectiveness ratio can affect the decision about which intervention to implement and indicate that the choice may differ from that implied by point estimates. For example, in Figure 1 a decision maker with a willingness to pay of £10,000 per quality adjusted life year (QALY) might prefer intervention C, which has a higher point estimates, over either A or B, due to the relative precision of its incremental cost-effectiveness ratio. Since this work, much progress has been made in defining, measuring and interpreting uncertainty in the context of using economic evaluation to aid both adoption decisions as well as defining the need for further research. It has also led to much greater emphasis on the systematic search, review, methods for eliciting expert opinion and analysis of evidence that influences the choice of parameter estimates in economic evaluations of health interventions (Griffin S and Claxton C 2011).

As uncertainty in both costs and effects can vary by intervention (e.g. Sassi et al, 2009) it is possible that the BC ratios presented in the Challenge paper could be differentially affected by uncertainty. While it is unusual for uncertainty to be reflected in BC cost ratios, the analysis of benefit by Jha and colleagues relies heavily on the value of DALYs averted and is not intrinsically different from the majority of economic evaluations presented in the health sector. Therefore analysis of uncertainty could be expected.

4.0 Evidence to substantiate, refute and counter the priorities recommended

Two exercises designed to help encourage and guide investment decisions for controlling chronic disease have recently been published. The WHO produced three related reports (WHO 2011a, 2011b, 2011c) outlining the 'best buys' for controlling chronic disease and detailed the costs of scaling up the proposed interventions (to a level where 80% coverage is achieved within 15 years). A 'best buy' was considered

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price) characteristics refers to real differences. Jha et al mention additionally variation in prices, scale of the intervention and epidemiological environment (*p30*).

to be an intervention that averts one DALY for less than the average annual income per capita but is also considered "cheap, feasible and culturally acceptable to implement"[6].

As Jha et al state, all five interventions proposed are, at least partially, reflected in the listing of 'best buys'. As such this serves as an important corroboration of the value of their investment proposal. However, there are two caveats to accepting this. First, further inspection of the 'best buys' indicates that several other interventions could have been selected, but the challenge paper is silent on both their non-selection and the reasons for their non-selection[7]. The missing interventions include entire areas such as controlling alcohol[8, 9,] as well as competing alternatives for addressing the risk factors already attended to[10]. Secondly, the reference point for these WHO reports was a focus on "four diseases; cardiovascular disease, cancer, diabetes and chronic respiratory disease….(which are) largely caused by four shared behavioural risk factors; tobacco use, harmful alcohol use, physical inactivity, and unhealthy diet" (WHO 2011c, *p10*). Therefore, confirmation is less convincing as a case for accepting that the best investments have been presented in the challenge paper, as good alternatives may exist outside of these disease areas.

A second exercise conducted by WHO has focussed on the cost-effectiveness of over 500 single or combined interventions for the prevention and control of non-communicable diseases and injuries in countries in sub-Saharan Africa and South East Asia that have high adult and child mortality (Chisholm and Saxena 2012, Chisholm et al 2012, Ginsberg et al 2012, Ortegón, Lim, Chisholm and Mendis 2012, Ortegon et al 2012, Baltussen and Smith 2012). This is interesting for a number of reasons: the analysis extends beyond the disease areas of the challenge paper and the 'best buy' analysis, including road traffic injuries, mental health, and sensory loss disorders; it provides a more accountable and direct comparison of a broader range of interventions; and, for the interventions that are not dominated[11] (within disease clusters), a probabilistic cost-effectiveness analysis indicates some degree of the uncertainty. However, there are still limitations with using this analysis as a critique

[6] This contrasts with 'good buys' which are other interventions that may cost more or generate less health gain but are still considered to provide good value for money.

[7] The need to select is, however, clear as the total cost of the package was expected to be $170bn with an average annual cost of $11.4 billion per year.

[8] Restricting access, enforce bans on advertising, raising taxes on alcohol, monitoring, advocacy/support.

[9] The authors have explained (personal communication) that excess deaths in Russia can be linked clearly to binge drinking but that the net effect in other populations is less clear. This decision is another link to the impact of linking morbidity only to mortality.

[10] For diet, these include promoting public awareness about diet and physical activity, replacing trans fat with polyunsaturated fat. For tobacco it includes smoke-free indoor workplaces and public places, health information and warning, bans on advertising, promotion and sponsorship. Other possibilities to reduce CVD and cancer risks not presented include; screening in primary care for CVD risk, counselling and multi-drug therapy for individuals with >30 CVD risk, prevention of cervical cancer through screening and lesion removal.

[11] An intervention that is more costly or less effective than other more efficient interventions

of options presented in the challenge paper. For example, the analysis is restricted to two WHO regions, one intervention proposed by Jha et al is excluded entirely (hepatitis B vaccination[12]), and the drug based interventions proposed in the challenge paper are potentially grouped slightly differently[13].

This second exercise, led by Chisholm, provides strong support for increasing tobacco tax as it is a particularly cost-effective intervention for both WHO regions (see Table 2). However, salt reduction and all salt based interventions were dominated by other options (within their disease/risk factor cluster), as was treatment of AMI with aspirin, ace inhibitor and beta blockers and all of the, drug therapy based, secondary/tertiary prevention of myocardial infarction. This indicates that other interventions could achieve greater DALY gain per $ spent.

Chisholm et al (2012) note that, compared with all other interventions for controlling chronic disease, "antibiotic treatment of chronic otitis media (a persistent inflammation of the middle ear) is the most cost-effective intervention in the two regions (<$Int100/DALY saved), while extraction of cataracts and proactive screening for hearing loss are among the biggest contributors to population health gain". The detailed results are provided in Table 3 and it can be seen that, even in comparison with tax increases for tobacco, these interventions are more cost-effective. However, with a population of 2 million needing cataract surgey in Africa and 4.2 million in South East Asia (Baltussen and Smith), the annual treatment is unlikely make a significant dent in the hypothetical budget facing the Copenhagen Consensus Panel if the number of interventions as restricted. However, this is unlikely to be the case for an intervention such as treatment based on absolute risk of a cardiovascular event in next 10 years with statin, diuretic, β blocker, and aspirin for cardiovascular risk of 5% (CVD-11). In this case, annual DALYs saved per million population is 3,163 at a cost of Int$ 0.33 per capita and both an average and incremental cost-effectiveness ratio of Int$104 per DALY averted.

5.0 Conclusion

Whether an additional investment of upto $75 billion should comprise the five interventions proposed by Jha and colleagues is a moot point. There are a number of reasons to suppose other interventions could provide a better return, such as cataract surgery, antibiotic treatment for otitis media and primary prevention of CVD. However, the cost-effectiveness analysis on which the latter suggestions are made do not account for the level of health system support needed. Jha et al do discuss this at length and it would have been interesting to see both a quantification of health system support needed for the proposed interventions as well as understanding why this would not support the range of alternative interventions highlighted in the recent series of BMJ papers led by Chisholm.

[12] Because treatment of liver disease was considered not to have strong evidence of effectiveness and aspects of prevention of hepatitis B and cirrhosis were 'covered' already in some of the alcohol interventions evaluated (Ginsberg et al 2012).

[13] This isn't entirely clear as the WHO based analysis does allow combinations of therapies.

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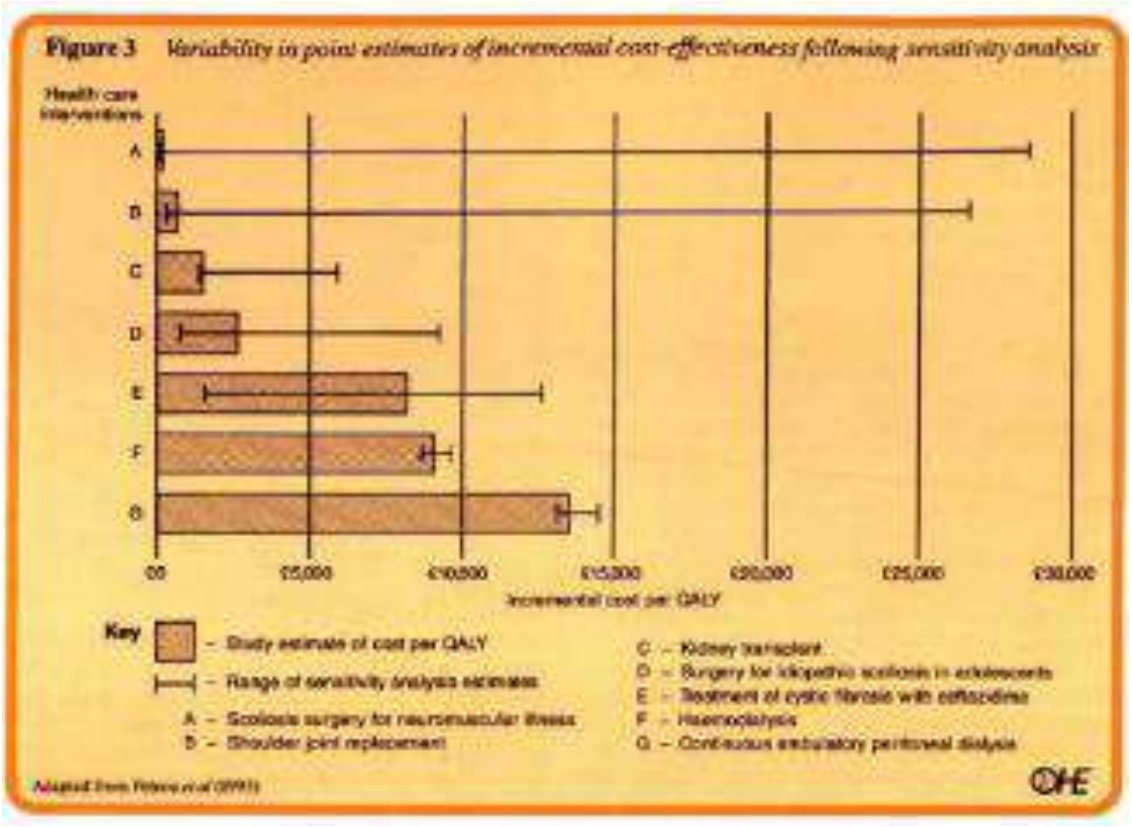
Figure 1: Variability in point estimates of incremental cost-effectiveness following sensitivity analysis



Source: Briggs (1995)

Table 1: Replication and extension of Jha et al estimate for hepatitis B vaccination

	Jha et al estimates	Less favourable assumptions	More favourable assumptions
Birth cohort	136,000,000	136,000,000	136,000,000
Average cost vaccination	3.6	4.6	2.7
Annual cost of vaccinating all children	489,600,000	625,600,000	367,200,000
Proportion vaccinated	0.75	0.64	0.75
New proportion to be vaccinated	1	1	1
1% linear cost	4,896,000	6,256,000	3,672,000
Extra % coverage re expected cost	122,400,000	225,216,000	91,800,000
Deaths from Hep B	600,000	1,400,000	600,000
Deaths assumed potentially savable from HBV given current and future vaccination coverage	150,000	176,400	150,000
DALYs lost per death	20	20	20
DALYs	3,000,000	3,528,000	3,000,000
Value of death/DALY averted	1,000	1,000	1,000
Value of death averted	150,000,000	176,400,000	150,000,000
Value of DALY averted	3,000,000,000	3,528,000,000	3,000,000,000
Undiscounted B:C ratio (death)	1	1	2
Undiscounted B:C ratio (DALYs)	25	16	33
=1/EXP(r*n)	0	0	0
discounted deaths (3%, 40yrs)	45,179	39,360	60,985
discounted DALYs	903,583	787,203	1,219,709
Discounted value deaths	45,179,132	39,360,160	60,985,449
Discounted value DALYs	903,582,636	787,203,205	1,219,708,979
Discounted B:C ratio deaths	0	0	1
Discounted B:C ratio DALYs	7	3	13

Table 2: Costs and effects of a 50% increase in tobacco tax (from 40-60%)

	WHO Africa Region	WHO South East Asia Region
Annual DALYs saved per million population	687	3,043
Annual cost per capita (Int $)	0.31	0.27
Average cost-effectiveness ratio (Int $)	448	87
Incremental cost-effectiveness ratio (Int $)	448	87
Sensitivity	horizontal ellipse stretching from roughly Int$ 0.1-0.7 per capita and 200-1,2 DALYS averted per year per million population (i.e. most uncertainty with effectiveness)	horizontal ellipse stretching from roughly Int $0.1-0.9 per capita and 1,200-5,500 DALYS averted per year per million population (i.e. most uncertainty with effectiveness)

Source: Ortega et al (2012)

Table 3: Costs and effects of 2 alternative interventions for investment

	WHO Africa Region	WHO South East Asia Region
Costs and effects of achieving 95% coverage of antibiotic treatment for otitis media		
Annual DALYs saved per million population	670	634
Annual cost per capita (Int $)	0.01	0.01
Average cost-effectiveness ratio (Int $)	20	15
Incremental cost-effectiveness ratio (Int $)	63	24
Sensitivity		
Costs and effects of achieving 95% coverage of cataract, extracapsular cataract extraction with posterior chamber lens implant		
Annual DALYs saved per million population	5,486	6,447
Annual cost per capita (Int $)	0.64	0.63
Average cost-effectiveness ratio (Int $)	116	97
Incremental cost-effectiveness ratio (Int $)	116	97
Sensitivity	Probabilistic analysis undertaken but no results given in paper	Probabilistic analysis undertaken but no results given in paper

Source: Baltussen and Smith (2012)