# SETTING PRIORITIES IN HEALTH RESEARCH USING THE WORLD HEALTH ORGANISATION MODEL: DEVELOPMENT OF A QUANTITATIVE METHODOLOGY USING TUBERCULOSIS IN SOUTH AFRICA AS A WORKED EXAMPLE

By

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Supervised by

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Minor Dissertation for the degree of

**MASTERS IN PUBLIC HEALTH**

**(SPECIALISING IN HEALTH ECONOMICS)**



At the

**Health Economics Unit,**

**University of Cape Town**

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## Template for submission of dissertation corrections/revisions

| | |
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| **Candidate:** | Mr Damian Hacking |
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### Examiner 1 – (Give name of examiner if known)

| | Original dissertation | | Corrected/Revised dissertation | |
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| 1 | Coment 1, Contents page | • Unfortunate that the Table of Contents ended up with error messages in lieu of page numbers. Probably a function of converting from MSWord to pdf. | Now on pg BB | Table of contents has been amended to prevent this error |
| 2 | Comment 2, pg 11 | • P. 11, "Decide upon stakeholder composition". Of note was lack of emphasis on the funders of health research. One could argue that funders are typically the target audience of such exercises – it is they who have to be convinced of the legitimacy of the exercise. Thus, representatives of funding agencies would typically be a key group to involve in a priority setting exercise. | Now on pg BB | More emphasis has been placed on the importance of funders as the key decision makers: *"Decision makers in health research priorities are principally two agents, the researchers themselves, and the governing bodies who enable them to do the research (research funders are a particularly important part of this group). So while these two are obvious candidates, a broader stakeholder participation in priority setting is also vital for various reasons, from philosophical beliefs that society should have a say in the direction of research, to ensuring that there is buy-in from the participants who may be the object of the research. Furthermore…"* |
| 3 | Comment 3, pg 12 | • P. 12, section 1.2.3. Arguably, the plan for translating priorities into research should be put into place before the priority setting exercise. A priority setting exercise may turn out to be entirely useless if, ex-post, it is found that funders do not "buy in" to the priority setting exercise. So the plan for turning a priority setting exercise into research funding, and research, needs to be established ex-ante. Related to the previous point, this may involve including research funders in the priority setting exercise / process. | Now on pg BB | This is a good point, and I wholeheartedly agree with the reviewer, but it is currently not an explicitly stated component of any priority setting exercise. Because section 1.2 is on how research priorities are currently set, and not how they should be set, no revisions were made to this section. |

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| 4 | Comment 4 & 7 pg 15 and | deliver curative care for ear infections, for example). And related to the second-to-last paragraph on p. 15, research that improves, for example, the delivery of vaccines (for example, by having community health workers deliver them, rather than fully trained nurses) would impact not only on the efficiency, but also the cost-effectiveness. In short I agree that there are many problems with the sub-divisions in the model.<br>• Must express concerns about starting with a disease-specific lens. While the TB example might suggest otherwise, is this not likely to lead us towards "vertical" rather than "horizontal" research questions. How would you ever address questions like:<br>• What is the appropriate health budget envelope for country X (i.e. health vs. other sectors);<br>• How best do you incentivized CHWs to provide a basic package of interventions; … | | The ability of health systems to change cost-effectiveness has been made more explicit in section 1.4.3 "…however it does not take into account that the improvements in the health system might change the ~~effect use of a non-cost effective intervention has, thus increasing its cost-effectiveness~~cost-effectiveness of a non-cost effective intervention as these figures are often modelled on certain premises of the health system."<br>This is a good point, the model does not capture the potential gains in pure health systems research. One potential solution to this would be to sum the results of ALL diseases to get an idea of the total contribution health systems research could make. Otherwise it is just a limitation of the model<br>Furthermore, the disease specific concern has been addressed in the discussion of the manuscript as follows "A final limitation to the model is the potential for a disease-specific lens being used to define research priorities, as this would exclude pure health systems research. ~~However, this can~~This could be addressed by summing all the subsections of the amended WHO model across all diseases analysed to get a general idea of how much health systems research is required relative to basic research and biomedical research, however the validity of such a simple summation is unclear. " |
| 5 | 5 | • P. 17. I'm not at all sure that it is true to say that "a detailed methodology to quantify efficacy of interventions…" is true. In fact, much of clinical epidemiology (and clinical trials) is geared towards doing precisely this. Perhaps this statement is somewhat more true if one considers public health and health systems interventions – although I would still argue that you are on somewhat shaky grounds with this assertion. | | Agreed. This assertion has been removed: "We will therefore adapt the WHO model axes to more readily incorporate comparable data, and develop a unique methodology for constructing and subdividing the box." |
| 6 | 6 | • P. 19. I think use of the term stakeholders is somewhat misleading. I commenced reading this section thinking it would tell me how different "stakeholders" contributed to the development of the methodology, or the TB case example. Instead, it is a description of the target audience. I think this section is very important. I would have argued that it probably needs to be somewhat more nuanced. Is a single model suitable for all of the stakeholders? Do they all have the same primary goals for a research prioritization exercise (I would argue strongly that they do not.) And given that they do not, who was the primary stakeholder group, or target audience, that you had in mind as you went about writing up the thesis. My sense is that the primary target audience is probably that listed in the second-to-final paragraph – research institutions / universities. | | Section 4 title changed to "Potential Impact" and 4.1 to "Target Stakeholders". An additional paragraph has also been added at the end of section 4.1: *"Because this is a heavily methodological dissertation, and because the methodology only broaches one particular component of the priority setting process, it is the priority setting institutions initially listed which will primarily be interested in the methodology developed in this dissertation. These groups also have impact on all the other stakeholders listed above, and are more frequently consulted by the stakeholders above on priority setting. Nevertheless, some of these stakeholders will have their own priority setting exercises, and hence it is still important to target them.* |

**Commented [SC1]:** Some error in this sentence?

**Commented [SC2]:** Yes, this is possible, but I don't know if it would work. There might be added value to a health systems intervention that is not associated with a simple summation (it might be a multiplicative function). So I think that it needs to be stated as a strong limitation of the model, and of many priority setting exercises where diseases or programmes are taken as the starting point

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| 7 | 8 & 9 | • Interesting questions regarding the extent to which you allow current (or perhaps slightly dated, or perhaps extrapolated from other countries) data on burden of disease drive research. What if you instead have forward looking research questions, for example, about how to best prepare for climate change or new / emerging diseases; how does an LIC prepare for a future wave of chronic illnesses or diseases of the elderly. One needs to invest in such research in a "preventive" manner… but this does not fit nicely with any of the research priority setting processes.<br>• P. 38. Ah, here I see expressed my concern about the uncertainty of research needs in the future! Well done. | | This is true. One could use speculative DALY data, where available, to make predictions about the future needs of research. Because this is addressed, as noted by reviewer, no amendments made. |
| 8 | 10 | • P. 40. I'd be cautious of any assertion that priority setting exercises have led to better health in the countries where they have been conducted. I suspect that this is a piece of quantitative research that still needs to be done! Problematic is that there are likely to be many confounding factors – I suspect that countries that embark on research priority setting exercises are wealthier, more likely to be democratic, more likely to have freedom of press, more / better quality higher-level education institutions. | | Agreed, that there is very little thorough evidence of the benefits of priority setting, in part due to the lack of investigative studies. Wording has been changed to reduce the assertiveness of this claim *"Nonetheless, even with this limitation, it appears to be better to base allocation of resources according to an imperfect priority process, as opposed to no process, as evidenced by marked improvements in health in those countries which successfully set priorities [16]. Unfortunately this is an area where very little evaluation has been done, and so the strength of argument is largely intuitive and not empirically based."* |
| 9 | 11 | • P. 42. Figure 1.1 Be careful to label the y-axis (in the two disease specific examples provided) as DALYs per person. | | Labelling corrected |
| 10 | 12, 16, 17, 20 | • P. 47. Section 4.3.4. Consistency of language – the title of this sub-section is cost-efficiency, but then the term cost-effectiveness is used throughout. Links back to the general comment that definitions of efficacy, efficiency and effectiveness should be made clear somewhere early in the paper.<br>• P. 62. For my purposes, I think that a working definition of efficiency needs to be provided. In economics terms, efficiency and cost-effectiveness mean almost the same thing, do they not? That is, they are both about minimizing wastage – having the greatest impact using as few resources (usually monetized) as is possible. But here, I think that efficiency is being used to describe some combination of coverage, provider compliance, patient compliance… all proximal outcomes that might be improved for health policy and systems research. GIVEN THE TERMS EFFICIENCY AND COST-EFFECTIVE(NESS) ARE CENTRAL TO THE DESCRIPTION OF THE WHO MODEL, AND USED REPEATEDLY, I WOULD STRONGLY SUGGEST THAT AUTHORS PROVIDE CLEAR DEFINITIONS, BOTH IN THE THESIS DOCUMENT AND IN THE MANUSCRIPT.<br>• P. 62, in the first para on problems with the WHO model, you use the terms cost-efficiency and cost-effectiveness, which given my baseline confusion, makes me more confused.<br>• Figure 10, I am really having problems with this differentiation between efficiency and cost-effectiveness. | | Section 4.3.4 amended to cost effectiveness.<br>All referrals to 'cost-efficiency' have been amended to either 'efficiency' or 'cost-effectiveness' to reduce ambiguity.<br>An additional paragraph has been added to section 2.3.1 to outline these differences in the initial description of the WHO model: *"It is important to note that the WHO model differentiates between 'efficacy', 'efficiency' and 'cost effectiveness'. In this context, efficacy refers to the ability of the interventions to treat a disease. ~~given the current context of the health system.~~ Efficiency on the other hand, refers to the~~is~~ context under which the intervention operates, and the degree to which it can help, or hinder, the efficacy of the intervention Importantly, the model assumes that a more efficient health system will only impact the number of people receiving the intervention, and not the efficacy of the intervention (~~for our definition we will assume that increases in efficiency can also increase the efficacy of an intervention).~~ Finally, cost-effective refers to a particular subset of the* |

**Commented [SC3]:** Very nice

**Commented [SC4]:** Intuitively, I don't think that these definitions are the same as the ones that I have in my head where:

Efficacy means "it works"
Efficiency means either doing the right thing (allocative efficiency) or doing the right thing in the right way (technical efficiency)
Cost-effectiveness means: allocating resources such that health is maximised.

Effectiveness is normally also in this list, and this means it can work in practice or in context.

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| | | | | *health system, namely that of financing.Again, the model assumes that more expensive drugs do not have a higher efficacy, but rather are more able to reach the population (~~again, we will assume that more expensive drugs might also have a higher efficacy, even if the cost per unit of efficacy is much higher).~~ For example, a drug may have an efficacy of 60% and a population coverage of 50% in a rural population in a low income country. Using a better drug in the same context would result in an efficacy increase. Improving the route of administration of the drug would increase the population coverage and hence improve the efficiency of that intervention. Using a more expensive drug, that has the same efficacy~~same efficacy~~ but is more stable and hence can also reach a larger population, is a change in the cost-effectiveness."* I understand that these are not the intuitive definitions of the three terms, but in the context of the model this is what they appear to be referring to. No definitions of the three terms are given in the original paper. |
| 11 | 14 | • P. 60. The description of the background (in the abstract) feels relatively lengthy. I think the results section could be made clearer. What is clear is that potential DALYs improved with improvement of the intervention (at 96.3%) is not mutually exclusive from DALYs that could be averted with existing but non cost-effective interventions (56.9%) add to greater than 100%. While the reason for this will become clearer in the main paper, I think the results will be confusing for readers coming to the paper afresh. (You've addressed the problem in the WHO model of mutual exclusivity, but I fear that this may not be entirely intuitive to readers.) | | Background was shortened a little bit: "***Background:*** *Setting priorities is important in health research as there are limited resources available for research. Various guidelines exist to assist in the priority setting process, however priority setting still faces significant challenges, such as clear ranking of identified priorities…"*<br><br>Results were also rewritten slightly to make it clearer "***Results:*** *The amended model shows that South Africa has a TB burden of 1 009 837.3 DALYs. 0.009% of DALYs are unavertable with existing interventions, 96.3% of DALYs could be averted with improvements in efficiency. Of the remaining DALYs, a further 56.9% could be averted with existing but non-cost-effective interventions."* |
| 12 | 15 | • P. 61. In a manuscript, figures should be referred to sequentially throughout the paper – the first figure referred to should be figure 1, not figure 8 (… in retrospect I do appreciate that they were numbered sequentially throughout the thesis!). | | Figure numbering has been retained for the purposes of the dissertation, but will be amended when submission to the journal occurs |
| 13 | 18 | • P. 62, I do think the point about adapting the axes so that the figure represents the total burden of disease is a highly important one. A weakness of the paper is that, by focusing on a single disease (TB) rather than comparing between two or more different diseases, I do not think the revised model fully addresses this weakness. | | Agreed. A comparison between different diseases could be made, and ultimately with the adoption of the model SHOULD be made, relatively easily. Tuberculosis as a worked example was just used as a proof of concept of the methodology. The figure on 110 give an idea of what research fields within TB should be prioritised, and in to what degree, but yes would ideally need to be compared to other |

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| | | • p. 110 highlighted to me that the proposed figure (used here for Worked example: Tuberculosis) really is not very meaningful in the absence of comparator figures for other diseases. That is, this figure alone gives me no sense as to whether investment in TB research (relative, for example, to research on malaria or on community health workers) is a "good buy". | | disease profiles in an actual priority setting exercise using this model. |
| 14 | 19 | • P. 64. What deserves discussion is that DALYs unavertable is not just a function of available interventions… it is a function of social-determinants of health (e.g. literacy and road infrastructure and nutrition) as well as things that you may not be able to effect (e.g. climate, exposure to migratory animals, etc.). | | This has been discussed more thoroughly: "The resultant quadrangle was assumed to estimate that portion of the DALYs unavertable with existing interventions, as these are the best figures that any country has been able to achieve. However, even in the best performing countries used to construct this estimate there are other determinants of health, such as climate. These factors may prevent optimal treatment of a disease (e.g. monsoons) or assist in the treatment's efficacy (e.g. warm climates). Thus there is a degree of uncertainty around the estimate." |
| 15 | 21 | • Okay – so some major assumptions. The total area that can be reduced through existing but non-cost effective interventions was calculated using a ratio from DCPP for all intervention types, not just for TB? Secondly, in both methods used in Step 3, the assumption is made that the ratio between the axes remains fixed… seems a strange assumption, as intuitively, for example, I would have thought health policy and systems research to have a greater impact on prevalence + incidence than on DALYs per person. Am I wrong-headed in this thinking? | | No, the ratio was calculated just using the TB interventions of the DCPP report. Thesis was amended to clarify this: *"The degree of the disease which is avertable using existing but non-cost-effective interventions was calculated using TB cost-effectiveness data from the Disease Control Priorities Project report [11]. This report models efficacies of current treatments for TB in 6 global regions…"*<br><br>Intuitively, the reviewer is probably correct, but in the absence of any hard data to support this, the ratio was not changed. |
| 16 | 22 | • P. 66-67. I suspect that for a journal submission, authors are going to run into a problem of excessive word-count, but perhaps I am wrong. For me, within the results section, there is too much discussion about the robustness of selecting DALY pp and prevalence & incidence data from one country vs. another. I think readers will quickly become lost in these lengthy paragraphs. Leave much of this for the discussion section – a short description of strengths and weaknesses of the model. | | The Health Research Policy and Systems journal format allows for the combination of results and discussion in one segment. It was felt that this was a good format to adopt as it allowed for the explanation of why certain country values were used over others in the ultimate construction of the model. It was felt that this would be easier for the reader to read than showing the final constructed model in the results section, and then going into the discussion of why these values were selected, and their individual limitations. |
| 17 | 23 | • P. 69. A very thoughtful discussion of study limitations. This does, however, give the paper quite an academic slant, and leaves the reader wondering what "take home" messages there are for policy makers – I suppose the clearest message is that investments in health systems research may be relatively important (in terms of reducing total burden of disease… but not necessarily in terms of the cost-effectiveness of the research). This feels like rather a weak message. Are there other messages for policy makers that can be highlighted in the discussion / conclusions section? | | Added an extra few lines to the conclusions to address this take home message concern: *"Nevertheless, policy makers can use this model in its current form as an efficient way to graphically illustrate burden of disease data for multiple diseases, as well as highlight the relative challenges in tackling those diseases (health systems, basic research, etc.), both within the disease and between diseases. This is useful in steering the desired composition of health research as a whole and* |

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| | | | | *health research within a specific disease field."* |
| 18 | 24 | • Appendices 1 & 2: You probably need to find a way (e.g. footnotes) to make the source of the data in each column of these two tables. (The assumption being that these would not ultimately be part of the published manuscript, but might be made available by HaRPS as online resources.) | | Footnotes added as suggested. |
| 19 | 25 | • Note that formatting of the boxes in the policy briefs, with figures overlapping text, meant that I could not fully read the boxes. However, I think I generally got the idea. | | Formatting errors have been amended. |
| 20 | 26 | • p. 107. As I was reading the policy brief I wondered who the target audience for this would be. And while it is easy enough to say policy makers in (research) funding organizations, in government, in civil society, etc., one does have to recognize that each is going to have a slightly different set of goals. I wonder if this should not be made more explicit. This might be as simple as saying "while it is recognized that policy makers at different levels, or within different organizations, may have different goals or mandates, it is assumed that all have, as a primary goal, extending access to health care (preventive and curative) towards reducing morbidity and mortality"... or something to this effect. | | Agreed. A comment has been added under the 'how to rank' section "This policy document reports on the development and feasibility of using such a quantitative model via an adaptation of a framework proposed by the World Health Organisation. While policy makers at different levels may have different primary goals, they all have at some level a desire to reduce morbidity and mortality through their research priorities, and hence this methodology is of relevance to them all." |

## Examiner 2 – (Michael Thiede)

| | Original dissertation | | Corrected/Revised dissertation | |
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| 1 | Comment 1, pg AA | The project proposal delineates the candidate's ambitious plan to improve and operationalize the framework presented and applied in the 1996 report. Here, it would have been desirable to explain the limited focus of this particular framework. The candidate could have substantially sharpened his own stated research focus by acknowledging the objectives and the context of the original approach.<br>It would have been helpful to describe in more detail the context in which such an approach might be useful to consider within a broader toolkit for setting priorities in health research. What are the particular objectives that such a framework can achieve? Which objectives cannot be achieved? What are the various paradigms under which priority setting takes place in different environments: How do the principles of cost-effectiveness, equity etc. relate to each other in different contexts and at different levels? Which factors currently drive the research agendas in different contexts and at different levels (including economic/industry interests, capacity/expertise, etc.)? Who are the stakeholders and what are the *processes* that determine how *stakeholders* interact in priority setting?<br>The manuscript's background section is characterised by a similarly broad claim to tackling the field of priority setting as critically described in the comments on the dissertation's preceding sections. It may be useful to further clarify the specific objectives of the exercise of amending the "WHO model" by highlighting that - while there are complex consultative processes surrounding any attempt to set priorities for health research that have to take into account issues ranging from research capacity to equity considerations - this piece of work focuses exclusively on improving a specific tool to provide a quantitative assessment of needs and (potential) interventions to address them with a view to their relative cost-effectiveness. It may also be useful to re-emphasise the particular context within which the "WHO model" was originally discussed. | Now on pg BB | An additional paragraph was added at the end of section 1.4.3 "Lastly, it is important to note that the model does not account for all relevant concerns in a priority setting process, such as issues of equity, buy-in, cost, and feasibility of research. Therefore it is important to realise that this model can only contribute to a priority setting process, and that consultations with stakeholders and other data sources would still be required for a holistic priority setting exercise." As well as at the end of section 2.1. "Importantly, this only seeks to amend the model in its current function, and does not attempt to account for other contextual issues such as equity and feasibility that would be addressed in a broader priority setting process." |

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| 2 | Comment 2, pg CC | It would also have been necessary to acknowledge (as has been done in the key reference document, the Ad hoc Committee's report) that health research falls into very distinct scientific categories, such as the biomedical sciences, population sciences or health policy sciences, with respective implications and limitations - and that purposes of R&D vary between 'fundamental research', 'strategic research' and 'intervention development and evaluation'. What are the objectives/ justifications under these different purposes? It may not suffice to claim that priorities have "[t]raditionally ... been set by researchers themselves", as the author hypothesises on p. 3 (underlined with a reference from indigenous health research in Australia). | Now on pg DD | An extra bit was added to section 1.4.1: "These three areas of research may all have different purposes (e.g. basic research may be conducted for the pursuit of knowledge, whereas health systems research may be conducted to improve equity). Ultimately, however, all research endeavours seek to ameliorate the burden of disease and increase the quality of life of populations." Section 1.2 about the traditional setting of research priorities was also bolstered with additional evidence from the "Health Research Prioritisation at the WHO" report: *"Almost a third of priority setting exercises were conducted without stakeholder consultation, and even when consultation occurred the use of a priority setting tool or framework was rare."* |
| 3 | Comment 3, pg EE | The candidate could have further strengthened the literature review by providing definitions of key terms, such as performance and accountability (section 1.1.2). Also, the presentation of the concept of rational decision-making, which is central for the presentation of the case, remains superficial as it oversimplifies competing paradigms in normative ethics. | Now on pg FF | These have been defined: *"Performance is defined as how well researchers used their resources and the degree to which they achieved their stated goals, and setting priorities helps to act as a performance indicator, as it sets goals and allows for the determination of whether these goals are achieved in a timely and efficient manner [13]. Accountability is the degree to which the outcomes of research match these stated goals. By clearly stating research goals, there is a degree of accountability if these goals are not met. "*<br><br>The concept of rational decision making was kept intentionally light as this is not a philosophical paper and it was felt that too much depth would have been unnecessary. However, this oversimplification has been acknowledged with the following amendment: "*Multiple philosophical approaches to rationality can be taken when it comes to prioritisation and distribution of resources, with Table 1 presenting a simplified overview of the three prevailing philosophical viewpoints (for a more in depth analysis, see reference [15]):*" |
| 4 | | Possibly a chronological presentation of the discussion around health research priority setting would have been useful, acknowledging the 1990 report by the Commission on Health Research for Development and the development after the 1996 report by the WHO Ad Hoc Committee whose focus lay mainly, as per its title and mandate, on "future intervention options". The Global Forum for Health Research was established as a direct result of the 1996 report and its work, then, fed into the 2006 resolution of WHO's Executive Board, which highlighted the importance and relevance of priority setting. There is also plenty of experience available from countries that have set priorities for health research since the early 2000s. | | The chronological summary in section 2 has been expanded to include these details, as such: "*Methods for priority setting have evolved over time, with the first serious attempt being the Essential National Health Research Framework (ENHR), which was developed in 1990 by the Commission on Health Research for Development, and is still the basis for most priority setting exercises. Following on from this the World Health Organisation (WHO) released the "Investing in Health Research and Development" report in 1996, wherein an alternate, quantitative* |

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| | | | | *based method was proposed. This led to the formation of the Global Forum for Health Research, which in 2006 passed a resolution with the WHO's Executive Board highlighting the importance and relevance of priority setting. The WHO method has since been incorporated into the ENHR and led to the development of the Calibration Adjusted Matrix (CAM) model…"* |
| 5 | | A slightly more structured presentation of the methodological literature around the benefits and pitfalls of DALYs could have complemented the literature review (including a brief review of some ideas discussed in the 1996 report and its Annexes 1 and 2). | | The DALY section has been restructured to include a basic background to the reasons for the DALY arising and how it is constructed. This is then followed by a brief discussion of the pros and cons, and finally the reasons for using it in priority setting: *"The DALY (Disability Adjusted Life Year) was first conceptualised following the Global Burden of Disease study conducted by the World Bank in 1992. One of the major drawbacks of the study was that it focused primarily on mortality as an outcome, and did not accurately account for the impact of nonfatal diseases. Thus, the DALY was constructed to incorporate both mortality and disability due to an illness into a single measure [43]. Four basic tenets surround the construction of a DALY value. Firstly, any indicator of health impact of a disease should include both mortality and altered health status. As such, DALYs are a combination of the number of years of life lost due to a disease, as well as the decrease in the quality, due to the disease, of those remaining years of life lived [43]. For example, if a disease reduced a patient's quality of life by 25%, then for every four years living with the disease, the patient would have suffered 1 DALY. The second tenet states that the only demographic considerations should be age and sex. This is because older people and men, on average, have less years of life to lose if they contract a fatal disease, and so their DALY scores should be weighted to account for this. The third tenet states that like health outcomes should be treated as like. In other words, if two individuals of the same age and sex contract a disease that results in their death, then the DALYs caused by those deaths should be treated as equal, irrespective of the personal differences between those two individuals (such as socioeconomic background or even if different diseases caused their deaths). Finally, the fourth tenet states that time (in this case number of years) should be the unit of measurement for burden of disease.*<br>*The DALY has many strengths as disease burden indicator. Primarily, it* |

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| | | | | *allows for the quantification of nonfatal diseases, which can have a very high burden on the population. It also provides a standard metric to measure the outcome of a specific intervention, making it particularly well suited to priority setting. It also makes projections on the future impact of a disease which allows for forward looking priority setting [49]. The DALY is currently also the most widely accepted burden of disease indicator, and is argued by its proponents as being the crucial measure of burden of disease for priority setting in health research [43], and hence there is a wealth of DALY data available for many diseases and countries, even though it does have some limitations and criticisms.*<br>*The major conceptual criticism of the DALY is that it measures the quantity of ill-health of a disease as opposed to the burden. The distinction being that the burden is influenced by factors such as social support and economic status, amongst others, of the people inflicted with the disease [50]. This is a powerful argument, supported by real-world evidence[51], and so attempts are being made to quantify DALYs in a more comprehensive manner, which takes into account the socioeconomic factors influencing disease burden [52]. Many of the other criticisms against the DALY are methodological issues: weighting by age and discounting future life for example. Some of these criticisms can, and have, been addressed by changes in the DALY methodology [53].*<br>*Despite these criticisms and shortcomings, the DALY is still widely used by international organisations such as the World Bank and WHO, and is the most readily available and accepted data type. Furthermore, Rosenberger suggests that the best practice for deciding on priorities in health research is to consult with either QALY (Quality Adjusted Life Years) or DALY estimates to get an idea of the burden of disease [18]. As such, the DALY will be used in construction of the amended model, bearing in mind that it is an imperfect estimate."* |
| 6 | | translate into research priorities may be a bit overoptimistic. Two further limitations could be highlighted: Firstly, the approach appears to ignore problems of scope by assuming linearity in effectiveness and costs. Secondly, the approach hardly accounts for risk and uncertainty. | | True. This has been added as an extra limitation: *"This model also does not fully account for the host of potential confounding variables, such as economies of scope and climate. While these are acknowledged as limitations of the model, no attempt is made to control or adjust the model for them."* |

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| | | supervisor. (The candidate may also want to reconsider the manuscript's title, which currently suggests that there may be one single approach used by WHO for setting research priorities.) | | While the WHO may use other methods, this is the one principally proposed by them. Therefore the manuscript title has been slightly amended to "*Setting priorities in health research using the World Health Organisation **proposed** model: Development of a quantitative methodology using tuberculosis in South Africa as a worked example"* |

**Student signature**: _____ **Date:** _____

# SETTING PRIORITIES IN HEALTH RESEARCH USING THE WORLD HEALTH ORGANISATION MODEL: DEVELOPMENT OF A QUANTITATIVE METHODOLOGY USING TUBERCULOSIS AS A WORKED EXAMPLE

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## SUMMARY

Priority setting in health research is important as it allows for the optimal distribution of limited resources, increases the efficiency of research and satisfies a desire for social accountability. Most priority setting frameworks set and rank priorities using a combination of consultation with data and stakeholder input. The legitimacy of stakeholder input is questionable due to potential bias of the stakeholder's interests, their rationality in decision making, and the use of irrelevant data. This is particularly important in the ranking stage, as most priority setting methodologies rely on stakeholder working groups to rank priorities, with minimal quantitative input. The World Health Organisation (WHO) has proposed a model for ranking of priorities by research area using quantitative inputs. However, a precise methodology for this model has not been developed. Therefore, the aim of this dissertation is to develop a basic quantitative framework, using the WHO model as a guideline, as a starting point for the development of a comprehensive quantitative methodology for ranking priorities.

# 1. INTRODUCTION

It is increasingly recognised that research in health has long-term importance in the overall health of a population [1]. However, the benefits of research are often hard to measure due to the fact that research does not occur in isolation, and scientific advancement is usually the product of multiple research endeavours of varying success. Nevertheless, attempted assessments of health research point to an up to 5-fold return on investment from an economic standpoint [2]. This favourable return suggests that health research is an economically sound investment in tackling the health problems of the world. However, this does not negate the need for setting of priorities in health research.

## 1.1 WHY SET PRIORITIES IN HEALTH RESEARCH?

Priorities in health research are set for three main reasons: to distribute limited resources [3], to increase the efficiency of research [4] and to allow for accountability in research [5]. The distribution of limited resources can be accomplished by any priority setting process, but in order for it to improve efficiency and accountability, the priority setting exercise has to be adopted by the entire research community, which is largely a product of *how* the priorities are set..

### 1.1.1 Limited resources

In 2004, a collective of Health ministers from around the globe met in Mexico to discuss the future of health research financing. At this summit it was decided that 2% of a countries health budget should be allocated to research [6]. Because each country has a varying burden of disease, resource availability and need for research, this figure is largely arbitrary and meant to act as a guideline more than a hard and fast rule. In 2011, the South African Department of Health spent 0.37% of its budget on research, which is not even close to reaching the modest goal it has agreed to [7]. Benefits from research are often only seen in the long term [1], which could explain why they are not prioritised in budgeting when competing with immediate health problems that also demand investment.

However, even if the 2% budgetary allocation were met, there are still human and infrastructural resources that limit research. The capacity to do research is far less than the potential research questions that could be answered. Furthermore, the process of research and the gain of new knowledge often leads to more research questions. As such, there will always be more research need than the ability to do so, and hence it is imperative that priorities be set, so as to maximise use of these limited resources.

### 1.1.2 Research efficiency

The major health problems of the world are not localised to specific countries or populations [8]. Many diseases can cross borders, or even continents, and with the advent of globalisation this is not just limited to infectious diseases (the spread of the western diet for example, has led to increases in obesity and diabetes levels in the developing world [9]). Thus, it is important for researchers to collaborate on research endeavours, as it allows for the generation of vital data

that could not be created alone, reduces the needless duplication of similar research and allows the research community to tackle global problems in a holistic manner (this is not only important for global health problems, but is also true for local health problems and the local research communities which may be doing research in that area). Furthermore, collaboration strengthens research capacity in developing countries where it is often most needed [10], increasing their efficiency. In order to have efficient global collaboration endeavours, it is important to have defined research agendas [11], which can best be achieved through a priority setting process.

### 1.1.3 Accountability

Lastly, with the decline in funding for research, as well as the increase in participatory research and the increased public interest in the direction and equity of research areas, it is felt that research funders and institutions should have a higher level of accountability to society. Hence, priority areas should be set in a transparent and systematic manner, ideally with societal involvement. This ensures that resources are distributed in an ethical manner, and also allows for benchmarking of the performance and progress of health research [5].

## 1.2 HOW ARE RESEARCH PRIORITIES SET?

Traditionally, health research priorities have been set by researchers themselves, with at best limited peer review guiding the scope and direction of the research [12]. Almost a third of priority setting exercises were conducted without stakeholder consultation, and even when consultation occurred the use of a priority setting tool or framework is rare [13]. The research community tends to assume that excellence in research is more important than the particular focus of the research [14], and in the absence of any official process for priority setting, this is how research is usually steered. However, researcher driven priority setting is problematic, as there is no guarantee of a rational, non-biased basis behind the subconscious priority setting of the researcher, nor is there any inherent collaboration between researchers. Furthermore, it does not take into account the desires of the recipients of the research, namely the health seeking community, who are often also involved as participants in the research. Thus, a more standard methodology for setting priorities is preferred.

Currently no gold standard method for setting research priorities exists, however the Council on Health Research for Development (COHRED), arguably the international authority in such matters, has published a framework to ensure the success of any priority setting endeavour [15]. While they do not advocate for a particular methodology, the framework highlights three key areas to bear in mind when conducting a priority setting exercise.

### 1.2.1 Assess the situation

In the preparatory work leading up to the priority setting exercise two factors have to be decided upon: which stakeholders are going to be involved and what data is going to be relevant. These two factors rely primarily on who is going to implement the priorities, what the priority process is going to focus on, budget constraints and whether a structured model is going to be used [16]. These decisions are made by the steering committee of the priority

setting exercise, and so it is important that the committee has legitimacy in the eyes of all potential stakeholders, as well as experience with priority setting processes.

*Decide upon stakeholder composition*

Decision makers in health research priorities are principally two agents, the researchers themselves, and the governing bodies who enable them to do the research (research funders are a particularly important part of this group). So while these two are obvious candidates, a broader stakeholder participation in priority setting is also vital for various reasons, from philosophical beliefs that society should have a say in the direction of research, to ensuring that there is buy-in from the participants who may be the object of the research. Furthermore, because health research is often multidisciplinary, it is important to ensure that the stakeholder composition is broad enough to cover all relevant disciplines, including health researchers, government officials, health practitioners, sociologists and economists. At the same time, the number of stakeholders will be limited based on logistical reasons and requisite expertise needed for the priority setting process. It is equally important to ensure that there is adequate public participation, to ensure issues of equity and public interest are satisfied. A suitably broad stakeholder composition lends legitimacy to the priority setting outcomes as it will have allowed for consultation with all relevant and interested groups [17].

*Gather relevant information*

There are three categories of information that are required for any priority setting exercise. Firstly, information on the governance and management structure of the health research system to help identify stakeholders. Secondly, an understanding of the current research sphere to give an idea of capacity and help shape the focus of the priority setting exercise. And lastly, but most importantly, performance indicator data, which includes burden of disease data and any other relevant data to help guide the setting of priorities [18].

### 1.2.2 Set the priorities

The setting of priorities consists of identifying areas of research which should be prioritised, and then ranking those areas against each other in order of importance.

*Identifying priorities*

Once the stakeholders have been gathered, and the relevant data disseminated, it is up to the organisers to decide how priorities will be set. There are various models proposed to guide priority setting, chief among these are the Essential National Health Research (ENHR), Calibration Adjusted Matrix (CAM) and Child Health and Nutrition Research Institute (CHNRI) models [18].

Briefly, the ENHR proposes the formation of a small working group of experts to devise a process for priority setting, followed by a larger workshop with broader stakeholder input to define and rank research priorities. It allows for large flexibility for composition of the working groups and stakeholders, as well as the methods for identifying priorities, but provides a framework for running and managing the process, including suggestions on managing stakeholders and deciding upon ranking matrices [19].

The CHNRI employs a similar methodology, only it is more explicit about the methods used to identify and rank priorities due to a perceived oversight of public health prioritisation in the ENHR strategy. Furthermore, because it is more technically challenging, it suggests involving a

narrower composition of stakeholders, by limiting it to only those with the relevant expertise [20].

The CAM attempts to consolidate data from three dimensions: The public health dimension, which includes the burden of disease as well as cost-effectiveness of interventions; the institutional dimension, which looks at whether a health problem is an individual or community problem, as well as whether it is a health service or infrastructure problem; and finally the equity dimension, which attempts to include social imbalances in health which should be addressed by priority setting. While the CAM is a very comprehensive model which draws on many data sources, it makes no attempt to rank or weight the dimensions. It is also very exhaustive and highly resource intensive to construct [21].

*Ranking priorities*

Once a list of priorities has been drawn up (either research areas or specific questions), it is suggested by COHRED that they be ranked. Ranking can be done by either a consensus or metrics based approach. Consensus approaches rely on a majority rule system, whereas metrics based approaches attempt to score priorities using a scoring system and pool stakeholders or working groups' scores. The criteria and processes for ranking differ, and are outlined in each of the models mentioned above, but are usually done by smaller working groups of stakeholders. Importantly, it is at the stage of ranking of priorities that the most subjective input occurs. This is typically where values such as equity, economics and viability come into practice, all of which can be weighted differently depending on the model used and stakeholder values [22].

### 1.2.3 Make priorities work

Finally, once the priorities have been set and ranked, three issues remain to be completed. Firstly, a plan must be enacted to translate the priorities into actual research. Secondly, some system for on-going re-evaluation and assessment of priorities in the future must be implemented. And lastly, in order to facilitate this, the results of the priority setting process must be disseminated in the most transparent and interpretable way possible [23].

Assessment of priority setting practices in real life show limited success in this final stage, particularly in implementation [17]. In part this could be due to lack of knowledge; high technical skills required to interpret and implement the priorities; and incorrect infrastructure to enable priority dissemination. Clearly, there is a problem with the current methodologies in terms of implementation and follow-through of priority setting, and this could be due to the challenges faced during the initial priority setting process.

## 1.3 CHALLENGES FACING PRIORITY SETTING

### 1.3.1 Stakeholders

Broadly speaking, the main challenge facing any priority setting exercise is the management of stakeholders. While it is important that stakeholder input is obtained, managing stakeholders and measuring the worth of their input is difficult and often problematic. One example is the observation that when stakeholders of differing compositions are given the same priority setting tasks, there is often a disparity in consensus of what the priorities should be [4]. For

example, researchers and clinicians (who one would assume to be experts in the topic) will develop priority areas that are different to a broader stakeholder group [24]. This could be due to one of two explanations. Firstly, the researchers and clinicians could have a bias towards research priorities that are favourable to them. Alternatively, the broader stakeholder opinion could dilute the specialist knowledge to an extent that priorities merely become a representation of popular opinion and less scientifically rigorous. Unfortunately it is not always easy to identify which factor is in play, making it difficult to strike the right balance between stakeholder participation that is broad enough to represent all interests, but also narrow enough to make an informed decision.

### 1.3.2 Data handling

As stakeholder groups become more diverse and inclusive, there is an increased problem of stakeholders with different backgrounds struggling to understand the relevant data and hence make truly informed decisions [25]. As a result, priority setting processes are often time consuming and receive a low response rate from stakeholders. This problem is compounded further in cases where there is a dearth of relevant data for stakeholders to refer to, such as in the ranking of priorities. This problem also arises in situations where there are multiple types of data that are relevant to the decision making process, such as: disease burden data, cost-effectiveness data, and a mix of qualitative and quantitative data. Furthermore, once the priorities have been set, the communication of these in a clear and comprehensible manner to relevant parties is often problematic [18].

### 1.3.3 Ranking process

While the identification of priority areas is generally performed by an assortment of expert stakeholders and justified using the results of rigorous quantitative and qualitative studies, the ranking of these areas is often decided by stakeholder opinion alone and hence is often the most contentious issue. Part of the problem is that there is little standardisation between working groups when it comes to priority setting processes [26]. For example, the Centre for Global Health's 2010 priority setting workshop had working groups rank a random seven (out of twenty three) previously defined priority questions. Amongst the four groups, three methods for ranking were independently developed and used: grading based on feasibility, operationilisability, usefulness and relevance; examining the importance of the topic associated with each question; and prioritising relative to questions on the same topic [26]. The outcomes of these three methods are not comparable, and heavily value-laden.

This is the particular problem that this study will focus on, namely how priority setting methods struggle with legitimacy in ranking of priority areas. Youngkong et al. suggest that quantitative techniques should be used to help provide general guidance in the ranking of priority areas, and that qualitative inputs should be used to define specific research areas of focus [27]. While it is not possible to easily quantitate certain value-laden criteria such as equity, there are quantitative models which attempt to tackle the ranking of research areas (basic, clinical, biomedical, public health etc.) such as the model proposed by the World Health Organisations (WHO) Ad Hoc Committee on Health Research Relating to Future Intervention Options.

## 1.4 THE WHO MODEL

### 1.4.1 Background and structure

The WHO model was released as part of the 1996 *Investing in Health Research and Development* report and represents one of the few quantitative models proposed for priority setting and ranking [28]. It is a very basic model which presents the total Disability Adjusted Life Years (DALYs) inflicted on the population by a given disease as a quadrangle. DALYs are a measure of disease that incorporate the years of life lost due to a disease, as well as the years lived with a disability due to a disease. On the y-axis, the percent efficacy of interventions for the health problem are mapped, while on the x-axis the percent coverage of these interventions in the disease population are mapped (Figure 1). The model then attempts to dissociate what percentage of the quadrangle is currently being averted through the mix of intervention efficacy and population coverage; what percentage is unavertable irrespective of interventions used or coverage obtained (which implies a need for basic research); what percentage could be averted with improved efficiency (health systems research); and finally what percentage is avertable with existing interventions but currently not cost-effective (biomedical research). These three areas of research may all have different purposes (e.g. basic research may be conducted for the pursuit of knowledge, whereas health systems research may be conducted to improve equity). Ultimately, however, all research endeavours seek to ameliorate the burden of disease and increase the quality of life of populations.

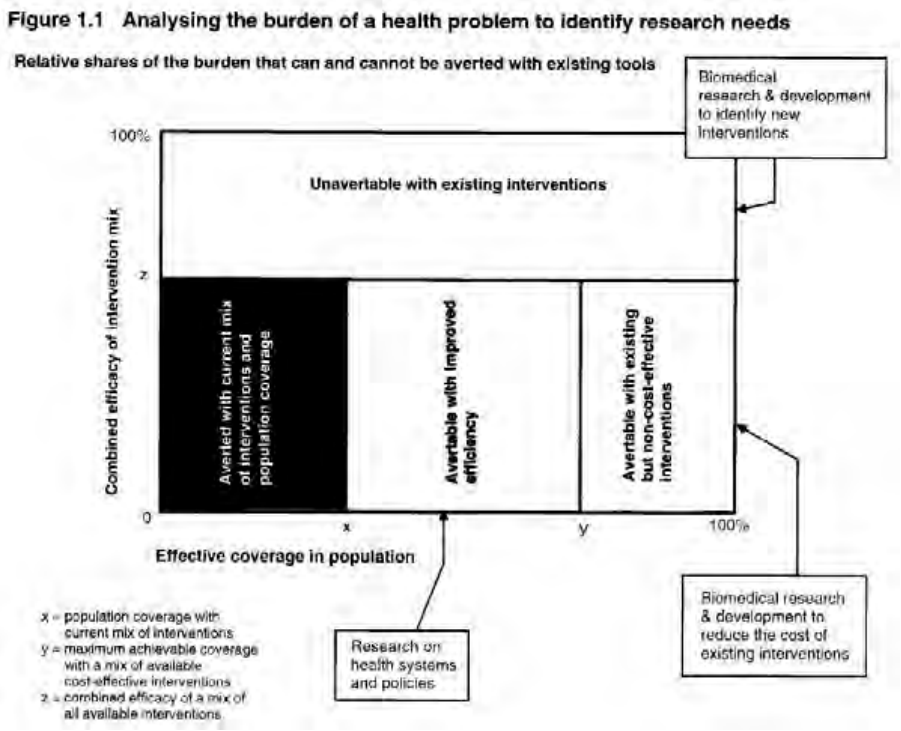


**Figure 1: The WHO priority setting model** [28].

### 1.4.2 Problems addressed by WHO model

The WHO model can contribute to any priority setting process by addressing the issues of rigour in ranking, and by assisting with data summation and interpretation.

*Ranking*

There currently exists no defined quantitative method to rank priorities, neither within a disease nor between diseases, and the WHO model is novel in that it attempts to establish such a quantitative method for ranking. This method would fit in well with the existing priority setting processes, and would serve to compliment, as opposed to replace, them. It would seek to bring a quantitative element to the ranking process, which reduces the possibility for stakeholder bias (stakeholders would however still have to agree with the constructs, assumptions and inputs of the model, and then the model would make all the complicated inferences where bias can otherwise usually creep in). This model only concerns itself with ranking of research areas however, and thus does not solve the issues of quantifying value laden concepts such as equity.

*Data interpretation*

The WHO model also summarises data in a pictorial representation, which can potentially bridge the understanding gap seen in larger stakeholder groups. It also makes the abundance of data easier to understand and interpret [29]. Furthermore, it can be used to present the results of the priority setting and ranking process in a clear and easily comprehensible manner for dissemination into the research community.

### 1.4.3 Problems with the WHO model

While the WHO model is a promising model, there are a number of inconsistencies in the model and the 1996 report that need to be addressed. Primarily, while it is suggested that construction of the quadrangle should be as quantitatively based as possible, no normative methodology for construction of the model is provided. Secondly, while the model purports to represent DALY data [28], there is an incongruence between the axes of the current model and the area of the quadrangle which is supposed to represent total DALYs. Finally, there are certain premises of the model, such as mutual exclusivity of its various partitions, which limits its functionality

The 1996 WHO report refers readers to annex 1 of the report as a guide for the construction of their proposed model. Annex 1 is the seminal paper by Murray and Lopez entitled *"Global patterns of cause of death and burden of disease in 1990, with projections to 2020"* and discusses the methodology used to construct DALY measurements. At no point in this paper is any mention made of using a quadrangle to represent the DALY burden, let alone of how to divide it up into the partitions suggested in the 1996 report. Therefore it is unclear how this paper is meant to guide any researcher in the construction of the WHO model. It does however reinforce the notion that this model should be based on DALY measurements. This leads to the second problem of the axes of the model.

If the total area of the quadrangle in the WHO model is the total DALYs attributable to a disease in a population, then it should follow that the product of the x and y axes should be equivalent to these DALYs. It is unclear how the product of 'efficacy of intervention mix' and 'effective coverage in the population' is equivalent to total DALYs. A more suitable value for the axes that allows for both coverage and efficacy measurements, as well as incorporating a total DALY score as its product, is thus required for the model to be internally consistent.

Furthermore, there are two premises of the model which limit its functionality. The first premise is the subdivisions of the model. The model assumes that improvements in health system efficiency and use of non-cost effective drugs will only improve coverage in the

population, and not the efficacy of the intervention. There is no reason to believe this will always be the case.

The second premise is that the disease population is a static figure that is not changed by improvements in health systems efficacy or use of non-cost effective interventions. In other words, the current model (figure 1) assumes that improvements in health systems efficiency would improve coverage by a certain percentage, say from 30 to 70%. It then assumes that using a non-cost effective intervention would increase coverage by the remaining 30%, however it does not take into account that the improvements in the health system might change cost-effectiveness of a non-cost effective intervention, as these figures are often modelled on certain premises of the health system. These two premises of the model limit the functionality of the model and hence would need to be addressed before any methodology can be constructed.

Lastly, it is important to note that the model does not account for all relevant concerns in a priority setting process, such as issues of equity, buy-in, cost, and feasibility of research. Therefore it is important to realise that this model can only contribute to a priority setting process, and that consultations with stakeholders and other data sources would still be required for a holistic priority setting exercise.

# 2. AIMS AND OBJECTIVES

## 2.1 AIM

The aim of this dissertation is to develop a methodology that ranks research priorities in a quantitative manner. This will make the ranking process more objective, and will allow priorities to be contrasted against each other more easily when engaging in a prioritisation exercise. In order to do this we will be using the WHO model as a guideline to develop a more refined quantitative model for ranking. We will then explore quantitative methods to construct this model. We will use tuberculosis (TB) in South Africa as a worked example, as it has some of the most comprehensive databases of any disease. Importantly, this only seeks to amend the model in its current function, and does not attempt to account for other contextual issues such as equity and feasibility that would be addressed in a broader priority setting process.

## 2.2 OBJECTIVES

The objectives of this dissertation are as follows:

1. Amend the WHO model to address its current limitations.
2. Construct a burden of disease assessment for TB in South Africa using the amended model.
3. Divide this quadrangle into the four components outlined by the WHO using various quantitative methodologies, namely:
   -Currently Averted
   -Unavertable with Existing Interventions
   -Avertable with Improved Efficiency
   -Avertable with Biomedical Research
4. Critically analyse the results generated

# 3. METHODS

## 3.1 STUDY DESIGN

This dissertation will draw on international datasets at the country level, and hence is most close to an ecological study design [30]. Ecological studies attempt to draw inferences about relationships between variables at a population level. These relationships are then applied to other populations or individuals to try and make predictions about outcomes. For example, an ecological study may find an association between circumcision and reduced levels of HIV in one population, and therefore predict that other populations with high levels of circumcision would have proportionately lower levels of HIV. There are limitations in an ecological study, primarily that there are always a host of confounding variables that could be influencing the population and hence make the observation unique to that population and not generalizable. Furthermore it is usually impossible to draw any causation, merely association, between two variables. Lastly, trying to make any inferences about individual behaviour based on population level observations compounds the risk for confounding variables and causation, and is known as the ecological fallacy. In our study we will not be making inferences from the country level to the individual level, and so there is no risk of ecological fallacy. Furthermore, it is not a classic ecological study in that it is not trying to elucidate relationships between variables at a population level. Rather, we will be using country level statistics, and extrapolating them to other countries in order to construct the WHO model. There may still be confounding variables which influence our statistics and limit these extrapolations, but we will take cognisance of these variables and try to account for them where possible, or else acknowledge them as limitations of the model.

## 3.2 PROPOSED METHODOLOGY

The WHO model in its current state represents a good model for deconstructing a disease into priority research areas, but there are two problems which first need to be addressed: there is no normative methodology for construction of the box, and secondly the box itself has some axis and construction inconsistencies.

We will first address the axis issue, as this will guide the subsequent development of a methodology for constructing the WHO model. The original model proposes 'combined efficacy' as the y-axis variable (Figure 3), and 'effective coverage in the population' as the x-axis variable, both with a range of 0% to 100%. This approach envisages a situation where the combined efforts of research seek to treat 100% of the diseased population with an intervention that is 100% effective at restoring them to full health. However, it is not clear what the scale of 0-100% exactly means in real terms, and it does not allow for cross comparisons between these quadrangles for different diseases, as 50% efficacy in treatment of a mild disease is not equivalent to 50% efficacy in treatment of a lethal one. We will therefore adapt the WHO model axes to more readily incorporate comparable data, and develop a unique methodology for constructing and subdividing the box.

We will next address the inconsistencies in the construction of the WHO model. Amendments will be made to address the issues of subdivision of the model, and the application of these subdivisions to a static disease burden.

Once the model has been developed we will then attempt to apply it to TB in South Africa, drawing upon numerous datasets. Because it is a WHO model that should be implementable for a host of diseases, we will try to limit the data to that provided by the WHO and readily available for a host of diseases. We will use the example of TB to explore the issues surrounding the construction of the model and to get an idea of its feasibility and validity.

# 4. POTENTIAL IMPACT

## 4.1 TARGET STAKEHOLDERS

There are a host of stakeholders relevant to this dissertation. First and foremost are institutions involved in priority setting processes. This includes the National Health Research Council of South Africa (NHRC) chaired by Dr Bongani Mayosi, as well as international priority setting bodies such as the Council on Health Research for Development (COHRED) and the World Health Organisation (WHO).

Secondly, funding bodies may be interested in the results of the exercise where it applies to TB, as well as the methodology more generally. This includes national funders such as the Medical Research Council (MRC) and National Research Foundation (NRF), as well as larger international funders of TB research.

Research institutions, such as universities, will be interested in the methodology employed in this dissertation to help guide their internal decision making processes surrounding the structure of their health research system. Individual TB researchers may also be interested in the results to advocate for greater focus on their area of interest (although the results may also argue that there should be lesser focus on their area of interest, and they may oppose the model).

Finally, national policy makers may be interested in the outcomes of this research in assistance in the formulation of policy guidelines surrounding research priorities.

Because this is a heavily methodological dissertation, and because the methodology only broaches one particular component of the priority setting process, it is the priority setting institutions initially listed which will primarily be interested in the methodology developed in this dissertation. These groups also have impact on all the other stakeholders listed above, and are more frequently consulted by the stakeholders above on priority setting. Nevertheless, some of these stakeholders will have their own priority setting exercises, and hence it is still important to target them.

## 4.2 WINDOW OF OPPORTUNITY

In a local context, there is also currently a window of opportunity for research in priority setting, as various research institutions and funding bodies are currently reviewing their prioritisation processes:

The University of Cape Town has recently released its Strategic Plan for Research 2013-2020, part of which includes setting priorities

> *"…[in] alignment between the FHS research strategy and that of the Provincial Government of the Western Cape and national agencies, such as the National Health*

*Research Committee (NHRC) of the DoH, the Department of Science and Technology (DST) and the Medical Research Council (MRC).”* [31]

Furthermore, the MRC has recently come under new management and is interested in the processes it uses for decision making in funding too. In 2001, it released a report about its priority setting process, suggesting the model of the WHO as the way forward [32], however it is unknown whether any follow up on this process was ever made.

In a more international sphere, priority setting in health research is an area that is receiving increasing interest, however quantitative methods for priority setting are a particular area of research which has received little attention thus far, and so one of the indirect aims of this study would also be to stimulate more interest and debate in this field. The WHO released a report in 2010 stressing the need for a higher degree of standardisation in priority setting approaches, and a dire need for more normative research in this area [13].

Finally, The Institute for Health Metrics and Evaluation, headed by Professor Christopher J L Murray, has also released their latest data on burden of disease estimates for 2010 [33], and this is likely to impact on priority setting processes, although the incorporation and interpretation of this data is not going to be easy due to the aforementioned problem of stakeholders understanding data. The development of a tool to incorporate such quantitative data is thus well timed.

# 5. LOGISTICS

## 5.1 TIME FRAME

The dissertation is expected to be completed over a 6 month time frame, from September 2013 to February 2014 dependent on time taken to receive ethical clearance. Because the datasets are readily available, the first 2-3 weeks will be devoted to amassing and extracting the relevant data. We will then develop the model over the next 2 to 3 months, refining it based on the outcomes of our data input. The data analysis and methodological development component is scheduled to be finished by December, allowing 2 months to write up the finalised method and results generated.

## 5.2 BUDGET

Because this dissertation requires no new generation of data, and merely an analysis of pre-existing data and the development of a model, there are no budgetary requirements.

## 5.3 ETHICS

Similarly, because there is no sensitive data involved, nor any ethically contentious issues, it is not felt that there are any ethical concerns. Granted, if the priority setting exercise results in incorrect priorities being set, this could have ethical ramifications. However, because the methods used will be transparent and clearly reported, their worth and the ethical implications of their use can be measured by individual stakeholders prior to implementation. Nonetheless, the dissertation proposal will be submitted to the University of Cape Town Human Research Ethics Committee for approval prior to commencement.

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# PART B: LITERATURE REVIEW

# 1. PRIORITY SETTING

Over 50 million deaths (roughly 90% of deaths worldwide) are caused by disease [1]. Countering this burden completely, and simultaneously, is a near impossible challenge, and therefore priorities are set in healthcare delivery (for example, the Millennium Development Goals set by the WHO) in order to focus efforts on the most vital and effective areas. Furthermore, it is increasingly recognised that health research is essential to combat disease, particularly for the long term health of a population[2], and so similar priorities must be set in research. Measuring the benefit of research is complex, yet tentative figures suggest a return of investment of 30% in basic research [3], and an up to five fold return on investment in health research [4]. Research is required not only to develop new methods for tackling disease, but also to figure out ways to operationalize existing methods given the poor infrastructure and resource constraints of many developing countries, which shoulder a disproportionately high burden of disease [5]. Given the importance of health research, it is instructive to understand why there is a need to set priorities, and how these priorities are set.

## 1.1 WHY SET PRIORITIES IN HEALTH RESEARCH

The main reasons for setting priorities in health research are to allocate limited resources, and to increase the efficiency and accountability of research.

### 1.1.1 Resource constraints

An estimated $US1 trillion is spent on research and development globally, however health research in particular still remains a vastly underfunded area, especially by government organisations [6]. Strikingly, only 5% of investment on health research is on health problems of the developing world, which account for over 93% of the global burden of disease [5]. Furthermore, even though the amount spent on research is very large, it is still less than what has been agreed is required to combat disease. For example, the European Commission has a target of 3% of gross domestic product (GDP) to be spent on research and development [7], yet the majority of its member states are not reaching that goal [8]. In South Africa, the government invested 0.37% of its 2011/2012 health budget on research, even though it has committed to spending 2% per annum [9]. The underfunding of health research, as well as the disproportionate distribution of research funds, means that priorities have to be set in research in order to get maximum returns on investments, particularly in developing countries.

Even if sufficient financial resources were made available, there is still a dearth of human resources available, especially in the developing world. There are an estimated seven million researchers globally, however due to the attractiveness of the developed world's capacity for

research, there is a high level of emigration of qualified researchers from developing countries where they are needed most [6]. This has resulted in researchers being classified as a scarce skill in many developing countries, South Africa included [10], as there are not enough researchers to keep up with the demand for research.

### 1.1.2 Performance & Accountability

Setting priorities allows researchers and research institutions to focus their work on specific areas or problems, with the research community acting with a concerted effort, instead of operating under disparate groupings [11]. Collaboration increases the efficiency of research, as it brings together multiple disciplines to focus on a complex problem and minimises the redundant duplication of work and resources, such as lab equipment and reagents [12].

Priority setting has additional benefits for performance and accountability. It helps consolidate and illuminate the current situation in healthcare, research and financing, which has value in streamlining and managing the research system. Performance is defined as how well researchers used their resources and the degree to which they achieved their stated goals, and setting priorities helps to act as a performance indicator, as it sets goals and allows for the determination of whether these goals are achieved in a timely and efficient manner [13].

Accountability is the degree to which the outcomes of research match these stated goals. By clearly stating research goals, there is a degree of accountability if these goals are not met. Furthermore, an inclusive priority setting exercise in setting research goals makes the researchers and research institutions more accountable to their funders, governments and the broader community. This satisfies two of the underlying principles of priority setting: that they should be legitimate and that they should be fair [14], and is also more frequently demanded by funders, such as governments, in order to justify spending to the public [4].

## 1.2 HOW PRIORITIES ARE SET IN RESEARCH

People are often not rational when it comes to decision making. The Rule of Rescue is one such example, and explains the inclination of individuals to prioritise any research on terminal diseases. This is an emotive response, which appeals to the psychological fear of death and subsequent desire to do anything to prevent it, irrespective of the cost to society or eventual benefit to the patient [15]. This is reinforced by data on countries where no official priority setting process is adopted, but rather ad-hoc priority decisions are made by researchers, resulting in increased inequities and static or burgeoning burdens of disease [16]. Because society is prone to such instinctual and irrational tendencies, it is not only important to set priorities, but to do so in a rational manner. Unfortunately there are competing philosophical ideas of what constitutes rational decision making behaviour when it comes to setting priorities, with the subject of what constitutes rationality an on-going philosophical debate [17].

### 1.2.1 Rational decision making

Multiple philosophical approaches to rationality can be taken when it comes to prioritisation and distribution of resources, with Table 1 presenting a simplified overview of the three prevailing philosophical viewpoints (for a more in depth analysis, see reference [15]):

**Table 1: Summary of the three main philosophical approaches to rationality.**

| Name | Guiding Principle | Advantages | Disadvantages |
|---|---|---|---|
| Utilitarianism | Maximise benefits to society. | Maximises use of limited resources. Quantifies benefits, which aids in decision making. | Hard to quantify benefit. Distribution of benefit amongst society not taken into account. |
| Egalitarianism | Equal benefits (or chance of benefits) for all individuals. | Highly equitable. Requires very little value judgements to be made, as distribution of benefits is equal. | Does not take into account differential need for resources. Does not maximise benefit of scarce resources in any way. |
| Prioritarianism | In situations where not all can benefit, gives priority to a certain group (e.g. the youth over the aged). | Allows for considerations of need and benefit. | Choice of variables used to give priority highly debatable (e.g. could equally give the aged priority because they have contributed more to society). |

Current international trends in priority setting tend towards a utilitarian point of view [18], although utilitarianism is no more valid than any of the other different prevailing philosophical viewpoints [19]. It is therefore important to follow a process which is clearly specified and objectively fair, irrespective of philosophical viewpoint. This requires that any priority setting exercise should be transparent about the grounds for decisions, evidence-based, inclusive of many stakeholders, appeal to rationale that all can agree are relevant, and have a clear appeals procedure. Combined, these principles are referred to as "accountability for reasonableness"[19], and allow for a diversity of philosophical viewpoints to be taken, while still remaining a rational process. The exercise of priority setting itself can be approached in two ways, either rational or incremental.

### 1.2.2 Rational and Incremental Approaches

Two broad approaches can be used for setting priorities, the 'rational approach' or the 'incremental approach' [20]. The rational approach stipulates that all available data relevant to the disease should be collected, and from analysis of this data 'valued priorities' should be created. The incremental approach involves setting priorities based on the current state of the research system, including political context, and only marginally improving what currently exists. The problem with the rational approach is that it is almost always impossible to have the complete gambit of relevant data, and it does not take into account the way human behaviour influences the translation of priorities into research. In other words, even if priorities are set on perfect evidence and knowledge, if there is no political will or buy-in from the researchers, then the priorities will not be translated into research outcomes. The incremental approach can address these translational problems. Priority setting also needs to be responsive to the changing burden of disease and health landscape, and as such it cannot be too time consuming as it must be performed on a regular basis [21] [22]. This favours the incremental approach, as

it is a less exhaustive and hence less time consuming approach. However, this also means that the incremental approach is not as sensitive to changing research needs as the rational approach is, and can propagate unnecessary research based on historical precedent.

As such, most priority setting methods tend towards a rational approach, but acknowledge the lack of complete data and the importance of the nature of decision making highlighted by the incremental approach. Therefore, they usually use a combination of the two, drawing upon stakeholder input in conjunction with quantitative and qualitative data. However, the way this data is gathered, interpreted and implemented varies.

# 2. PRIORITY SETTING METHODS

Priority setting methodologies typically consist of two exercises: the identification of a set of priorities, followed by the ranking of those priorities in order of importance. The priorities are generally defined based on those areas which have the greatest need for research, but can also take into consideration factors such as equity, feasibility and social desirability [23]. While the latter factors are important, they are often not evidence-based and are instead determined by stakeholder input. Stakeholder input is value-laden, and introduces the potential for bias, and hence any priority setting exercise that involves stakeholder input must be done in the most transparent way possible. This can best be achieved by following a pre-specified method, although there is currently no specific method that is universally agreed as the gold standard.

Methods for priority setting have evolved over time, with the first serious attempt being the Essential National Health Research Framework (ENHR), which was developed in 1990 by the Commission on Health Research for Development, and is still the basis for most priority setting exercises. Following on from this the World Health Organisation (WHO) released the *Investing in Health Research and Development* report in 1996, wherein alternate, quantitative based method was proposed. This led to the development of the formation of the Global Forum for Health Research, which in 2006 passed a resolution with the WHO's Executive Board highlighting the importance and relevance of priority setting. The WHO method has since been incorporated into the ENHR and led to the development of the Calibration Adjusted Matrix (CAM) model, which also seeks to include issues of feasibility and equity in a more defined manner. In addition, the Child Health and Nutrition Research Initiative (CHNRI) constructed a separate model adapted from the ENHR, after a perceived lack of relevance of the current ENHR processes in child health research priority setting.

Each method, outlined below, has strengths and weaknesses. They are all theoretical models which provide guidelines of various comprehensiveness on how to complete a priority setting exercise, however their feasibility in practice is often largely untested. Attempts to follow the models comprehensively (e.g. Argentina) have struggled with certain problems in implementation and have only been able to partially complete the process. Therefore, most organisations which follow a priority setting method adapt it to their situation and do not follow the process meticulously. Looking at the models in practice, and in particular the challenges faced, will thus be instructive in reflecting on common themes and the difficulties of priority setting in health research.

## 2.1 ENHR

### 2.1.1 Theory

The Essential National Health Research framework was developed in 1990 and resulted in the formation of the Council on Health Research for Development (COHRED) in 1993 to promote the use of, and advance, the framework. Since COHREDs inception, the ENHR has been updated and refined routinely, to its present form as outlined in Figure 1 [24].

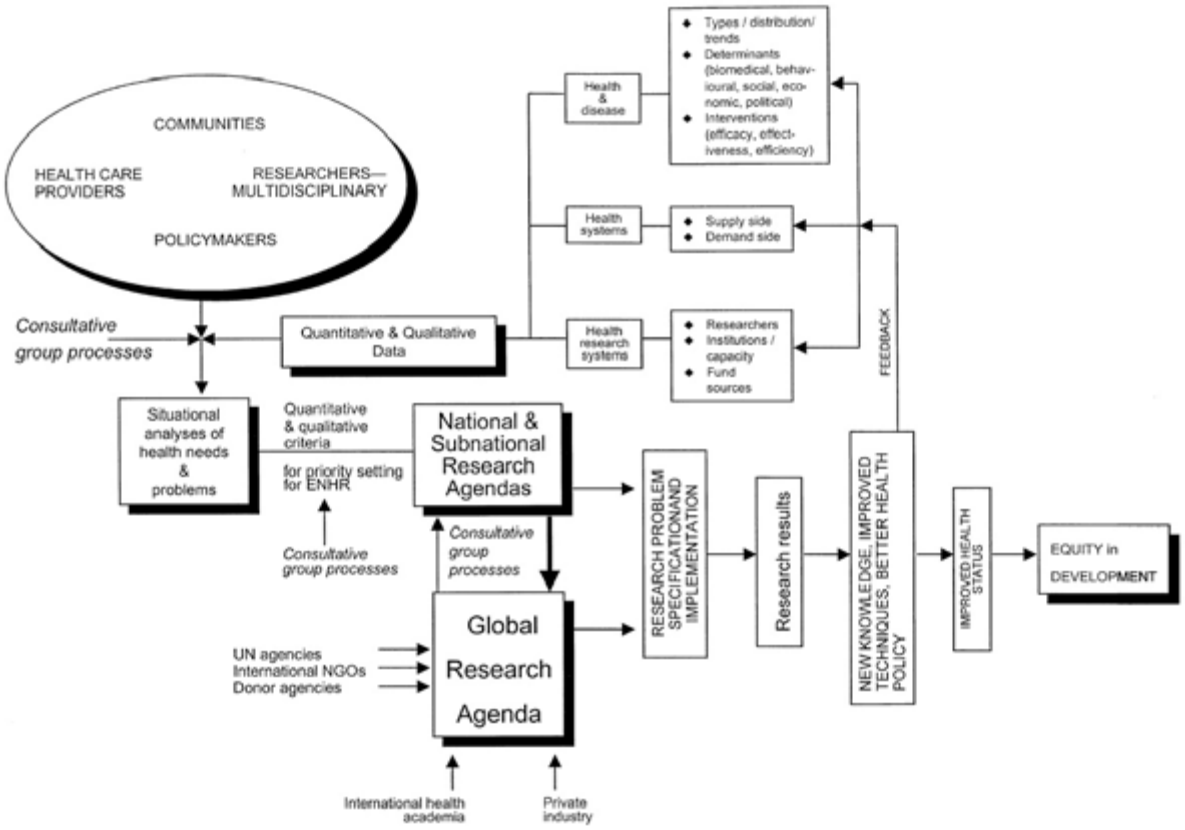


**Figure 1: ENHR organogram**[24]**. The organogram includes the composition of quantitative and qualitative data inputs used to set research agendas, the interface between national and global research agendas, the translation of set research agendas into research results, and the feedback of these results into the quantitative data used in priority setting.**

Briefly, the ENHR framework suggests that an executive committee be commissioned to steer the priority setting exercise. This committee should have the requisite leadership skills and have legitimacy in the community. The committee then identifies stakeholders relevant to priority setting. Guidelines are provided by the ENHR model on gathering and identifying stakeholders: researchers, policy makers, community members, private sector and NGOs should all be included, and there must be equitable representation from different social demographics (Figure 1). A select group of stakeholders then perform a situation analysis of the current health situation which scientifically assesses the health status of the country; the status of the health system and the research system; as well as the users' health wants and needs. An emphasis is placed on equity when it comes to situation analysis. This is also the stage at which the bulk of quantitative, burden of disease data is presented.

Broad research areas are then decided upon by all the stakeholders using the situation analysis as a guideline. These research areas are subsequently compared with global trends, and adjustments made if deemed necessary. Stakeholders are then further asked to draft up a list of criteria for ranking of priority areas. Criteria can include factors such as economic impact, community concern, impact on health, and availability of cost effective interventions. Scores are then assigned to the degree of fit for each criterion. For example, economic impact could be ranked as follows:

| | | | | |
|---|---|---|---|---|
| **Economic Impact** | None (0 points) | A little (1 points) | Some (3 points) | A lot (10 points) |

The weighting of scores within and between criteria is decided by the stakeholders and reflects the value judgements they make on the need/desirability of each criterion. Some criteria can also be binary and viewed as deal breakers: e.g. is it feasible? yes/no. Once a working scoring module has been agreed upon, all research areas are scored. This process results in a list of ranked priority areas, which can further be shortlisted into high priority research areas.

In addition, the ENHR acknowledges that implementation of the research priorities can only be accomplished if the priority areas are supported. It suggests many ways this can be done, such as encouraging interdisciplinary work, financial incentives, having a mechanism for dissemination of the priorities, having a mechanism in place to monitor research and assessing resources available for the priority areas [24].

The strengths of the ENHR framework are that it involves multiple stakeholders in setting the priorities, and that it allows for quantitative input during the situation analysis. The main drawback is that stakeholder input can be very subjective and not evidence based; this is especially true in the ranking exercise as points and weightings are assigned to the criteria in an essentially best guess estimate, and are not necessarily objective or evidence-based.

### 2.1.2 Real-world example: NHRC

The National Health Research Committee (NHRC) is the official decision making body in South Africa for priority setting in health research. A priority setting summit was held in 2011, and subsequently a report released on the priority setting exercise and findings [9]. The basic methodology used at the summit was an adaptation of the ENHR method. Priorities were decided upon by the committee after hearing presentations by a panel of experts, invited delegates and various research findings of NHRC sub-committees from the previous year. The committee involved multiple stakeholders from various fields and identified key priority areas. Within those areas, experts presented on strengths, weaknesses and opportunities (SWOT analysis) for research in each field. Delegates then broke away into smaller commissions in order to discuss priority research questions. This resulted in 5-10 key research questions per area being identified.

The NHRC process differed from the ENHR strategy as it lacked the key component of scoring or ranking the priority questions identified. The strengths of the NHRC methodology are that it involved many participants' inputs, had some factual basis (as experts presented data to help guide the development of research areas and questions) and the outcome of specific questions helped guide exactly *what* research should be done, as opposed to a more generic statement on their being a need for more research in a particular area. The main weakness is that it did not rank these questions in any way, so it is unclear which questions should be prioritised within each disease, nor between diseases. Using a quantitative ranking tool, like the WHO model described in section 2.3 below, would help to give a weighting to the questions and address this shortcoming.

In terms of impact, The University of Cape Town has taken cognisance of the NHRC priorities in its Strategic Plan for Research 2013 [25], however it remains to be seen if this will impact the

nature of research conducted at the institution. Because the summit was held in 2011, and the results only published in April of 2012 it is too early to gauge whether the NHRC's exercise will have any significant impact on national research outputs.

## 2.2 CAM

### 2.2.1 Theory

The Combined Approach Matrix (CAM) follows on from the advocacy of the ENHR that a systematic process should be used when setting priorities, but expands the model to make it clearer what specific factors should be considered. The CAM can be either a two dimensional or three dimensional matrix, with the two dimensional matrix composed of a public health axis and an institutional axis, while the three dimensional matrix contains an additional equity axis. Within each axis are subgroups, as outlined in Figure 2 below, which when combined present a holistic view of a particular disease. For example, if the CAM model were applied to cervical cancer it would allow the determinants (public health axis) to incorporate both health sector problems, such as service delivery, as well as household problems, such as male headed households limiting women's access to healthcare (institutional axis).

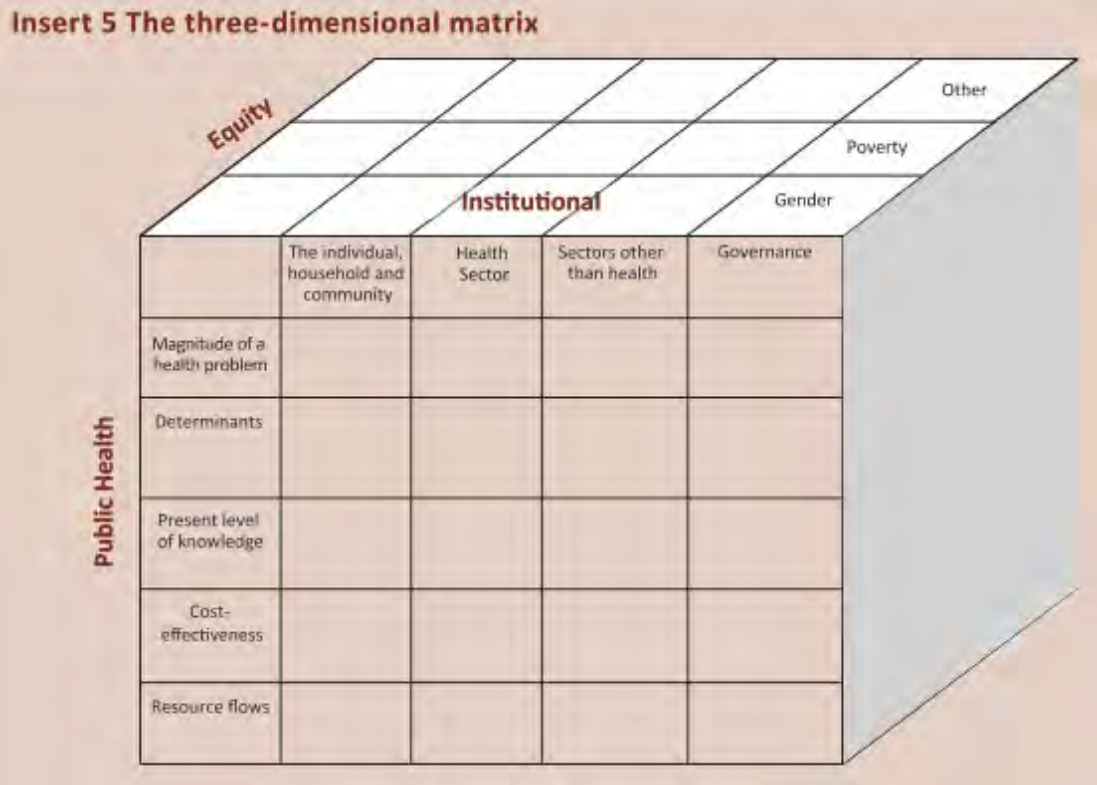


**Figure 2: The Combined Approach Matrix (3D)** [26]**. The matrix is comprised of three axes: equity, institutional and public health. Further subdivisions can exist within these axes, for example gender and poverty are listed as equity issues. More subdivisions can be added to each if desired, such as ethnicity or sexual orientation on the equity axis.**

The methodology used to fill out the CAM is not clearly defined, but follows the same basic principles as the ENHR: stakeholders are identified and invited to participate in the construction

of the matrix, in consultation with the relevant scientific data. Gaps in the ability to fill out the model are themselves considered to be research priority areas.

The CAM models main strength is its attempt to detail the complete gambit of contributing factors to priority setting in a systematic manner, including issues of equity. However, the CAM suffers from the same subjectivity of the ENHR strategy when it comes to ranking of these contributing factors, as well as in the ranking of priority areas relative to each other. However, one of the recommendations that the model makes is the use of the WHO model in order to assist with the completion of this ranking [26][27].

### 2.2.2 Real-world example: Argentina

The National Academy of Medicine in Argentina attempted to apply the CAM model between the periods of 2005 to 2009. Great effort was made to follow the methodology entirely and the process was generally considered successful by the National Academy. However, two major concerns arose during the exercise. The first was the composition of the stakeholders and decision makers consulted, as it was felt that individuals would push their own agendas in priority setting [28]. Secondly, it was felt that a clear and transparent methodology for setting priorities was lacking, and while the CAM output did give an indication of the scope of the problem, it did not help with ranking [28].

The priority setting exercise has only recently been completed, and because of this there have as yet been no attempts to measure its impact in Argentinian health research. However, it was noted by the National Academy that the priority setting process itself had had positive impacts in increasing dialogue and collaboration between various stakeholders that were involved in the exercise [29].

## 2.3 THE WHO MODEL

### 2.3.1 Theory

The guidelines proposed by the World Health Organisations (WHO) *Investing in Health Research and Development* report [30] use burden of disease, measured using Disability Adjusted Life Years (DALYS), as their basis. Briefly, DALYs are a measure of the number of years of life lost, either directly through fatality or theoretically because of disability, due to a disease (the DALY concept is more thoroughly explored in section 4.3.1.). DALY data is represented as a quadrangle, with the percentage of diseased individuals receiving interventions on the x-axis, and the resultant efficacy of these interventions on the y-axis (Figure 3). The quadrangle is then broken up into 4 partitions to elucidate the nature of research required to increase either the efficacy of interventions, or the percentage of individuals receiving treatment.

The first partition of the quadrangle is the burden of disease which is unavertable with existing interventions. Thus, it reflects where basic and clinical research into new treatment options is most required to improve intervention efficacy. The second partition is the degree of disease burden that is currently being averted, and while it provides no guidelines for priority setting, has informative value as a benchmark for performance of the current health system. The third partition is the burden of disease which could be averted with improved efficiency, and reflects where research into improved health systems and policies could increase coverage of

interventions in the population. The final partition is what is avertable with existing interventions, but in a non-cost effective manner, and represents areas of biomedical (and public health) research to reduce the costs of current interventions and hence make them more widely accessible [30].

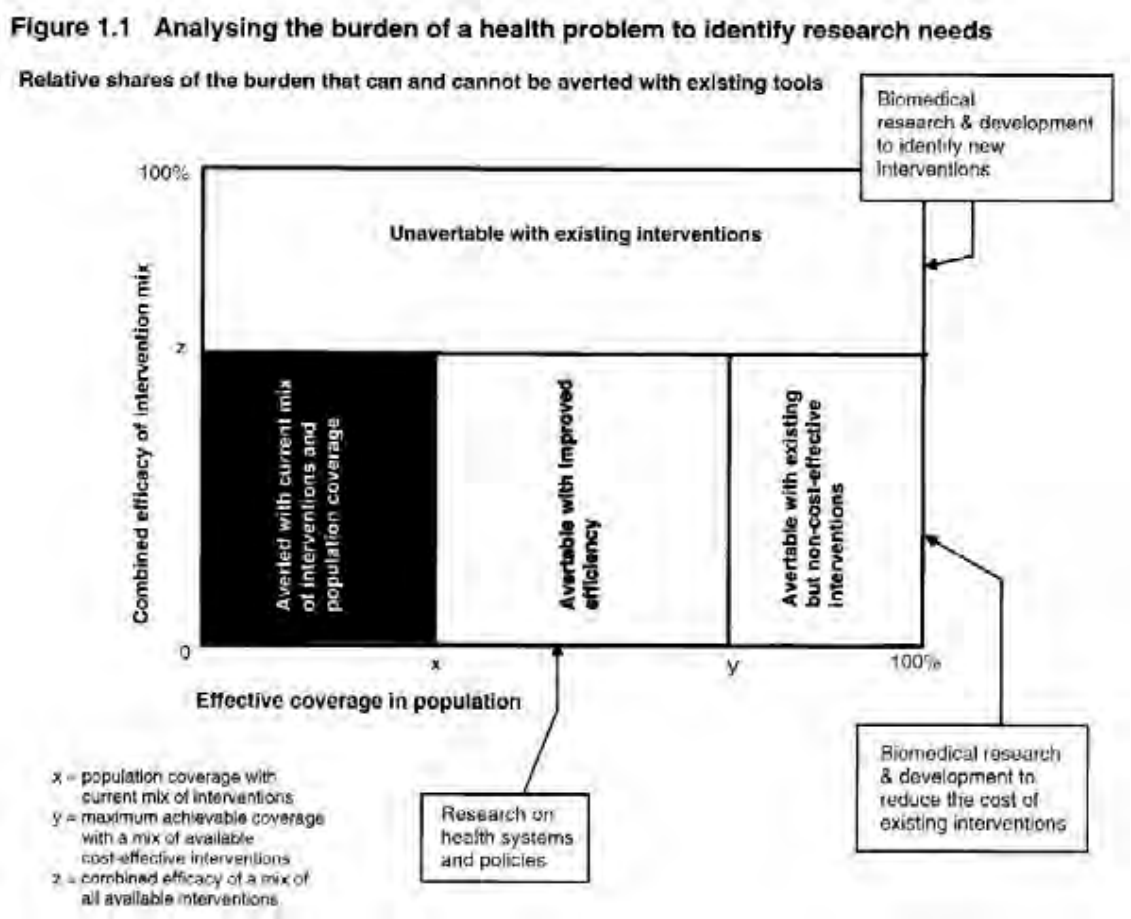


**Figure 3: WHO quadrangle** [30]**. Burden of disease is depicted as a quadrangle representing all DALYs caused by the disease. Percentage efficacy of interventions, as well as effective coverage in the population are the two axes proposed to combat the DALY burden. On the y-axis, the maximum efficacy currently attainable (z) delineates the remaining portion of the burden that is unavertable with existing interventions. On the x-axis, (x) represents population coverage, whereas (y) represents potential gains in coverage from improved efficiency, with the remaining gains possible via use of existing but non-cost-effective interventions.**

It is important to note that the WHO model differentiates between 'efficacy', 'efficiency' and 'cost effectiveness'. In this context, efficacy refers to the ability of the interventions to treat a disease . Efficiency on the other hand, refers to the context under which the intervention operates, and the degree to which it can help, or hinder, the efficacy of the intervention. Importantly, the model assumes that a more efficient health system will only impact the number of people receiving the intervention, and not the efficacy of the intervention. Finally, cost-effective refers to a particular subset of the health system, namely that of financing. Again, the model assumes that more expensive drugs do not have a higher efficacy, but rather are more able to reach the population. For example, a drug may have an efficacy of 60% and a population coverage of 50% in a rural population in a low income country. Using a better drug in the same context would result in an efficacy increase. Improving the route of administration of the drug would increase the population coverage and hence improve the efficiency of that intervention. Using a more

expensive drug, that has the same efficacy but is more stable and hence can also reach a larger population, is a change in the cost-effectiveness.

The main strengths of the WHO model (Figure 3) are that it uses quantitative data only, and hence has less chance for bias. Furthermore, the model generates proportional outcomes (i.e. using this model gives an idea of how much basic research should be done in a disease relative to how much health systems research). Proportional outcomes allow comparisons to be made between diseases and fields, for example how much basic research in TB should be done (either in terms of resource allocation or research output) relative to basic research in HIV or even public health research in HIV.

The WHO models shortcomings are that it does not take into account stakeholder interests, equity issues, costs of research, or identify specific research questions. Instead, it leaves these issues to the discretion of stakeholders or researchers. Nor does the model discern between direct healthcare provision and service level healthcare provision such as sanitation, as the CAM model attempts to. Nonetheless, as a tool for organising and ranking data that feeds into the CAM model, it is potentially very useful. The final problem is that the *Investing in Health Research and Development* report only provides the guideline for the dissection of the burden of disease, and limits their methodology to "consultation of the literature and experts", so there is no clear quantitative methodology to construct the WHO model.

### 2.3.2 Real-world example: WHO ad hoc committee

In conjunction with the release of the priority setting model (Figure 3), the WHO ad hoc committee also released its attempts to apply the model to various disease states, including TB. This was done through best guess estimates, consultation with the available literature and consultation with relevant experts in the fields. The committee then attempted to analyse the impact of their TB priority setting exercise by looking at the change in TB publications between 2004 and 2009, eight years after initial publication of the priority setting results. An increase from 20 priority relevant publications in 2004 to 56 in 2009 was noted, although no alignment of these relevant publications with the ranking of the priorities was measured [31]. Furthermore, only absolute changes in numbers of priority relevant publications were assessed, not changes relative to total TB publications (including non-priority relevant publications, which may have also increased substantially over the time period).

Unfortunately the report contains very few references to the data sources used and experts consulted by the committee, nor the methodology used to interpret and construct the model. Therefore, it is hard to gauge the validity of their results. Developing a defined algorithm for the WHO model would help address this validity concern. This thesis will attempt to develop such an algorithm.

## 2.4 CHNRI

### 2.4.1 Theory

The Child Health and Nutrition Research Initiative (CHNRI) framework was developed due to the perceived failure of current priority setting methodologies in recognising the importance of health systems research, and instead having a bias towards basic research. This resulted in

certain diseases which are highly prevalent in child health, such as diarrheal disease, being neglected, because effective interventions already exist and hence when stakeholders identified key research areas it was often left off the list [32]. In many respects the CHNRI is similar to the ENHR and CAM strategy, only it seeks to broaden the stakeholder participation and definition of what constitutes a research area to include areas similar to those defined by the WHO model:

> *"health policy and systems research will reduce disease burden by improving efficiency of health systems in delivering the interventions, implementation research will aim to improve existing non-affordable interventions to make them feasible and affordable in low-income settings, while other types of research will seek new and non-existing interventions."*[32]

It is also similar to the CAM model in that it includes notions of equity, affordability and feasibility. However, the CHNRI suffers similar drawbacks to the ENHR and CAM model in that scoring is still value laden and subjective. Indeed, the CHNRI lists 20 universal challenges for priority setting, number 11 of which is "Development of a simple quantitative way to rank competing research options" [33].

### 2.4.2 Real-world example: MRC

In 2007 the Medical Research Council (MRC) of South Africa embarked on a priority setting exercise using the CHNRI framework [34]. Six academics led the working group, and together they identified 63 research options to address the seven main causes of mortality in children under 5 (9 research options per cause of mortality). Furthermore, it was stipulated that an equal number of research options should come from each research field (health systems, biomedical and basic research). This list of research options was then scored by six technical experts using a CHNRI conceptual framework. These scored options were then opened to scoring by a wider stakeholder group.

Some of the limitations of the MRC exercise included the fact that even though all three research fields were given equal consideration, it did not comment on whether this was an equitable distribution (highest distribution to highest need). Furthermore, the priority setting process was limited to a relatively small number of research options because the academics who led the working group felt that an exhaustive list would not be feasible from a human resources perspective. Finally, although the weighting model used was opened to a large stakeholder group, it was found that this input had little to no effect on the scoring of the options initially performed by the technical experts. Nonetheless, the MRC priority setting exercise has resulted in governmental policy changes as well as an acknowledgement by national research funders, including the MRC itself, of a need to align funding decisions with the research priorities [35]. As of yet, no formal assessment of the nature of research being funded nationally has been conducted, so it is unclear whether the policy changes have resulted in a change in practice. However, at a global level at least, the CHNRI reports that investments have begun to align with priorities set in their field [14].

# 3. LIMITATIONS OF PRIORITY SETTING

## 3.1 METHODOLOGICAL LIMITATIONS

While the methods described in section 2 appear to have had some success in effecting change in research agendas, they nonetheless all suffer from limitations, both in terms of the information used to set the priorities, and in terms of the involvement of the stakeholders and how their input is handled. Combined, these limitations affect the legitimacy of the priority setting process.

### 3.1.1 Limitations with respect to information

Many priority setting frameworks advocate the use of evidence in priority setting, however there is often a paucity of reliable data to use in developing countries, whose scant resources make priority setting even more essential. Thus, any quantitative models should require as few data inputs as possible [36]. Because the data is also likely to be numerous, and the stakeholders involved in priority setting are likely to be a heterogeneous mix, it is important to present all available data in a condensed yet comprehensible manner [36].

### 3.1.2 Limitations of stakeholders

Determining and recruiting an equitable composition of stakeholders (to achieve legitimacy) is a major struggle for many priority setting endeavours. However, even if such a composition is achieved, there still arise many difficulties in decision making by stakeholders, in particular scoring mechanisms for competing priorities. Stakeholders can lack the technical knowledge to make informed decisions, or can make biased decisions in their favour. One of the proposed solutions is the creation of an algorithm using a transparent set of criteria to assist with selection amongst competing research priorities [16], however there has been limited research in the area of developing such an algorithm.

### 3.1.3 Legitimacy

Given the limitations on knowledge and problems with stakeholder input, current priority setting methods encounter difficulties with objectivity and complexity. These problems limit their perceived legitimacy, which can impact on the translation of priorities into research outcomes. Based on experience with developing countries' priority setting processes, quantitative heavy methods, such as the WHO model, can ameliorate these two problems. In particular, quantitative models can bring legitimacy to ranking of priority areas, and assist with the presentation and interpretation of complex quantitative data [36].

## 3.2 PHILOSOPHICAL LIMITATIONS

Given the current methodological limitations of priority setting, some scientists and philosophers argue that it is not a worthwhile endeavour as the outcomes are likely no better than more effortless ad hoc decisions would be. Even if a legitimate priority setting process were developed, there are still some arguments against setting priorities. Firstly, the inherent

uncertainty of the future makes it impossible to account for the needs of the future and hence set relevant priorities in the present [37]. The counter argument to this is to accept some degree of uncertainty about the future, but to emphasize that priority setting still has some predictive value and prepares research better for the future than no priority setting at all [16].

A second argument against priority setting is the observation that many of the world's most important scientific breakthroughs have come from areas that are not research priorities at the time, and that by setting priorities in research areas as opposed to encouraging research excellence, such discoveries may be stifled [38]. This is a valid argument, and hence it is important that research priorities should be framed in terms of the general areas required, with enough academic freedom for the researchers to use their own problem solving techniques and innovative thinking. This ties into a further concern, that of priority setting being viewed as a bureaucratic process that seeks to enforce the direction of research. This can potentially be met with resistance by the researchers if they do not feel they are involved in the priority setting process and hence are being forced to do research against their will. This is also a valid argument, and highlights the importance of having an appropriate stakeholder composition in the setting of priorities. Cognisance of these limitations can be seen in most priority setting methodologies when put into practice.

## 3.3 PRACTICAL LIMITATIONS

The practical limitations in setting research priorities include: buy-in from researchers, resource distribution and the defining of research by area.

### 3.3.1 Researcher buy-in

Generally, in order for researchers to willingly conduct research in priority areas they must agree with the priorities set. This is achieved principally through a consultative process with researchers in the setting of priorities. Unfortunately, in many developing countries where priorities are set, insufficient knowledge dissemination networks exist, and hence many researchers, funders and institutions are not even aware of national priorities, let alone invited to participate in there formulation [39].

Researcher buy-in can also be encouraged with proper management. There are rules and regulations which govern researchers, either at a national or institutional level, which require them to focus their research in priority areas, such as the European Charter for Researchers [40]. This top down managerial approach does not always result in research alignment, although the proper financial and career incentives do appear to be effective [41].

### 3.3.2 Resource distribution

Even if funders and researchers are made aware of research priorities, the current models do not specify what this means in practical terms, with respects to financial and infrastructure distribution. Different research areas incur different costs, with their outcomes not always matching the investments [42]. Basic research can be very expensive and only result in marginal improvements in health, whereas some health systems research can incur a negligible cost and result in significant improvements in health. Unfortunately very little data exists on the 'cost-

effectiveness' of field and disease specific research and hence priorities can only guide the distribution of resources to a limited degree. Nonetheless, even with this limitation, it appears to be better to base allocation of resources according to an imperfect priority process, as opposed to no process, as evidenced by marked improvements in health in those countries which successfully set priorities [16]. Unfortunately this is an area where very little evaluation has been done, and so the strength of argument is largely intuitive and not empirically based.

### 3.3.3 Classification of research

Lastly, research does not always neatly fit into the defined categories decided upon by priority setting exercises. For example, HIV vaccine research could lead to a cheaper intervention, cure currently unavertable disease and be more easily integrated into the health system, and hence would fall into all three categories of the WHO model. Similarly, public health research that is not disease specific, such as health worker motivation, could have significant impact on priority areas yet could easily be overlooked by the classic ENHR model. Indeed, Health systems research in general is often ranked low as a priority when priority areas are analysed in isolation to each other [22]. Therefore, any priority setting tool must be able to account for this and produce a holistic view of research priorities, which allows for cross-disease and cross-discipline comparisons to be made.

# 4. DEVELOPMENT OF A QUANTITATIVE MODEL

This dissertation will attempt to develop a quantitative model for the ranking of priorities, based off the principles of the WHO model. It will then define a methodology for construction of the quantitative model. In order to do this, the burden of tuberculosis (TB) in South Africa (SA) will be used as a worked example.

## 4.1 PROBLEMS WITH THE WHO MODEL AND AMENDMENTS

The WHO model in its current state has a few limitations. Starting with the y-axis, the combined efficacy of an intervention, a DALY scale[43] is used with 100% efficacy being equivalent to 0 DALYs per person in the disease population. However, use of a percentage scale limits the cross comparability of the WHO model between diseases, as any efficacy less than 100% will represent a variable number of DALYs. For example, an efficacy of 0% for TB could result in 5 DALYs, whereas an efficacy of 0% in HIV could result in 16 DALYs, as illustrated in Figure 4 below. This problem could be addressed by instead using an absolute DALYs per person scale, and not a percentage efficacy scale.

If using such an approach, construction would start at 0 DALYs, and expand during the completion of the model (Figure 5), as the length of the axis will vary by disease. A further consequence would be that instead of seeking to increase intervention efficacy to 100%, the amended model would instead seek to reduce DALYs per person to 0. The second component to the WHO model, the x-axis of 'effective coverage in the population', is similar to the y-axis in that coverage percentage is not an absolute figure and thus limits cross comparability. Each disease has a unique burden, and so achieving 100% coverage may equate to treating or preventing 100 cases in one disease, and 10 000 in another. The amended model will therefore use absolute disease burden figures on the x-axis instead. Similarly, the goal of the new model will be to reduce absolute disease burden to 0, as opposed to increasing effective coverage to 100% in the original model.

The change of these two axes will allow for a more practical interpretation of the WHO model, and allow for cross comparisons between diseases due to the use of standard health metrics. Furthermore this will absolve the inconsistency between the axes and the area of the WHO quadrangle being equivalent to the total DALY burden of disease, as DALYs per person multiplied by absolute disease burden is a more accurate reflection of the total DALYs of a disease than coverage multiplied by efficacy. DALY and disease burden data is also more readily available, compared to efficacy and coverage data, and so the model will be easier to construct.

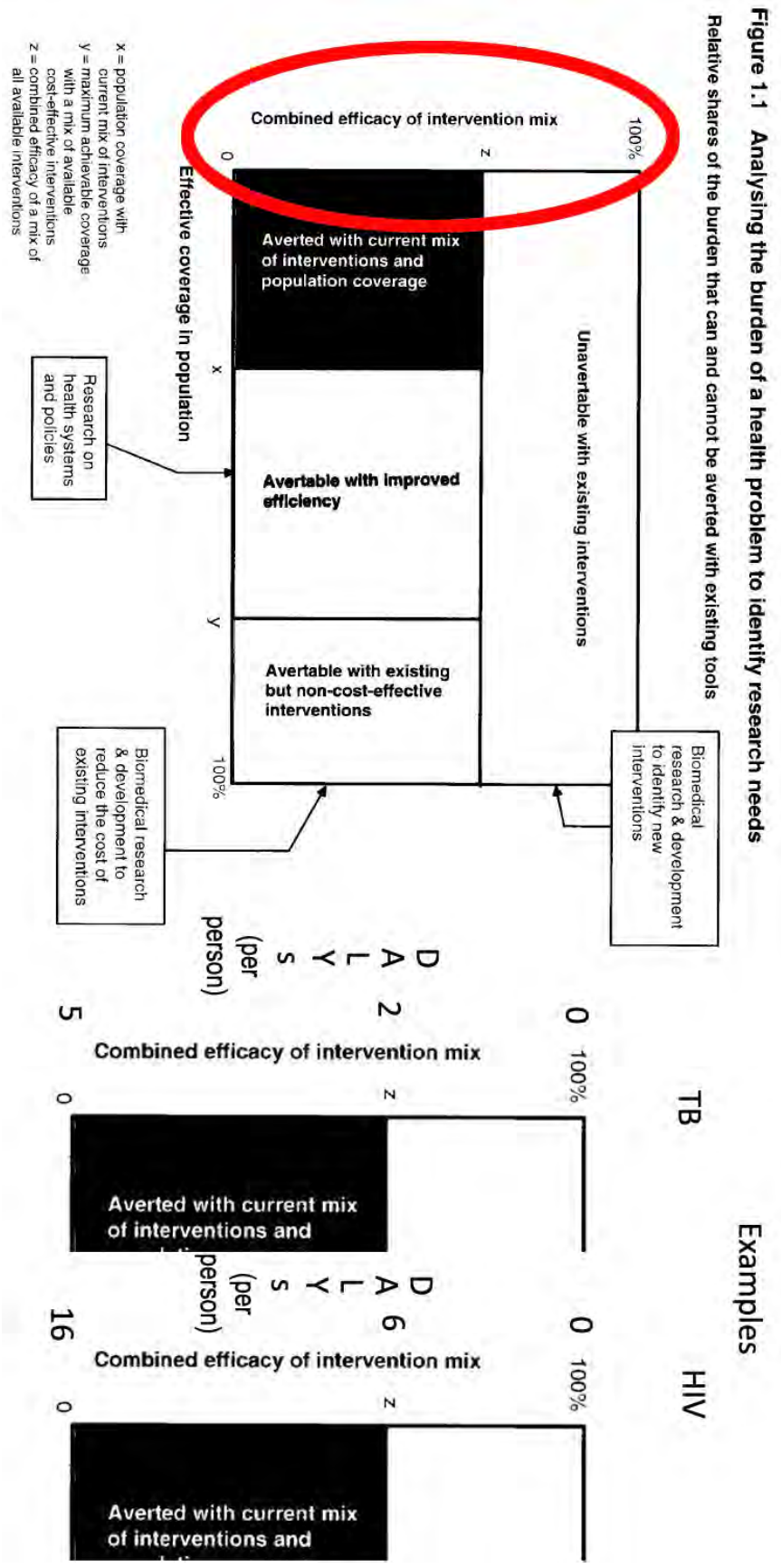


**Figure 4: Breakdown of the y-axis of the WHO model. 100% efficacy of an intervention mix can equate to averting a different number of DALYs depending on the disease being analysed, as illustrated with TB and HIV on the right.**

The second problem with the WHO model involves the way it is subdivided into its various components. The current manner of division limits the effect of improvements in health systems efficiency and use of non-cost effective interventions to only improving coverage in the population. However, these changes could also increase the efficacy of the intervention mix, and hence the model will be amended to allow for this (Figure 5). Furthermore, the WHO model applies the effects of these two improvements to the current DALYs of a disease independently of each other. This is problematic, as if improvements using one strategy were made, reducing the DALY burden of disease, then the impact of the second strategy should be applied to this revised DALY burden and not the original DALYs. The methodology of the construction of the amended model will address this issue by nesting the components within each other.

The amended model will therefore have a slightly different 'inverted' format, as represented in Figure 5, whilst retaining the fundamental essence of the original WHO model. The two axes will be inverted, in the sense that the goal will now be to reduce both axis values (0 DALYs pp and 0 disease burden) as opposed to reaching 100% coverage and intervention efficacy.

This same four subdivisions of the original WHO model will still apply (Unavertable with existing interventions, Averted with current mix of interventions and population coverage, Avertable with improved efficiency, and Avertable with existing but non-cost-effective interventions), however the amendment will have the following consequences:

- the 'averted with current mix of interventions and population coverage' section used to map the percentage of DALYs averted by an intervention, in a percentage of the population with the disease. The new model will map what additional DALYS pp would exist in the absence of the current intervention mix, as well as how much larger the absolute burden of the disease would be.
- The 'unavertable with existing interventions' section used to describe the maximum percentage of efficacy attainable with existing interventions, irrespective of cost or health system constraints. The new model will instead describe the maximum reduction in DALYs pp and disease burden attainable with current interventions, regardless of cost or health system constraints.
- The 'avertable with improved efficiency' and 'avertable with existing, but non cost effective interventions' sections in the original model detailed the additional percentage coverage possible in the population with improved efficiency of the health system or use of non-cost effective interventions. The new model will describe the reduction in DALYs pp and disease burden possible with improvements in efficiency and use of non-cost effective interventions. Furthermore, the new model will detail the consequences of improving efficiency first, and then using non-cost effective interventions on the remaining DALYs (and vice versa), as opposed to applying both to the original DALYs. This new quadrangle will henceforth be referred to as the burden of disease (BoD) box.

No methodology has been described to subdivide the quadrangle proposed by the WHO model, other than the very vague 'consulting with the literature and relevant experts' [30]. Therefore an original methodology for subdividing the amended model was developed. In order to do this, TB in South Africa was used as a worked example.

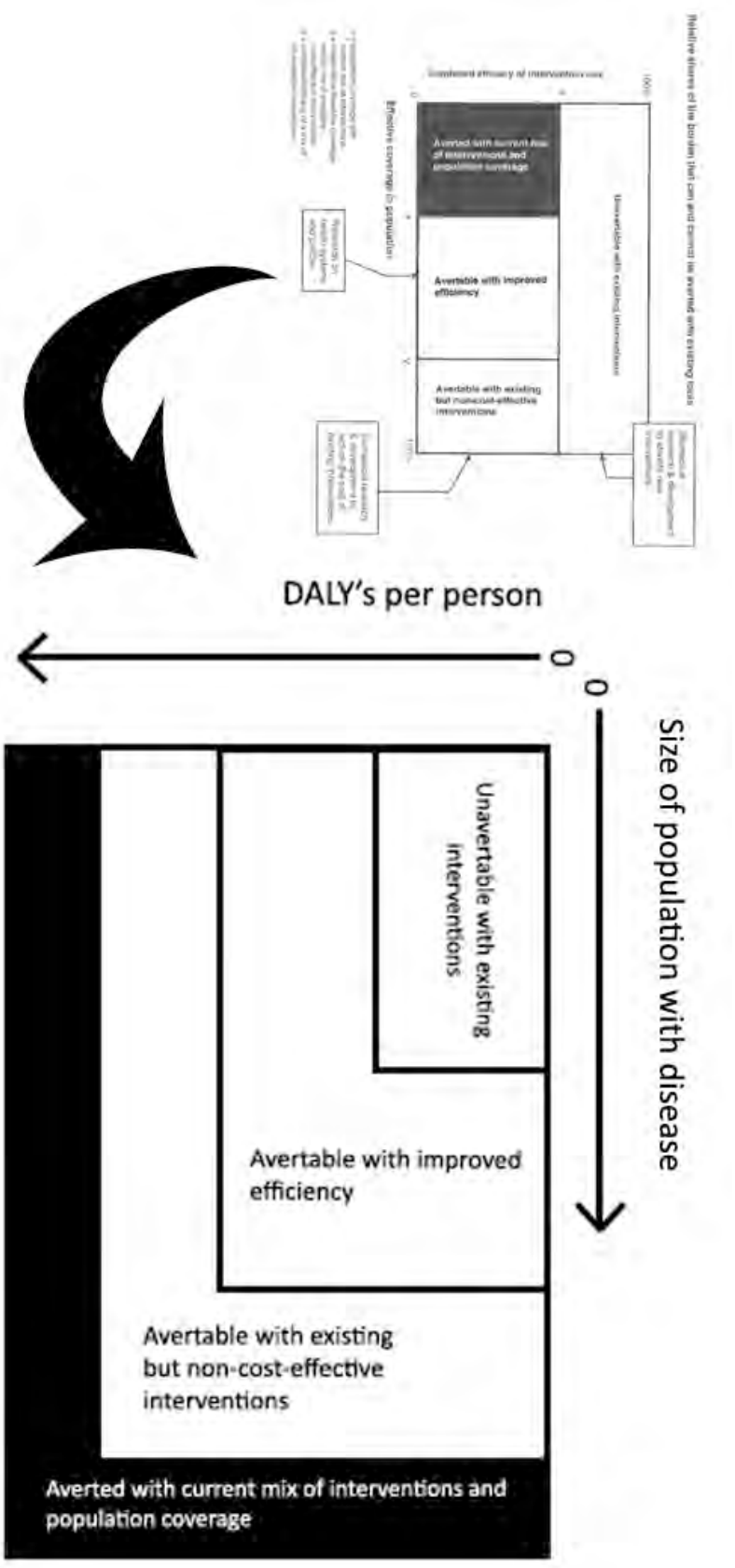


**Figure 5: Amendment of the WHO model. The 'combined efficacy of intervention mix' axis is replaced by a 'DALYs per person' axis, and the 'effective coverage in the population' axis is replaced by a 'size of population with disease' axis. Improvements in efficiency and use of non-cost-effective interventions are now allowed to impact both axes, and are nested within each other.**

## 4.2 TUBERCULOSIS

Amongst infectious diseases, TB is the second highest contributor to deaths worldwide, second only to HIV (although the two are closely linked) [44]. For this reason reduction of TB is part of the 6th Millennium Development Goal of the United Nations [45]. TB is also a disease of the resource poor developing world [44], and hence setting priorities in its research is of particular importance.

TB is an appropriate disease to use as a worked example as many priority setting exercises have focused on it (e.g. the WHO has published a list of 77 research priority questions for TB covering a host of topics [31]). This is useful as it will allow comparisons of priority setting outcomes of the amended model with those of other methods to see where there is agreement and disagreement. Furthermore, TB is an ideal candidate for a worked example as there is a plethora of data available on TB, with over 99% of cases reported on [46], and hence any methodology developed should at the very least be able to be applied to TB.

## 4.3 TB DATA

In order to address the problem of data paucity in developing countries, data sources will be limited to those that are widely available for as many countries as possible. As such, WHO report statistics will mostly be drawn upon, in particular the Global Burden of Disease and the Global Tuberculosis reports, which gather data from as many of the WHO member states as possible. In cases of missing data for member countries, the WHO also extrapolates figures using a combination of modelling based on similar countries' data and corroborating indirect evidence within the country [47].

The WHO has been collecting data on TB in conjunction with the STOP TB program since 2001, and has amassed a rich database from over 1000 partners (in more than 100 countries) of burden of disease, financial and epidemiological data [48]. This wealth of data makes it a suitable starting point for developing a model on setting research priorities as it gives an idea of the 'gold standard' potential data that could be available for a disease. Thus any priority setting model should at the very least be able to be constructed using the TB dataset.

### 4.3.1 DALYs

The DALY (Disability Adjusted Life Year) was first conceptualised following the Global Burden of Disease study conducted by the World Bank in 1992. One of the major drawbacks of the study was that it focused primarily on mortality as an outcome, and did not accurately account for the impact of nonfatal diseases. Thus, the DALY was constructed to incorporate both mortality and disability due to an illness into a single measure [43]. Four basic tenets surround the construction of a DALY value. Firstly, any indicator of health impact of a disease should include both mortality and altered health status. As such, DALYs are a combination of the number of years of life lost due to a disease, as well as the decrease in the quality, due to the disease, of those remaining years of life lived [43]. For example, if a disease reduced a patient's quality of

life by 25%, then for every four years living with the disease, the patient would have suffered 1 DALY. The second tenet states that the only demographic considerations should be age and sex. This is because older people and men, on average, have less years of life to lose if they contract a fatal disease, and so their DALY scores should be weighted to account for this. The third tenet states that like health outcomes should be treated as like. In other words, if two individuals of the same age and sex contract a disease that results in their death, then the DALYs caused by those deaths should be treated as equal, irrespective of the personal differences between those two individuals (such as socioeconomic background or even if different diseases caused their deaths). Finally, the fourth tenet states that time (in this case number of years) should be the unit of measurement for burden of disease.

The DALY has many strengths as disease burden indicator. Primarily, it allows for the quantification of nonfatal diseases, which can have a very high burden on the population. It also provides a standard metric to measure the outcome of a specific intervention, making it particularly well suited to priority setting. It also makes projections on the future impact of a disease which allows for forward looking priority setting [49]. The DALY is currently also the most widely accepted burden of disease indicator, and is argued by its proponents as being the crucial measure of burden of disease for priority setting in health research [43], and hence there is a wealth of DALY data available for many diseases and countries, even though it does have some limitations and criticisms.

The major conceptual criticism of the DALY is that it measures the quantity of ill-health of a disease as opposed to the burden. The distinction being that the burden is influenced by factors such as social support and economic status, amongst others, of the people inflicted with the disease [50]. This is a powerful argument, supported by real-world evidence[51], and so attempts are being made to quantify DALYs in a more comprehensive manner, which takes into account the socioeconomic factors influencing disease burden [52]. Many of the other criticisms against the DALY are methodological issues: weighting by age and discounting future life for example. Some of these criticisms can, and have, been addressed by changes in the DALY methodology [53].

Despite these criticisms and shortcomings, the DALY is still widely used by international organisations such as the World Bank and WHO, and is the most readily available and accepted data type. Furthermore, Rosenberger suggests that the best practice for deciding on priorities in health research is to consult with either QALY (Quality Adjusted Life Years) or DALY estimates to get an idea of the burden of disease [18]. As such, the DALY will be used in construction of the amended model, bearing in mind that it is an imperfect estimate.

### 4.3.2 Disease burden

There are two measurements of disease burden that are relevant to priority setting, incidence and prevalence. Incidence is the rate of new or recurring cases of a disease, whereas prevalence is the number of individuals with the disease at a given period or point in time [54]. Some diseases have a high incidence but are cured relatively quickly and so have low prevalence, such as diarrheal diseases [55]. Others may have a relatively low incidence, but a high prevalence, such as chronic diseases like hypertension [56]. It is important to include both measurements, as research can be geared towards preventive interventions (which would reduce incidence), or curative interventions (which would reduce prevalence). Therefore, because TB is an infectious yet curable disease, it is most important to include incidence, yet because it can also last up to

three years if untreated [57], prevalence estimates are also important. Therefore both measures of disease burden must be incorporated into the model. A simple addition of the prevalence and incidence rates would result in overestimation of the burden (as some of the prevalent cases for the time period may overlap with incident cases for the same time period), however in the absence of any more sophisticated models for estimating disease burden it is a crude estimate that allows both measurements to be captured, even if it is not a true reflection of the disease burden. Prevalence and incidence data for TB will be sourced from the WHO Global Tuberculosis Report, which provides annual estimates of TB prevalence and incidence for member states per 100 000 population. Data from 2004 will be used so as to chronologically match with the DALY data. It is important to note that only 19 member states derive their prevalence estimates from survey data, the remainder are inferred from incidence rate estimates and average duration of disease data, which does call into question the reliability of this data [44]. Nonetheless, the WHO data is currently the best data available, and in the interests of consistency, will still be used in the model, bearing in mind its limitations.

### 4.3.3 Financial

The financial data used in construction of the amended model will also come from the WHO Global Tuberculosis report, which has collected data from a subset of member states since 2006. It includes both government and donor funds, which make up to 41% of funding in some cases [44]. Costs include: first-line drugs, National Tuberculosis Control Programme staff, programme management and supervision, laboratory equipment and supplies, collaborative TB/HIV activities, operational research, surveys, hospital stays and clinic visits. Costs per patient treated are case-weighted (costs are adjusted relative to the specifics of the case, such as patient age, which may affect the costs) three-year averages between the years of 2004–2006, and are controlled for some confounders such as non-annual expenses on buildings, equipment, buffer stocks of drugs, etc. [44]. However, the financial data does not take into account economies of scope and hence could be confounded somewhat by issues such as pre-existing infrastructure that reduces the cost of delivery; nor do they account for economies of scale, which could reduce price with up-scaling of service delivery.

### 4.3.4 Cost-effectiveness

There are a wealth of published cost-effectiveness studies pertaining to TB, and other diseases, both communicable and non-communicable. The Disease Control Priorities Project (DCPP) has published an exhaustive review of such literature, with a focus on developing countries, containing summaries of cost-effectiveness for over 26 disease areas, including TB [58]. This was published in 2006, which does mean there is a slight chronological disparity between this data and some of the WHO data. Nonetheless, cost-effectiveness data will be used to calculate gains in efficiency with existing but non-cost-effective interventions.

## 4.4 Construction of the Amended WHO Model

When the WHO model was originally proposed, no methodology was detailed for its construction [30]. This has limited its applicability, and therefore the methodology used in construction of the amended model will be detailed in this section. This methodology will be used to construct the amended model for TB in South Africa, and may not be entirely

appropriate for all contexts, however it will provide a base methodology that can be adapted as required in other settings.

### 4.4.1 The BoD Box

In order to construct the BoD box for TB, DALY data from the WHO 2004 Burden of Disease dataset [59], which provides DALYs per 100 000 people for WHO member states, will be used. This will then be cross-referenced with the WHO Global TB Report dataset [60], which provides data on TB prevalence and incidence per 100 000. By dividing DALYs per 100 000 by the sum of prevalence and incidence (hereafter just referred to as disease burden) per 100 000, a crude estimate of the DALYs per person (DALY pp) can be gained:

**Equation 1:**

$$\frac{\text{DALYs per 100 000}}{\text{Disease burden per 100 000}} = \text{DALYs per person (pp)}$$

This will constitute the y-axis of the BoD box. The x-axis will simply be the absolute disease burden of TB for South Africa, extrapolated from the per 100 000 estimates to the entire population. Therefore the absolute area of the quadrangle formed will represent the absolute DALYs of TB in South Africa. The validity of an aggregate DALY score per person may raise concerns around issues such as equity, as DALYs are unlikely to be uniformly distributed across the population, but this is an issue that could be better addressed as a separate axis in priority setting, as advocated by the CAM model.

### 4.4.2 The currently averted section

The DALYs from TB which are currently being averted are equivalent to the additional DALYs that would be incurred if South Africa completely stopped treating TB. This includes both direct healthcare interventions, as well as broader social interventions such as sanitation. Trying to calculate the DALYs for TB in such a hypothetical case would be difficult, as TB (and indeed most disease) is complex, with multiple factors playing a role in its impact and subsequent DALY burden, and all of these would need to be accounted for. A far more useful comparison would be to determine what the worst possible prognosis for TB is in the world, and compare this to South Africa. In other words, the worst performing country in the world would represent the global lowest baseline of access to healthcare for TB (be it direct treatment, or indirect such as sanitation or social support), and hence the more accurate worst case prognosis for the disease (as opposed to a hypothetical complete absence of treatment scenario). Therefore, to get an idea of how many TB DALYs South Africa is currently averting, the DALYs pp (y-axis of the BoD box) in all the member states where data is available will first be calculated, using the same formula stipulated in section 4.4.1. Using this data a relative comparison of the country with the worst DALYS pp and South Africa's DALYs pp will be made, and the difference in DALYs pp will be appended to the y-axis as DALYs averted. Similarly, for the hypothetical worst absolute disease burden (x-axis), the member state with the worst disease burden per 100 000 will be used, and extrapolated to the South African population, using equation 2:

**Equation 2:**

*South African Population* x *Worst disease burden per 100 000 = Hypothetical absolute worst*

*100 000* *disease burden*

This equation allows South Africa's population size to be taken into account, and reflects what the disease burden in South Africa would be if their prevalence and incidence were as bad as the worst performing country. Importantly, one country might have the worst DALYs pp, whereas a different country may have the worst disease burden per 100 000, and the worst performer in either case will be used.

In this a way, a hypothetical box will be created of what South Africa's TB BoD box would be if it had both the worst DALYs possible as well as the worst disease burden possible (Figure 6). The difference between this hypothetical and the actual BoD box will give an idea of how many DALYs pp South Africa is currently averting through every avenue (not just direct health interventions, but also wider influences such as sanitation and infrastructure). Of course, as mentioned with the assumption of the worst DALY pp and worst absolute disease burden, this "currently averted" section may not be the true burden of disease averted, because even the poorest performing country is still providing some form of service delivery to ameliorate the burden of disease. Furthermore this model assumes that worst DALYs pp and worst absolute disease burden are mutually exclusive. It is hypothetically possible that the country with the worst disease burden may be particularly susceptible to contracting the disease, but that that same susceptibility confers some protection in reducing DALYs and hence it would never be possible to achieve a situation where a country has both the worst disease burden *and* the worst DALYs pp. Furthermore, there are potentially immutable factors such as genetic susceptibility of the population which exacerbate the disease burden or DALYs pp of the worst performing country, and hence are not transferable completely to a country which has a population with a different genetic makeup. An attempt could be made to control for such variables, but this would be complex and given the infancy of this model, is something best left for further studies if the model proves successful.

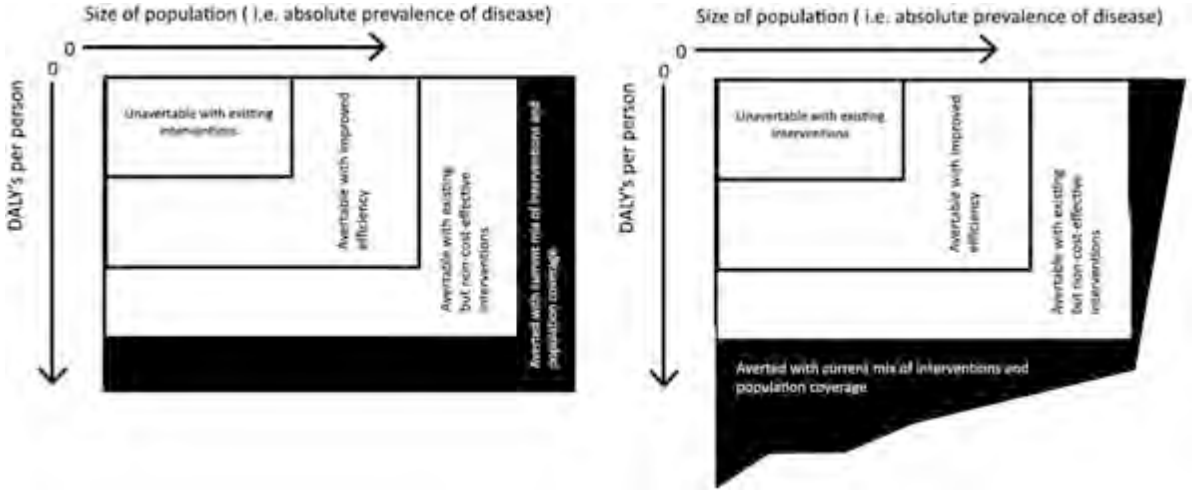


**Figure 6: The Currently Averted Section. On the left, averted DALYs are averaged. On the right, DALYs are presented as a distribution of individual DALYs per person. In both cases the total area of averted DALYs remains the same.**

Finally, while the total area will be a reflection of the disease burden averted, it may be the case that certain individuals have a worse prognosis, while others have a better one, and so the true reflection may be more like something illustrated in figure 6 above. However, in order to determine this it would require a lot more information, and as the total area of averted DALYs (black shaded area) remains the same in both cases, and because the distribution is not pertinent to the scoring process of priority setting in this study, it is not necessary to include in the model calculations. Furthermore, a mean estimate of how bad the burden of TB is will help control for confounding variables.

### 4.4.3 The unavertable with existing interventions section

A similar method will be used to construct the "Unavertable with existing interventions" section of the BoD box. In this case however, the country with the lowest DALY pp and the country with the lowest disease burden per 100 000 will be used, with the same extrapolations done to give a 'best case' scenario:

**Equation 3:**

*South Africa's DALY pp – Best DALY pp = Avertable DALYs with existing interventions*

**Equation 4:**

$$\frac{\text{South African Population}}{100\,000} \times \text{Best disease burden per 100 000} = \text{Hypothetical absolute best disease burden}$$

The premise of this method is that countries which have the lowest DALYs pp and disease burden respectively are using all available technologies to their fullest extent in a near perfectly functioning health system, and therefore any residual DALYs are much more likely to be attributable to a lack of known interventions than any other factor.

It is again assumed that disease burden and DALYs pp are mutually exclusive. That is to say, the interventions used by the particular country with the lowest DALYs pp do not indirectly increase its disease burden. Thus, the resulting 'unavertable' box is a hypothetical scenario where the best DALY reducing and disease burden reducing strategies are employed, irrespective of mitigating factors such as financial constraints. Furthermore, while it may also be true that particular individuals have lower DALYs, using the average DALY expectancy and not individual cases, helps control for possible confounding variables in individual cases, such as gender or genetics.

As with construction of the "currently averted" section, this methodology has limitations. Primarily, it is likely that even the country with the best outcome indicators still has financial constraints and flaws in policy and service delivery. Thus, there may be some component of this hypothetical 'unavertable' section that could be attributed to these factors, which may lead to an overestimation of how many DALYs are unavertable with existing interventions. Conversely, even the best performing countries are likely to have socioeconomic disparities which lead to some individuals not receiving service and technology available, which will lead to overestimation of how many DALYs are unavertable. Therefore, this methodology has a degree

of variance that could be either greater or lesser than the true value, and hence is only a rough estimate.

In addition, there may be immutable factors outside of the realm of health systems, such as climate or population density, which allow a particular country to achieve low DALYs pp. Because factors like climate cannot be altered, it may mean that what is unavertable in one country is not necessarily equivalent to what is unavertable in a country with different immutable factors, and hence lowers the validity of using these figures to make inferences about different countries. An attempt could be made to control for these variables, such as weighting based on variables of interest, however in the interests of simplicity and consistency of data sources, this methodology will focus only on extrapolations from the WHO burden of disease data and no other variables.

### 4.4.4 The avertable with improved efficiency section

In order to construct the Avertable with improved efficiency section, 'cost per patient treated' data provided by the WHO for a host of member states since 2006 will be used, weighted by treatment outcome, as detailed in equation 5:

**Equation 5:**

$$\frac{\text{Cost per patient treated}}{1 \,/\, [\text{DALYs pp (previously calculated, section 4.4.1.)}]} = \text{Weighted Cost per patient}$$

The numerator is the cost per patient treated, which must be minimised in the most efficient state. However, the outcomes of the patients treatment are also of interest, and hence the cost per patient will be weighted by the DALYs pp. Because the DALYs pp would also be minimised in the most efficient state, the denominator is 1/ [DALYs pp] so that a smaller DALY pp score would result in a larger denominator and hence a smaller weighted cost per patient score overall. For example, if countries A and B both spend US$10 per patient treated, yet country A has a DALY pp score of 1 and country B has a DALY score of 2, the resultant weighted cost per patient scores would be US$10 for country A and US$20 (10/[1/2]) for country B. Once cost per patient scores have been weighted, the member state with the lowest score can be determined and compared to South Africa's score. The ratio of these two scores will give an idea of the degree to which total DALYs could theoretically be averted with improved efficiency:

**Equation 6:**

$$\frac{\text{Best outcomes weighted score}}{\text{South Africa's outcomes weighted score}} = \text{Proportion of South Africa's DALYs avertable with improved efficiency}$$

Using the above examples of Country A and B, it would suggest that US$10/US$20 = 0.5 of the burden of Country B could be averted if they were as efficient as Country A.

The amended model will assume that the ratio of DALY pp to disease burden would remain essentially unchanged, and hence the shape of the 'Avertable with improved efficiency' box would remain congruent with the BoD box (i.e. the x and y axis ratios would remain fixed). An attempt could be made to tease out the exact changes in the DALY pp and disease burden ratios, however the model is primarily interested in what proportion 'Avertable with improved efficiency' contributes to the overall BoD box, and not what the actual distribution would be in

real life, so for the sake of simplicity of the model, an assumption of no changes in the ratio will be made. This is a limitation of the model as it is hard to tease out financing with respects to individual DALYs and absolute prevalence and incidence. For example, it could be that a particular country has very good preventive measures, but those who do develop TB suffer a high DALY due to poor treatment.

A further limitation of this methodology is the nature of the costs included in the 'cost per patient' calculation provided by the WHO, as previously outlined in section 4.2, which do not include economies of scale or scope. However this is not necessarily a problem in this case, as these can be viewed as health systems issues and hence it is appropriate to include them in the models calculation. For example, it may be that TB drugs need a well-run cold-supply chain, and the existence of this chain is driving down the DALY pp value in the best performing country (economy of scope). By including this variable in the efficiency calculation it includes that proportion of the disease which could be averted if health systems research were performed to elucidate the economies of scope and scaled that result in timely TB drug delivery (i.e. a well-run cold-supply chain).

The 'cost per patient' data given by the WHO are also in US dollars and do not take into account factors such as purchasing power parity or general economic differences between the countries being compared, which may confound the results. These values can be back converted to the original currency of the member state and then converted into International Dollars using a purchasing power parity conversion factor. This conversion will be performed on the data, and both results will be reported.

### 4.4.5 The avertable with existing but non-cost-effective interventions section

There are two potential approaches that can be taken to complete this final section. Firstly, from a theoretical standpoint it need not be calculated in any formal manner, as it should just be the remainder of the BoD box, once all other sections have been constructed and accounted for. Secondly, cost-effectiveness data can be consulted to estimate how many additional DALYs are reduced with more expensive treatment.

Comprehensive reviews of cost-effectiveness studies are detailed by the Disease Control Priorities Project report [58]. This report summarises the costs of various treatments as well as their efficacy in improving treatment outcome (expressed as a percentage) for various geographical regions. From this it can be extrapolated how many DALYs could be averted if the more effective, but also more expensive treatment was reduced in cost, using the equation below:

**Equation 7:**

$$\frac{\textit{South Africa's efficacy (based on current treatment programs)}}{\textit{Best Efficacy (irrespective of cost)}} = \textit{Increased ratio of DALYs avertable with improved biomedical research}$$

The results of equation 7 will inform a hypothetical reduction in the x-axis of the BoD box, but may not be instructive in disease burden measures depending on the type of modelling done. For simplicity's sake the assumption will again be made of an equal ratio in disease burden reduction. Importantly, these reductions will be applied to the remaining DALYs after the

reductions from improved efficiency (section 4.4.4) have been applied, and vice versa, with both outcomes reported on.

### 4.4.6 Validation

In order to validate the results of the amended model, comparisons can be made to the questions of the NHRC, the WHO results and the Argentinian CAM results. Both Argentina and the WHO addressed the issue of tuberculosis and HIV, and the NHRC developed priority questions around both diseases. The WHO results can be compared directly, while the Argentinian results can only address the unavertable component. Agreement with these three methodologies does not necessarily validate the results, however if it does agree with the results it would strengthen the argument for its use as applying the algorithm developed in this thesis would be less labour intensive and more evidence based than the current methods of priority setting.

Disagreement does not invalidate the models results either, as there would be no way to tell which of the results is closer to the truth as there is no gold standard of priority setting to compare to. Furthermore, the Argentinian and WHO results are not specific to South Africa, which limits their comparability. Thus the best that can be done is to ensure internal validity, which will be achieved by looking at how much of the BoD box constructed is accounted for by the four sections. If the four sections account for the majority of the DALYs it will indicate that there is at least some internal validity in the proposed methodology. The degree of the BoD box that remains unaccounted for once all the sections have been calculated should give an idea of the uncertainty inherent in the model. Assuming equal uncertainty in all four sections, a quarter of these remaining DALYs can be taken and expressed as a percentage of the total for each section to give a confidence interval estimate for the model's results.

While it is likely to be impossible to develop a specific methodology that is applicable to all diseases due to the variation in data availability with each disease, a particular generalizable *approach* to the construction of the amended model can nonetheless be developed.

For the Unavertable with existing interventions section the literature can be reviewed on those countries identified as having the lowest DALYs pp and disease burden per 100 000 to see if there is any agreement with them having exceptionally good health provision systems. A similar literature search can be performed on the worst performing countries used to construct the currently averted section.

Finally, it is important to remember that this model is only meant to feed into a broader priority setting process, such as the CAM. Hence, many of its limitations can be addressed, or taken into account, during such proceedings.

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# Setting priorities in health research using the World Health Organisation proposed model: Development of a quantitative methodology using tuberculosis in South Africa as a worked example

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## ABSTRACT (350 WORDS):

**Background:** Setting priorities is important in health research as there are limited resources available for research. Various guidelines exist to assist in the priority setting process, however priority setting still faces significant challenges, such as clear ranking of identified priorities. The World Health Organisation (WHO) proposed a Disability Adjusted Life Year (DALY) based model to rank priorities by research area (basic, health systems and biomedical), by dividing the DALYs into 'unavertable with existing interventions', 'avertable with improved efficiency' and 'avertable with existing but non-cost-effective interventions' respectively. However, the model has conceptual flaws and no clear methodology for its construction. Therefore, the aim of this paper was to amend the model to address these flaws, and develop a clear methodology by using tuberculosis in South Africa as a worked example.
**Methods:** An amended model was constructed to represent total DALYs as the product of DALYs per person and absolute burden of disease. These figures were calculated for all countries from WHO datasets. The lowest figures achieved by any country were assumed to represent 'unavertable with existing interventions' if extrapolated to South Africa. The ratio of 'cost per patient treated' (adjusted for purchasing power, and outcome weighted) between South Africa and the best country was used to calculate the 'avertable with improved efficiency section'. And finally 'avertable with existing but non-cost-effective interventions' was calculated using Disease Control Priorities Project efficacy data, and the ratio between the best intervention and South Africa's current intervention, irrespective of cost.
**Results:** The amended model shows that South Africa has a TB burden of 1 009 837.3 DALYs. 0.009% of DALYs are unavertable with existing interventions, 96.3% of DALYs could be averted with improvements in efficiency. Of the remaining DALYs, a further 56.9% could be averted with existing but non-cost-effective interventions.
**Conclusions:** The amended model was successfully constructed using limited data sources. The generalizability of the data used is the main limitation of the model. More complex formulas are required to deal with such potential confounding variables; however the results act as starting point for development of a more robust model.

## Keywords:

Priority setting, health research, quantitative model, WHO, tuberculosis,

## Background

The demand for health research far outstrips the current financial and capacity resources made available to do so [1], and hence it is important to set priorities when making decisions about what research to undertake. Furthermore, priorities should be set in a transparent, rational and systematic manner. This need was articulated by The Commission on Health Research for Development in 1990 [2], and led to the formation of The Council on Health Research for Development (COHRED), which celebrates its 20th anniversary this year. COHRED is arguably the world leader in priority setting in health research, and over the past two decades has fostered an international movement towards procedural priority setting. While COHRED does not endorse a specific priority setting process, they do provide general guidelines on best practices for countries that wish to set health research priorities [3]. Broadly, processes should involve quantitative data inputs as well as participation from stakeholders, such as researchers, funders, politicians, community members, health workers, economists and civil servants. These two inputs are then used to identify priorities, which can range from specific research questions to broader disease areas. The identified priorities are subsequently ranked in order of importance, usually with a greater focus on stakeholder input and less focus on quantitative data inputs. There are a variety of frameworks, like the Calibration Adjusted Matrix (CAM)[4] or the Essential National Health Research (ENHR) [5] framework, which provide guidelines on priority identification and ranking, such as what data is relevant, which stakeholders should be involved in the identification of research priorities, what criteria are used in priority identification and how the research priorities identified are ranked. However, despite the COHRED guidelines and a plethora of frameworks, priority setting still faces significant challenges, such as the uncertainty of health research outcomes, ensuring that the priority setting process is transparent and fair, and defining relevant criteria to identify and rank priorities [6]. This paper will address the challenge of subjectivity in ranking criteria, and the need for a clearly defined, transparent and quantitative methodology to rank priorities [7]. Importantly, this methodology must also be relatively simple, as priority setting can be most beneficial in resource scarce developing countries, which generally have a paucity of data and expertise relevant for ranking priorities [7].

Current ranking techniques are divided into two categories, either direct or indirect [3]. Direct techniques involve contrasting two priorities and selecting the one of greater importance, such as a discrete choice method. Indirect techniques utilise a scoring system which scores a priority based on a list of criteria, and then calculates a cumulative score using a formula that incorporates all the criteria listed. While this latter method increases the transparency and standardises ranking of priorities, the criteria used, and their weighting, is determined by stakeholder input and is therefore highly subjective. The World Health Organisation (WHO) proposed an alternative, quantitative-based, model for ranking priorities by research area in 1996, as outlined in Figure 1.

In this model, Disability Adjusted Life Years (DALYs) are used to construct a quadrangle for a particular disease. This quadrangle consists of two axes, namely how much of the population affected could be treated with interventions, and how effective the interventions could be at treating the disease. Four subdivisions are then listed. Firstly, how well the current interventions are working, both in terms of treatment efficacy and population coverage, defined

as the 'averted with current mix of interventions and population coverage' section. Secondly, what additional coverage could be obtained with gains in health systems and policy research, defined as the 'avertable with improved efficiency' section. Thirdly, what gains in coverage could be obtained with biomedical research to reduce the cost of interventions, defined as the 'avertable with existing but non-cost-effective interventions' section. And lastly, gains in effectiveness of interventions from basic and clinical research to identify new interventions, defined as the 'unavertable with existing interventions' section. By using this model, priority areas can be identified and ranked in terms of disease and research area automatically, as the area of a section would indicate the degree to which research in that disease field (e.g. HIV health systems and policy research) should be a priority relative to other disease fields. However, in its current state the WHO model has some major flaws, both in the methodology and inherent to its structure.

Firstly, one of the main assumptions of the WHO model is that the sum of all the components contributing to coverage and efficacy of interventions would neatly sum to 100% coverage and 100% efficacy. By way of example, in figure 1 current interventions (x value on x-axis) cover roughly 30% of the population, with an additional roughly 40% coverage possible with improvements in efficiency, and approximately 30% additional coverage achievable with use of existing but non-cost-effective interventions. However, it is possible to envisage a situation where just improving efficiency could increase coverage by an extra 60%, or just using non-cost-effective interventions could increase coverage by an extra 60%. The total coverage in such a case would thus be the baseline of 30% plus 120% if both efficiency improvements were made and non-cost-effective interventions adopted, to a total of 150% coverage. As it is not possible to achieve such a thing, it is important to adapt the model to show a relativistic improvement, as the problem arises due to the assumption of mutual exclusivity in the model. The model assumes that with the current burden of disease you could increase coverage by either increasing efficiency or using non-cost-effective interventions. However, these gains are both based on the current disease burden, but if improvements in efficiency were made, then the disease burden would change and the contribution that non-cost effective measures could make would only apply to the new disease burden. Thus it makes more sense to look at relativistic changes. That is to say, if improvements to efficiency were made, what would be the subsequent impact of adoption of non-cost effective interventions, or vice versa.

Secondly, the current construction of the WHO model assumes that use of non-cost effective interventions and increases in health system efficiency will only increase population coverage, and not the efficacy of the interventions, but there is no reason to assume that this will always be the case, and so the model would also need to be amended to allow for changes in both population coverage and efficacy from these two factors. Finally, the current axes are presented in terms of percentage coverage and percentage efficacy of interventions against a disease. However, because disease burdens vary, it limits the viability of cross-comparisons between diseases. Furthermore, it is unclear what 'coverage in the population' means, as it could apply to both provision of treatment for those with the disease, as well as preventive measures for the 'at risk' population. Therefore the axes of the model should also be adapted to present the results in terms of absolute disease burden figures, and not percentage coverage or efficacy. Furthermore, the y-axis of 'coverage in the population' must be more clearly defined and able to incorporate both curative and preventive measures.

It is perhaps for these reasons that the WHO model has largely remained unused, although it has been referenced as a model that could be incorporated into current priority setting frameworks, such as the ENHR or CAM frameworks [4]. This is compounded by the fact that even if the model were made theoretically sound, it is practically not an easy model to construct as data on treatment coverage and efficacy are not available, nor is it clear how to construct the quadrangle as no formal methodology for its construction was ever proposed. This paper has therefore focused on developing an amended model based on the principles of the WHO model, and attempted to define an explicit methodology for its construction using quantitative data. The viability of the amended model was then explored using Tuberculosis (TB) in South Africa (SA) as a worked example.

## Methods

### Amendment of WHO model

The axes of the amended model were changed to those of disease severity (as measured by DALYs per person) and disease burden (as measured by both prevalence and incidence). The revised model thus seeks to reduce severity and disease burden, and subsequently the size of the quadrangle, as opposed to increasing coverage and efficacy as in the original WHO model. Similar to the WHO model, the amended model acknowledges that there is a particular severity and burden of the disease that is unavertable with existing interventions, as well as a larger severity and burden that the current intervention mix is averting. In addition, the portion of the disease that is avertable, could be averted either via increases in efficiency of the health system or use of existing but non-cost-effective interventions, as stipulated by the WHO model. In the amended model, these two routes are allowed to have impact on both burden and severity measures of the disease (Figure 2).

The amended model also nests the 'avertable with existing but non-cost-effective interventions' section within the 'avertable with improved efficiency' section (and vice versa, if so desired), to address the issues of relativistic changes and mutual exclusivity in the original WHO model.

Finally, the revised model appends the additional disease burden and DALYs that are 'averted with current mix of interventions and population coverage' to the ends of each axis.

### Application of amended model to TB

The construction of the amended model for TB involved three stages, as outlined in Figure 3. To construct the x-axis, both incidence and prevalence estimates were consulted. The Global Tuberculosis Control report provides prevalence measures as point estimates of the number of individuals with a disease in the population at a given time based on survey data. It also provides incidence measures as estimates of new and recurring cases of TB over a one year period based on modelling. Disease burden was calculated as the sum of the incidence and prevalence per 100000 estimates for South Africa (SA). While the simple addition of prevalence and incidence estimates may result in overestimation of the disease burden (as some of the incident cases will be double measured by the point prevalence), it does allow for a more accurate reflection of diseases with high incidence but low prevalence (e.g. diarrheal diseases), as well as chronic diseases that may have a low incidence, but a much higher prevalence (e.g. hypertension). It also allows for both preventive measures, which largely impact disease

incidence, and curative measures, which impact disease prevalence, to be accounted for. Therefore it was important to include both measures of incidence and prevalence in the calculation of disease burden. The disease burden was then applied to SA's population size in 2004 to get an absolute disease burden score using equation 1:

**Equation 1**

*(prevalence + incidence per 100000) * (SA Population / 100000) = Absolute disease burden*

For the y-axis, SA's DALYs per person (pp) were calculated using equation 2, with age standardised DALY rates sourced from from WHO 2004 disease burden data [8] and TB prevalence and incidence rates from the 2004 Global Tuberculosis Control report [9].

**Equation 2**

*DALYs per 100000 / (prevalence + incidence per 100000) = DALYs per person*

This quadrangle therefore represents the entire DALYs of TB for SA, which can be attributed to the three mechanisms outlined in the amended model, namely: the proportion which is unavertable with existing interventions, the proportion which is avertable with improved efficiency, and the proportion which is avertable with existing but non-cost-effective interventions.

The second stage was to determine that component of the quadrangle which was currently unavertable with existing interventions, and to append the additional DALYs that are currently being averted. To determine this, DALYs pp and disease burden were calculated for each country where both data was available (appendix 1). Those countries which either had 0 DALYs, incidence or prevalence per 100000 were excluded. Of the remaining countries, the lowest DALY pp score was appended to the y-axis. For the x-axis, the lowest disease burden score was extrapolated using equation 3 the SA population to get a hypothetical absolute lowest disease burden for SA.

The resultant quadrangle was assumed to estimate that portion of the DALYs unavertable with existing interventions, as these are the best figures that any country has been able to achieve. However, even in the best performing countries used to construct this estimate there are other determinants of health, such as climate. These factors may prevent optimal treatment of a disease (e.g. monsoons) or assist in the treatments efficacy (e.g. warm climates). Thus there is a degree of uncertainty around the estimate.

**Equation 3**

*(country with combined lowest incidence + prevalence per 100000) *(SA Population/100000)*

To determine the degree of disease burden currently being averted, the worst performing countries, both in terms of DALYs pp and disease burden, were identified. The same methodology used to calculate the hypothetical best disease burden for SA was used to calculate the hypothetical worst disease burden for SA. These figures were then appended to the current DALY pp and disease burden estimates. The premise being that SA is averting at least as much as the difference between itself and the worst performing countries, if not more so, as even the worst performing countries are likely to be combating TB in some manner.

Two approaches were taken to subdivide the remaining disease burden (stage 3 of Figure 3). In the first approach, the component which could be averted with improved efficiency was first calculated, and then the remaining disease burden was used to calculate what could be averted with existing but non-cost-effective interventions. In the second approach, the component which could be averted with existing but non-cost effective interventions was first calculated, and then the remaining disease burden was used to calculate what could be averted with improvements in efficiency. For both cases, calculations were performed in the same manner. To determine the proportion avertable with improved efficiency, cost per patient treated (CPP) data from 2008 and 2009 (both in US dollars, and adjusted for purchasing power parity) was used. Data from 2008/9 was used as this data has only recently been recorded by the WHO and hence there was no data available for 2004. This value was weighted by DALY pp data to control for the potential differences in outcomes of the treatment, as such:

**Equation 4**

*Cost per patient treated / [1/DALY pp] = Weighted cost per patient*

In equation 4, countries with poor treatment outcomes (i.e. high DALY pp values) will have a small denominator, and hence their cost per patient will be inflated. Alternatively, countries that spend slightly more, but achieve better outcomes, will have a larger denominator and hence their cost per patient will be deflated. The ratio between SA's weighted CPP and the lowest weighted CPP obtained was hypothesized to represent the proportion of total disease burden reduction which could be obtained with improvements in efficiency. It was assumed that the reduction would be an equivalent reduction in DALYs pp and disease burden, and hence the ratio between the axes remained fixed. The degree of the disease which is avertable using existing but non-cost-effective interventions was calculated using TB cost-effectiveness data from the Disease Control Priorities Project report [10]. This report models efficacies of current treatments for TB in 6 global regions, as well as hypothetical best efficacies of interventions in those regions and their respective costs. The ratio between the highest average efficacy achievable by all the existing interventions mentioned in the Sub-Saharan Africa region (irrespective of cost) and the efficacy of SA's current intervention program was assumed to represent the proportion of the disease burden which could be averted with existing but non cost effective interventions. Similarly, it was assumed that this would be equally reflected in disease burden and DALY pp reductions, and hence the ratio between the axes remained fixed.

## Results and Discussion

### Construction of model

Table 1 summarises all the data used in construction of the amended model. SA had a DALY pp value of 1.48. The country with the lowest value was Kiribati with a value of 0.12, whereas the country with the highest value was the United Arab Emirates (UAE) with a value of 13.47 DALYs pp. This is a surprising result for the UAE, as dry climates are known to speed TB recovery [11]. Potential explanations for this include the relatively high contribution by emigrants from South and Southeast Asian countries [12], the increase in multiple drug resistant (MDR) TB, as well as a novel strain of TB among the indigenous population [13]. In terms of disease burden, UAE has a combined prevalence and incidence per 100 000 of 5.7, ranking 7$^{th}$ lowest amongst the member states (appendix 1).

**Table 1: List of figures used to construct amended model**

| Data Type | Value | Country |
|---|---|---|
| **DALY Data** | | |
| DALYs per person (PP) | 1.48 | South Africa |
| Best DALYs PP | 0.12 | Kiribati |
| Worst DALYs PP | 13.47 | UAE |
| **Disease Burden (DB) Data** | | |
| DB / 100000 | 1683 | South Africa |
| Disease Burden | 682 322.47 | South Africa |
| Best DB /100000 | 1.78 | Monaco |
| Best DB | 721.65 | South Africa |
| Worst DB/100000 | 3 342 | Namibia |
| Worst DB | 1 354 915 | South Africa |
| **Cost Per Patient (CPP)** | | |
| Weighted CPP | 404.45 | South Africa |
| Best weighted CPP | 14.29 | Yemen |
| Fold reduction | 28.30 | |
| Weighted CPP PPP adjusted | 621.33 | South Africa |
| Best weighted CPP PPP adjusted | 22.81 | Namibia |
| Fold reduction PPP adjusted | 27.24 | |
| **Cost Efficiency (DCPP) Data** | | |
| Sub Saharan Africa Baseline treatment active infection | 33% | |
| Sub Saharan Africa Best treatment active infection | 71% | |
| Sub Saharan Africa Best treatment latent infection | 80% | |
| Fold Increase | 2.15 | |

This suggests that relatively few people contract TB, but that it is a particularly severe strain. While this does call into question the validity of using UAE as a baseline for worst case scenario, the Cook Islands, Burkina Faso, Mali and Togo all have DALYs pp of greater than 9 (appendix 1), and have vastly disparate climates, genetics and disease profiles. Hence, a DALY pp value of 13.47 is within acceptable range, but a value between 9 and 13 could be a more conservative estimate. The lowest scoring country, Kiribati, has one of the highest incidence rates of TB in the Western Pacific region [14], however it also has stringent treatment guidelines, with patients being quarantined for two months during treatment, and then further confined to a specialised centre until fully healed [15]. This combination of high incidence and strict treatment could account for the resultant low DALY pp value. The small population may limit the generalizability of such a treatment, and this is supported by similar small countries also achieving low DALY pp rates (appendix 1), however it should be noted that larger countries like Australia and Switzerland have DALY pp values of 0.15 and 0.17, respectively. Therefore both UAE and Kiribati figures were used in the construction of the amended model as they did not deviate from the general trend of the member states (Figure 4).

In terms of disease burden, SA had a combined absolute incidence and prevalence of 682 322.5. Monaco had the lowest combined prevalence and incidence of 1.78 per 100 000, whereas Namibia had the highest with 3342 per 100 000. This extrapolated to a hypothetical best and worst disease burden for South Africa of 721.65 and 1 352 915 respectively. Again, the high levels of TB in Namibia, which is a desert area, are unexpected. Possible explanations for this include the high co-morbidity with HIV [16] as well as a high rate of drug resistant TB [17]. Interestingly, similar to UAE, Namibia appears to be plagued by a specific subset of TB which could be exacerbating its disease burden [18]. These differences in disease profiles do limit the generalizability of using Namibia as a worst case scenario, particularly as Namibia is unique in having both the highest incidence per 100 000 and the highest prevalence per 100 000 (by way of example Cambodia has the 2$^{nd}$ highest prevalence but only the 11$^{th}$ highest incidence). Namibia's disease burden score is also disproportionately high compared to the other top five countries (Cambodia, Swaziland, Central African Republic and South Africa) which range from 1683 to 1844 (Figure 4). On the other end of the scale, Monaco had the lowest disease burden score, however this was relatively similar to other low scoring countries. Therefore Monaco was used in the construction of the amended model, and both Namibia and Cambodia were used due to the potential of Namibia as an outlier. From this data the amended model was constructed as shown in Figure 5 (Namibia is included as a shaded extra).

The total potential DALYs that TB could inflict in South Africa are between 10 070 106.53 and 18 250 705.05 depending on whether Namibia was considered, however up to 94.5% of this was averted in 2004 due to the current intervention mix. Importantly, this includes not only direct healthcare such as curative and preventive medicine, but also includes broader interventions such as sanitation and access to health, as well as confounders such as strain subtype and genetic susceptibility to the disease. As a result of these factors, SAs actual burden of TB was 1 009 837.3 DALYs. Of this, 86.6 DALYs [0.009%] were unavertable with existing interventions (too small to be seen at the scale of Figure 5).

**Subdividing existing DALYs**

The weighted cost per patient (CPP) for SA was US$ 404.45, with the lowest weighted CPP being achieved by Yemen at a cost of US$14.29. The DCPP reports a lowest theoretical cost per patient based on their model of US$12, thus the DALY weighted figure is within range of their estimates. When adjusted for purchasing power parity, SA had a value of International (Int.) $621.33, and Namibia replaced Yemen as the most effective with a DALY weighted value of Int.$22.81 (compared to Yemen with a value of Int$24.29). Namibia has managed to continuously improve its health delivery in response to TB since 2004, the year in which it had its highest case notification rate of 16 156. In 2008 this had been reduced to 13 737, with an estimated 83% treatment success rate [19]. By using 2004 burden of disease data with 2008 financing data, it is likely that the figure for Namibia is an underestimation of its true cost-per-patient. Unfortunately, no chronologically matched data exists, which is a limitation of this model, and so it is the best estimate available. Furthermore, Namibia's Int.$ was in a similar range of other low scoring countries (Figure 4) and hence it was used to calculate potential improvements from efficiency. The ratio between SA and Namibia's Int.$ values was 0.035, which suggested all but 3.5% of the current burden of TB could be averted with improvements in efficiency.

The cost efficiency data from the DCPP assumed a baseline efficacy using the treatment active non-infectious intervention of 33% for Sub-Saharan Africa, with a best estimate of 71% efficacy.

Adopting the treatment latent infection intervention, which is currently not used in Sub Saharan Africa and hence has a baseline efficacy of 0%, would result in a best estimate of 80% efficacy. This means that efficacy could be improved 2.42 fold (80/33) using existing but non-cost-effective interventions.

Using these two ratios (the Int.$ CPP ratio and the DCPP ratio), the existing DALYs from TB were subdivided as illustrated in Figure 6. If improvements in efficiency were first adopted, then 972 757.1 [96.5%] DALYs could have been averted. The resulting 37 080.24[3.5%] DALYs could thus be reduced 2.42 fold with adoption of non-cost-effective interventions to leave a remainder of 15 322.41 DALYs (Figure 6). Alternatively if existing non-cost-effective interventions were first adopted, then 592 549.59[58.68%] DALYs could be averted. Of the remaining 417 288.45 DALYs, 96.33% could be averted with gains in efficiency, again leaving a remainder of 15 322.41 DALYs.

**Limitations**

Of the 15 322.41 DALYs remaining (1.52% of the original DALYs for SA), 86.6 are accounted for by the unavertable with existing interventions estimate. The remaining 15235.81 DALYs (1.51% of total DALYs for SA) represents the uncertainty in the model, as under ideal conditions all DALYS should be accounted for by the 4 subsections of the model. It is unclear what this error is attributable to, however the validity of the model can be confirmed by comparing it to the results of other studies. According to the DCPP, 71% of TB disease burden should currently be averted in SA, yet the amended model figures show 89.97% (or 94.5% if Namibia is included) is already being averted. This discrepancy suggests a 1.27 fold difference between the amended models calculations and the DCPP calculations. It is not immediately clear which figure is more accurate, as the DCPP has limitations such as being modelled on Kenya, and using deaths as opposed to DALYs to quantify efficacy. However, if the efficacy of the DCPP data was increased 1.27 fold, it would cover the majority of the unaccounted for DALYs. There is also a degree of uncertainty from the WHO sources of data, as a lot of the country specific data is based on estimates and crude modelling, and the financial data is supplied by the member states and not objectively verified. Finally, there is also a chronological discrepancy between these two data sources, as previously mentioned.

There are also some limitations with the assumptions of the model. The simplified addition of prevalence and incidence to get an estimate of disease burden is crude and requires more refinement. The model can be recalculated on the assumption that either prevalent cases or incident cases are the only contributors to DALY estimates (appendix 2). However, the WHO uses both prevalence and incidence figures in construction of its DALYs [20], and so it is inaccurate to attribute the total DALYs to one disease burden measure. The WHO uses a Generic Disease Modelling System (DISMOD) algorithm to compute prevalence and incidence contributions to DALY estimates, and this algorithm could also potentially be used to construct disease burden estimates. In terms of the accuracy of the DALY pp figures, untreated TB can have a ten year case fatality rate of 70%. Furthermore, those who survive can still be disabled by TB for as long as 10 years and TB is mostly a disease of young to middle-aged adults [21]. As such, the worst case DALY pp estimate of 13.47 DALYs is definitely within the range of what could be expected from TB. In terms of that which is unavertable, a 2006 Tanzanian study suggested that up to 93% of all disease burden was avertable with existing interventions [22].

The results suggest that 98.5% of the TB burden is avertable with existing interventions, which is a reasonable agreement with the Tanzanian figure.

The amended model also assumes no relatedness between disease burden and disease severity, and hence chooses the best and worst DALYs pp and disease burdens independently of each other. In reality it may be impossible to impact the disease burden without impacting the DALYs pp. For example, it is known that TB interventions have different efficacies depending on whether the disease is endemic or rare [10], and hence it may be impossible to achieve both the lowest DALYs pp and the lowest disease burden simultaneously, as the model assumes. The assumptions that disease burden and DALY data can be generalised from one country to another also brings in uncertainty, as there is a high likelihood of confounding variables playing a role. However, the identification and elucidation of these confounders which lead to such low DALY pp or disease burden scores are themselves health systems questions worthy of research.

This model also does not fully account for the host of potential confounding variables, such as economies of scope and climate. While these are acknowledged as limitations of the model, no attempt is made to control or adjust the model for them.

Furthermore, even if the model is assumed to be generally valid, there are still limitations with its applicability. Firstly, the amended model only looks at research area, and not all issues important in priority setting, for example equity. It is therefore important that this model be viewed as a component to feed into a more complex framework, such as the CAM model, and not an end to itself. In addition, while the model suggests the burden of disease which could be reduced by research area, it does not quantify how much should be spent on each of those research areas, as different research incurs different costs and have varying levels of cost-effectiveness [23]. If this data were available, then the areas of the model could be weighted as such to reflect cost-effectiveness. However, given that basic research is typically more expensive then health systems research, it would most likely exaggerate the results of the amended model. Thus, research into the cost-effectiveness of research is required, although this is a requirement for all priority setting processes, and not just this specific model. Lastly, defining what area research falls into is sometimes ambiguous. For example, a TB vaccine could both reduce the unavertable component of the disease, be cheaper than current interventions and be more effectively delivered to the population. The amended model nonetheless highlights the importance of health systems research investments, which traditionally has been a neglected area in research[24], and suggests that any TB research should have health systems at the forefront, even if it is a cross-disciplinary endeavour.

A final limitation to the model is the potential for a disease-specific lens being used to define research priorities, as this would exclude pure health systems research. This could be addressed by summing all the subsections of the amended WHO model across all diseases analysed to get a general idea of how much health systems research is required relative to basic research and biomedical research, however the validity of such a simple summation is unclear.

## Conclusion

This paper provides the first results at attempting to develop a quantitative-only model and methodology for the ranking of research priorities. At its current stage it is a grossly simplified

model, but is widely applicable with limited data inputs. Further refinements are still required, and it does not take into account other ranking relevant criteria such as equity, which would need stakeholder input. Nevertheless, policy makers can use this model in its current form as an efficient way to graphically illustrate burden of disease data for multiple diseases, as well as highlight the relative challenges in tackling those diseases (health systems, basic research, etc.), both within the disease and between diseases. This is useful in steering the desired composition of health research as a whole and health research within a specific disease field.

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## LIST OF ABBREVIATIONS

CAM – Calibration Adjusted Matrix

COHRED – Council On Health Research for Development

CPP – Cost Per Patient Treated

DALY – Disability Adjusted Life Year

DALY pp – DALYs Per Person

DISMOD – Generic Disease Modelling System

ENHR – Essential National Health Research

HIV – Human Immunodeficiency Virus

Int.$ - International dollars

MDR – Multiple Drug Resistant

SA – South Africa

TB – Tuberculosis

UAE – United Arab Emirates

WHO – World Health Organisation

## COMPETING INTERESTS

The authors declare that they have no competing interests.

## AUTHORS CONTRIBUTIONS

DH conceived of the study, and both DH and SC participated in its design and conceptualisation. DH developed the model and collected and analysed the data presented. SC helped to draft the manuscript, and both authors read and approved the final manuscript.

## ACKNOWLEDGEMENTS

Particular acknowledgement goes to Dr Gabriela Montorzi, from COHRED, for mentorship in research priorities, and advice with regards to the amendment of the model and application to TB. Thanks also to Dr Debbie Bradshaw, from the South African Medical Research Council Burden of Disease Unit, for her input on burden of disease data and analysis.

## FIGURE LEGENDS

**Figure 1:** WHO model for ranking of research priorities [8]. Ability to tackle the burden of disease is represented by the efficacy of interventions, and the coverage in the population. Improvements in coverage can be gained via either health systems research or biomedical research to reduce the cost of interventions. Efficacy gains can arise from research to identify new interventions.

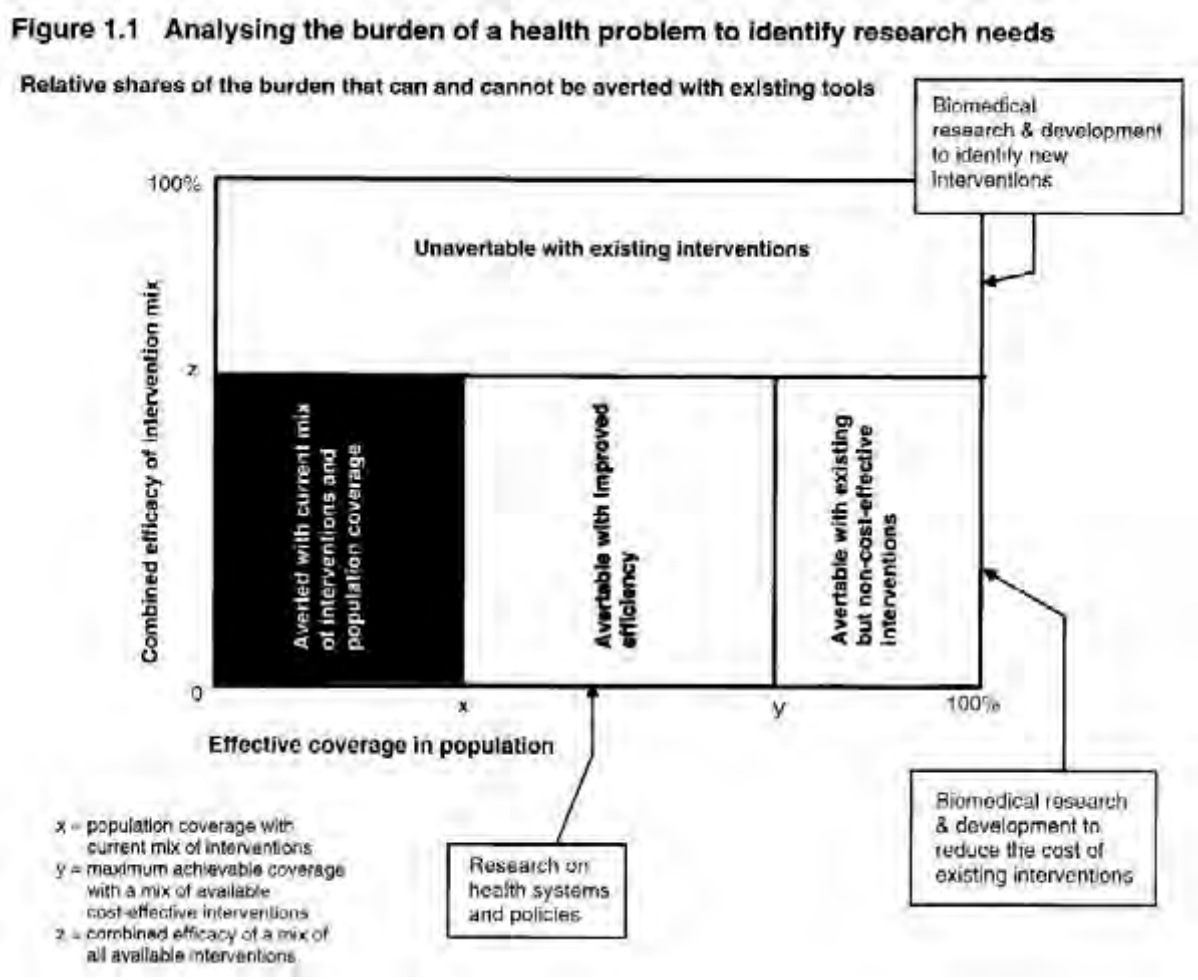
**Figure 2:** Amended model based off of original WHO model. DALYs are represented as a product of disease burden (incorporating both incidence and prevalence measures) and DALYs due to the disease per person. DALYs which are currently being averted are appended to the ends of the axes, while those that currently exist could be averted with either health systems research to improve efficiency, biomedical research to reduce the cost of existing interventions, or research on new interventions to tackle the portion of the burden that not even the best existing interventions can avert.

**Figure 3:** Construction of amended model. Stage One: Construction of the two axes to create the total DALYs attributable to a particular disease. Stage Two: Determination of the DALYs currently being averted as well as those unavertable with existing interventions, based off of best and worst performing member states. Stage Three: Division of current DALYs into those that could be reduced with improvements in health systems, and those that could be reduced with reduction in costs of existing interventions.

**Figure 4:** DALYs per person, Disease Burden and DALY weighted cost (purchasing power parity adjusted) for all member states. Lowest scorers are highlighted in green, highest in red, and South Africa in yellow for reference. Namibia and Eritrea are considered outliers in the Disease Burden and DALY weighted cost graphs respectively, and so the second highest countries are also included.

**Figure 5:** Amended model of TB DALYs for South Africa. South Africa has an average DALY per person (pp) score of 1.48 and and absolute disease burden of 682322. 0.12 DALYs pp and a disease burden of 722 is unavertable with existing interventions, but is too small to see at this scale. South Africa is currently averting a DALY pp figure of 13.47, and an absolute disease burden of between 747 595 and 1 354 915.

**Figure 6:** Subdivision of existing DALYs due to TB for South Africa. In the first graph, reduction from improved efficiency are calculated first, followed by reductions through use of existing but non-cost-effective interventions. In the second graph, these reductions are applied first, followed by the reductions from improved efficiency.

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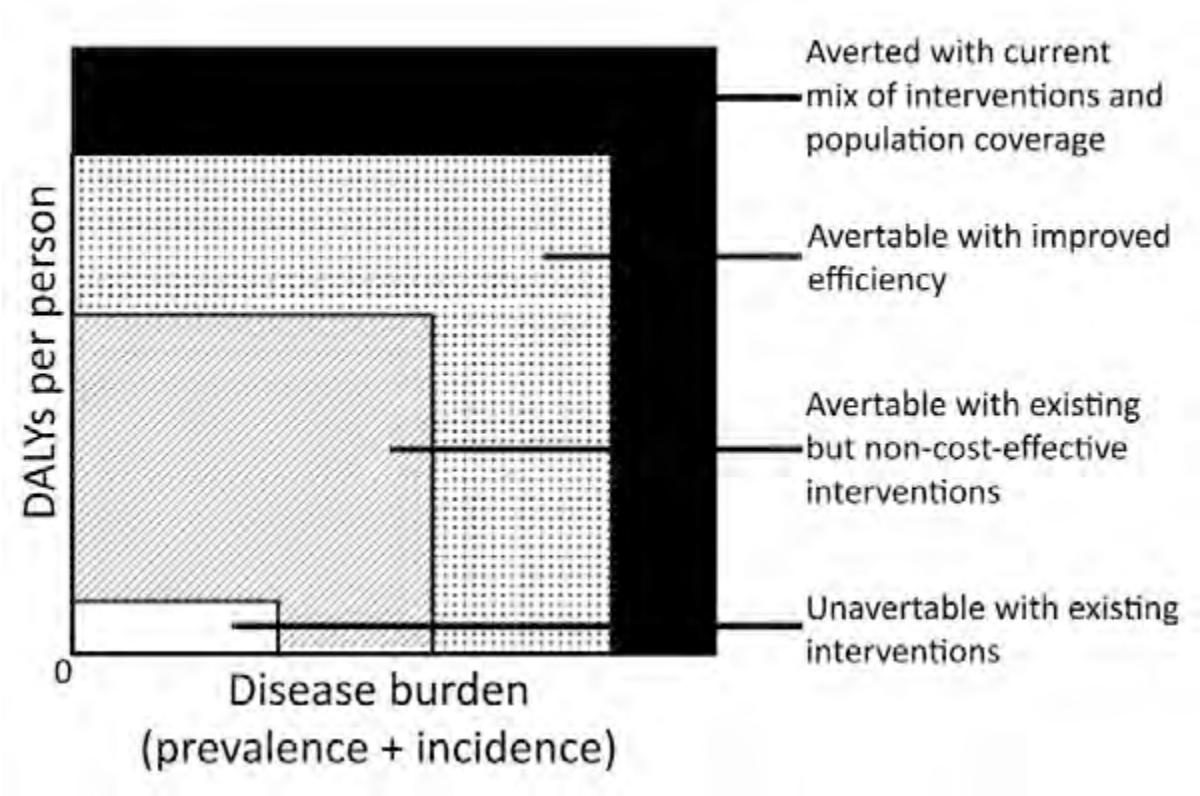


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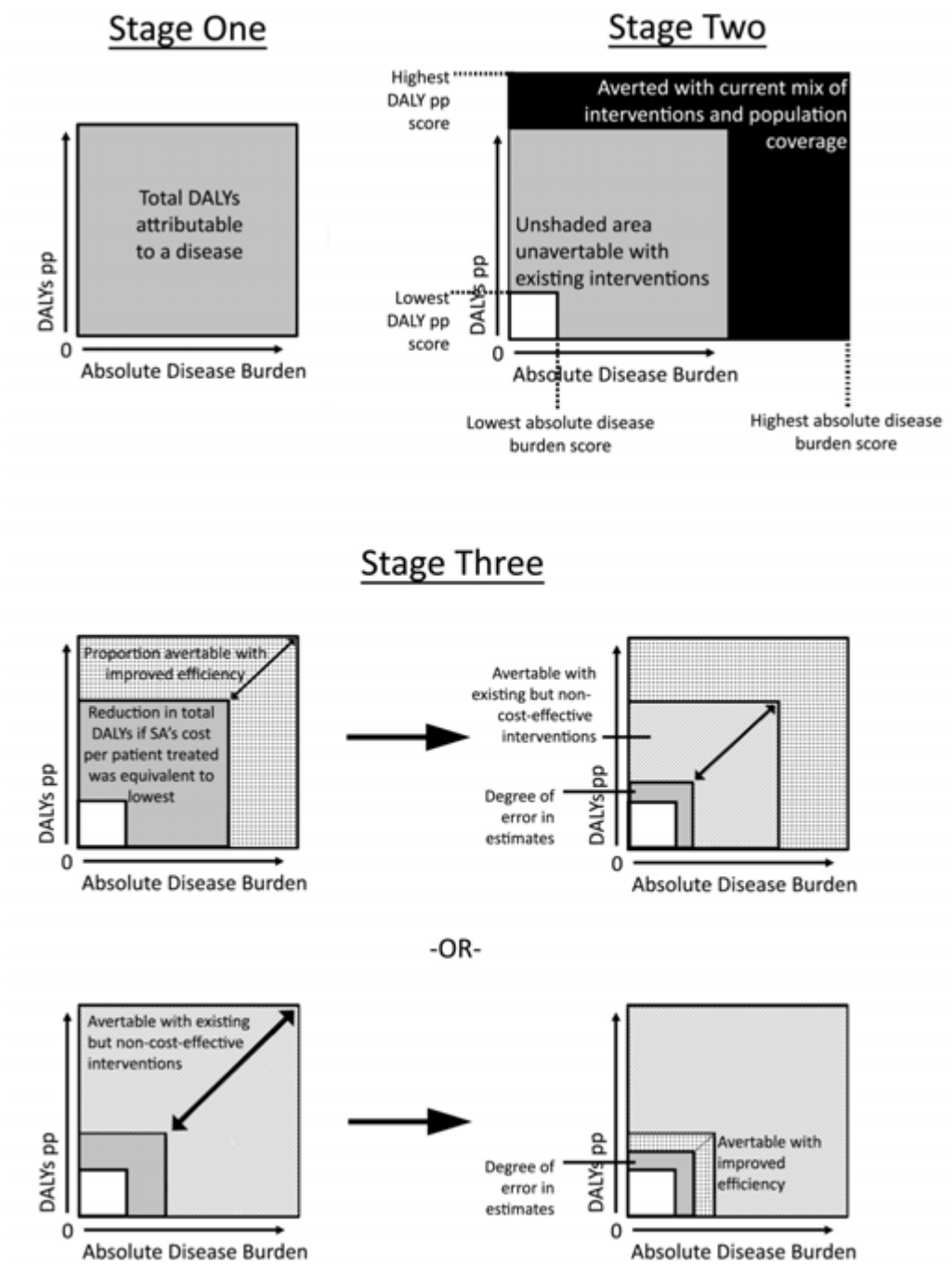


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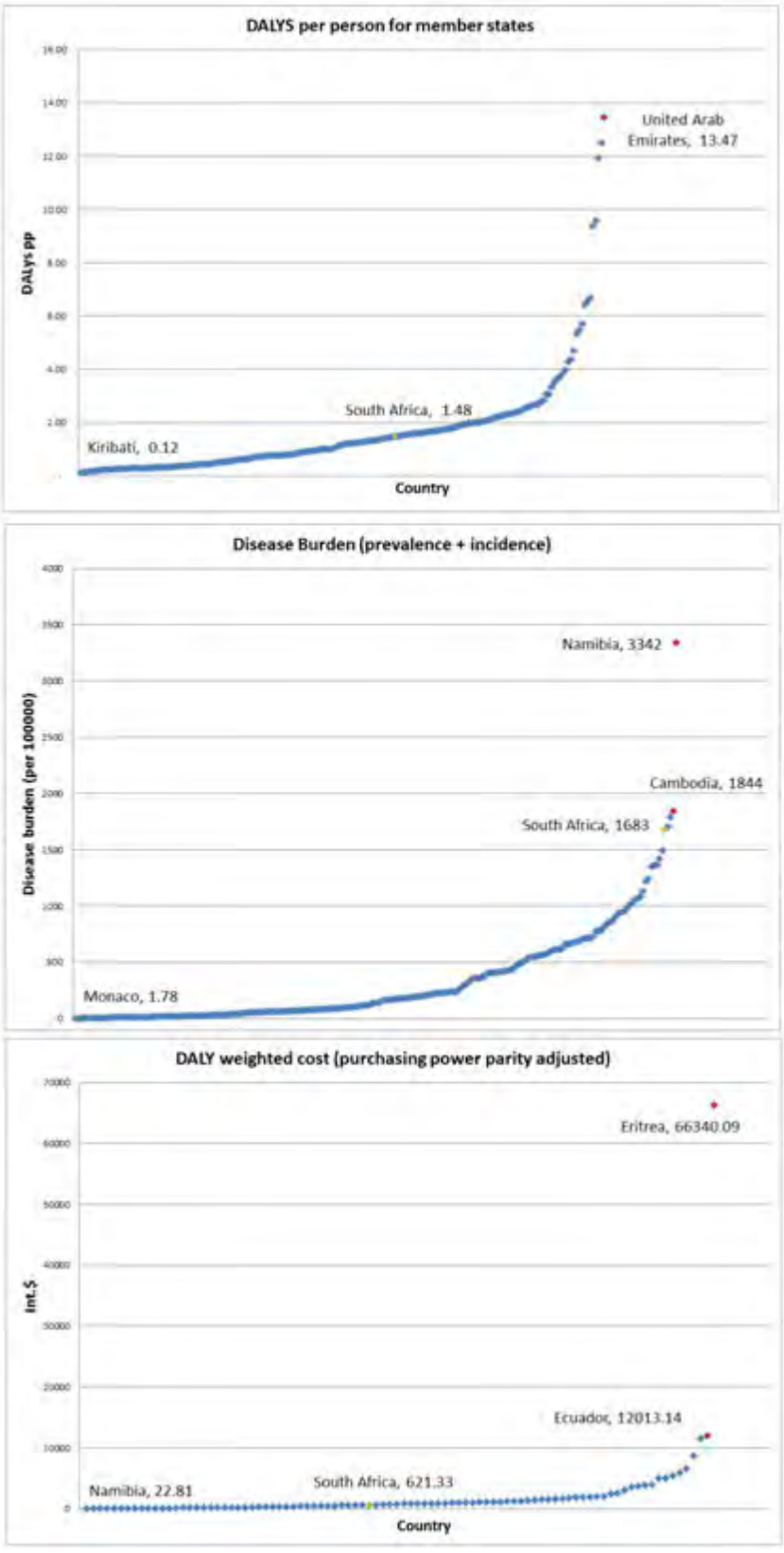


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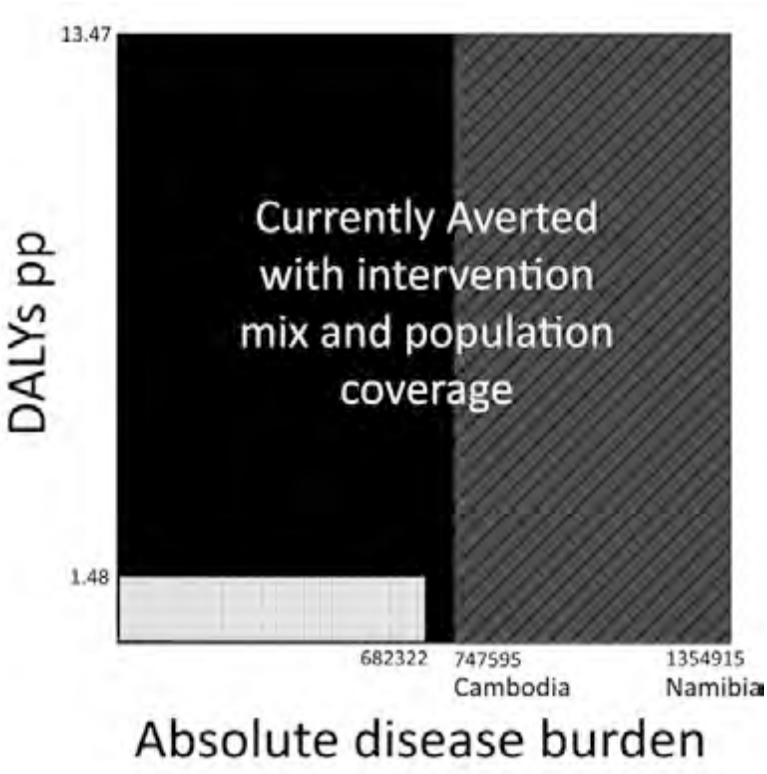


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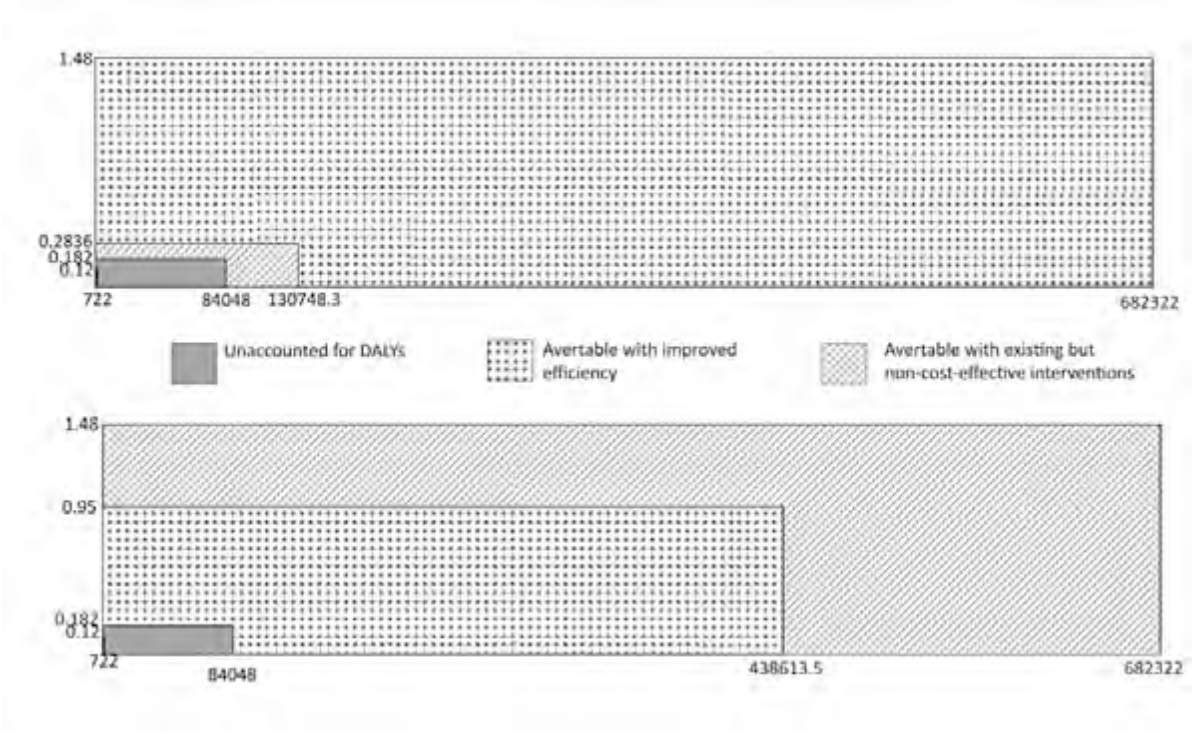


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## APPENDICES

Appendix 1: Country figures (Data Summary Table)

| Country | DALYS / 100 000 (2004)[1] | Prevalence / 100 000 (2004)[1] | Incidence / 100 000 (2004)[1] | Disease Burden (column 2+3) | DALYS pp (column 1/6) | Country Population (2004)[1] | Cost Per Patient Treated in local currency (2008 & 2009)[2] | DALY weighted cost per patient | PPP Adjusted Cost | DALY Weighted Cost PPP Adjusted |
|---|---|---|---|---|---|---|---|---|---|---|
| Afghanistan | 1 589 | 372 | 189 | 561 | 2.83 | 18553819 | 333.9346 | 945.8165483 | 689.0832 | 1951.718 |
| Albania | 59 | 27 | 20 | 47 | 1.25 | 3179442 | | 0 | #DIV/0! | #DIV/0! |
| Algeria | 64 | 130 | 87 | 217 | 0.29 | 27751086 | | 0 | #DIV/0! | #DIV/0! |
| American Samoa | | 18 | 11 | 29 | - | 51885 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Andorra | 11 | 17 | 13 | 30 | 0.35 | 63111 | | 0 | #DIV/0! | #DIV/0! |
| Angola | 875 | 310 | 270 | 580 | 1.51 | 11742960 | | 0 | #DIV/0! | #DIV/0! |
| Anguilla | | 55 | 22 | 77 | - | 9549 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Antigua and Barbuda | 3 | 5.5 | 4.3 | 9.8 | 0.29 | 66895 | | 0 | #DIV/0! | #DIV/0! |
| Argentina | 43 | 47 | 35 | 82 | 0.52 | 34420352 | 77.3195 | 40.23454819 | 181.1911 | 94.28594 |
| Armenia | 246 | 109 | 75 | 184 | 1.34 | 3290540 | 108.2037 | 144.7868436 | 157.8949 | 211.2784 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Aruba | | 8.2 | 6.4 | 14.6 | - | 76762 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Australia | 2 | 7.5 | 5.9 | 13.4 | 0.15 | 17921818 | | 0 | #DIV/0! | #DIV/0! |
| Austria | 7 | 17 | 13 | 30 | 0.22 | 7894229 | | 0 | #DIV/0! | #DIV/0! |
| Azerbaijan | 248 | 945 | 416 | 1361 | 0.18 | 7669735 | | 0 | #DIV/0! | #DIV/0! |
| Bahamas | 91 | 16 | 18 | 34 | 2.67 | 275426 | | 0 | #DIV/0! | #DIV/0! |
| Bahrain | 59 | 53 | 43 | 96 | 0.62 | 545329 | | 0 | #DIV/0! | #DIV/0! |
| Bangladesh | 1 362 | 454 | 225 | 679 | 2.01 | 115059015 | 25.1185 | 50.36855858 | 4304.934 | 8632.415 |
| Barbados | 4 | 5.4 | 4.7 | 10.1 | 0.35 | 262637 | | 0 | #DIV/0! | #DIV/0! |
| Belarus | 223 | 106 | 73 | 179 | 1.24 | 10293127 | | 0 | #DIV/0! | #DIV/0! |
| Belgium | 8 | 15 | 12 | 27 | 0.29 | 10057529 | | 0 | #DIV/0! | #DIV/0! |
| Belize | 161 | 43 | 40 | 83 | 1.94 | 214153 | | 0 | #DIV/0! | #DIV/0! |
| Benin | 458 | 110 | 76 | 186 | 2.46 | 5473217 | | 0 | 434.9904 | 1070.2 |
| Bermuda | | 6.8 | 5.3 | 12.1 | - | 61104 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Bhutan | 588 | 548 | 307 | 855 | 0.69 | 523417 | 3348.1092 | 2304.340641 | 7272.902 | 5005.585 |
| Bolivia (Plurinational State of) | 841 | 243 | 163 | 406 | 2.07 | 7304230 | | 0 | 300.9444 | 623.5328 |
| Bonaire, Saint Eustatius and Saba | | 6 | 0.69 | 6.69 | - | 18488 | | #DIV/0! | | #DIV/0! |
| Bosnia and | | 59 | 53 | 112 | | 3462032 | | 0 | #DIV/0! | #DIV/0! |

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|---|---|---|---|---|---|---|---|---|---|---|
| Herzegovina | 86 | | | | 0.76 | | | | | |
| Botswana | 1 063 | 591 | 773 | 1364 | 0.78 | 1546414 | 341.0421 | 265.7866553 | 560.7541 | 437.0163 |
| Brazil | 148 | 62 | 53 | 115 | 1.29 | 159398558 | 573.5483 | 738.2083593 | 656.0267 | 844.3655 |
| British Virgin Islands | | 4.7 | 3.6 | 8.3 | - | 18070 | | #DIV/0! | | #DIV/0! |
| Brunei Darussalam | 122 | 85 | 66 | 151 | 0.81 | 282000 | | 0 | #DIV/0! | #DIV/0! |
| Bulgaria | 51 | 81 | 56 | 137 | 0.37 | 8449971 | 4128.15 | 1543.853009 | 6796.483 | 2541.761 |
| Burkina Faso | 1 581 | 101 | 64 | 165 | 9.58 | 10401025 | 180.0903 | 1725.285272 | 324.6236 | 3109.93 |
| Burundi | 2 333 | 285 | 212 | 497 | 4.69 | 6017127 | 107.0442 | 502.525781 | 228.7816 | 1074.03 |
| CÃ´te d'Ivoire | 2 069 | 387 | 287 | 674 | 3.07 | 14253952 | 222.3401 | 682.527225 | 303.546 | 931.8086 |
| Cambodia | 2 266 | 1318 | 526 | 1844 | 1.23 | 10862069 | 141.3513 | 173.7064967 | 274.932 | 337.8637 |
| Cameroon | 604 | 394 | 317 | 711 | 0.85 | 13589699 | 82.4731 | 70.11554136 | 123.7221 | 105.1839 |
| Canada | 3 | 6.9 | 5.5 | 12.4 | 0.22 | 29009032 | | 0 | #DIV/0! | #DIV/0! |
| Cape Verde | 1 305 | 270 | 155 | 425 | 3.07 | 385101 | 466.5605 | 1432.266093 | 413.5754 | 1269.61 |
| Cayman Islands | | 1.9 | 1.5 | 3.4 | - | 31437 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Central African Republic | 1 708 | 939 | 763 | 1702 | 1.00 | 3247456 | 184.2757 | 184.9444185 | 251.4566 | 252.3691 |
| Chad | 1 931 | 212 | 151 | 363 | 5.32 | 6785842 | | 0 | #DIV/0! | #DIV/0! |
| Chile | 42 | 32 | 22 | 54 | 0.77 | 14174890 | | 0 | #DIV/0! | #DIV/0! |

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|---|---|---|---|---|---|---|---|---|---|---|
| China | 275 | 146 | 95 | 241 | 1.14 | 1201522570 | 189.2202 | 215.9534553 | 314.8542 | 359.3372 |
| China, Hong Kong SAR | | 125 | 98 | 223 | - | 6048024 | | #DIV/0! | | #DIV/0! |
| China, Macao SAR | | 113 | 88 | 201 | - | 391906 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Colombia | 153 | 56 | 39 | 95 | 1.61 | 35797965 | 866.0785 | 1397.463438 | 1526.205 | 2462.612 |
| Comoros | 235 | 68 | 36 | 104 | 2.26 | 482401 | | 0 | #DIV/0! | #DIV/0! |
| Congo | 1 655 | 512 | 430 | 942 | 1.76 | 2658948 | 145.6943 | 256.0136007 | 163.1492 | 286.6853 |
| Cook Islands | 130 | 7.8 | 6.1 | 13.9 | 9.36 | 18252 | | 0 | #DIV/0! | #DIV/0! |
| Costa Rica | 28 | 41 | 25 | 66 | 0.43 | 3384498 | | 0 | #DIV/0! | #DIV/0! |
| Croatia | 45 | 39 | 31 | 70 | 0.65 | 4658613 | | 0 | #DIV/0! | #DIV/0! |
| Cuba | 6 | 14 | 9.6 | 23.6 | 0.27 | 10847842 | | 0 | #DIV/0! | #DIV/0! |
| CuraÃ§ao | | | | 0 | #DIV/0! | 145939 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Cyprus | 8 | 4.6 | 3.6 | 8.2 | 1.00 | 837205 | | 0 | #DIV/0! | #DIV/0! |
| Czech Republic | 8 | 15 | 12 | 27 | 0.29 | 10322561 | | 0 | #DIV/0! | #DIV/0! |
| Democratic People's Republic of Korea | 260 | 605 | 344 | 949 | 0.27 | 21471407 | | 0 | #DIV/0! | #DIV/0! |
| Democratic Republic of the Congo | 1 898 | 514 | 327 | 841 | 2.26 | 42650247 | 190.6451 | 430.2699879 | 239.5707 | 540.691 |
| Denmark | | 10 | 8.3 | 18.3 | | 5212071 | | 0 | #DIV/0! | #DIV/0! |

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|---|---|---|---|---|---|---|---|---|---|---|
| | 6 | | | | 0.31 | | | | | |
| Djibouti | 3 181 | 871 | 619 | 1490 | 2.13 | 613219 | 20.5778 | 43.93110657 | 30.75249 | 65.65284 |
| Dominica | 12 | 20 | 14 | 34 | | 71350 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Dominican Republic | 334 | 116 | 85 | 201 | 1.66 | 7774932 | 357.2499 | 592.7850616 | 522.2096 | 866.5028 |
| Ecuador | 612 | 149 | 88 | 237 | 2.58 | 11173647 | 2419.3625 | 6246.83095 | 4652.62 | 12013.14 |
| Egypt | 75 | 34 | 22 | 56 | 1.34 | 61032081 | 540.3559 | 725.3474818 | 1144.283 | 1536.03 |
| El Salvador | 189 | 43 | 32 | 75 | 2.53 | 5663820 | 905.4206 | 2286.226251 | 1561.07 | 3941.769 |
| Equatorial Guinea | 1 141 | 313 | 206 | 519 | 2.20 | 428005 | | 0 | #DIV/0! | #DIV/0! |
| Eritrea | 1 705 | 185 | 126 | 311 | 5.48 | 3186063 | 5296.0846 | 29029.17743 | 12103.09 | 66340.09 |
| Estonia | 136 | 57 | 46 | 103 | 1.32 | 1467016 | | 0 | #DIV/0! | #DIV/0! |
| Ethiopia | 1 976 | 350 | 359 | 709 | 2.79 | 55281054 | 147.4628 | 411.0578664 | 297.7255 | 829.9206 |
| Fiji | 66 | 82 | 42 | 124 | 0.53 | 765725 | | 0 | #DIV/0! | #DIV/0! |
| Finland | 7 | 10 | 7.8 | 17.8 | 0.38 | 5086368 | | 0 | #DIV/0! | #DIV/0! |
| France | 8 | 14 | 11 | 25 | 0.32 | 57628904 | | 0 | #DIV/0! | #DIV/0! |
| French Polynesia | | 34 | 26 | 60 | - | 211583 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Gabon | 1 078 | 757 | 597 | 1354 | 0.80 | 1055707 | 262.4412 | 209.0094655 | 267.8666 | 213.3303 |
| Gambia | 1 076 | 378 | 244 | 622 | 1.73 | 1094974 | | 0 | #DIV/0! | #DIV/0! |

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|---|---|---|---|---|---|---|---|---|---|---|
| Georgia | 266 | 354 | 193 | 547 | 0.49 | 5157814 | 1509.878 | 733.8208697 | 2386.581 | 1159.91 |
| Germany | 5 | 10 | 8.2 | 18.2 | 0.28 | 81495194 | | 0 | #DIV/0! | #DIV/0! |
| Ghana | 1 189 | 173 | 125 | 298 | 3.99 | 16554855 | 480.9518 | 1919.075928 | 912.15 | 3639.627 |
| Greece | 8 | 7.5 | 5.9 | 13.4 | 0.63 | 10574134 | | 0 | #DIV/0! | #DIV/0! |
| Greenland | | 227 | 178 | 405 | - | 55631 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Grenada | 2 | 8.6 | 4.3 | 12.9 | 0.17 | 99313 | | 0 | #DIV/0! | #DIV/0! |
| Guam | | 42 | 32 | 74 | - | 143492 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Guatemala | 361 | 118 | 65 | 183 | 1.97 | 9788284 | 319.6153 | 631.109185 | 464.6974 | 917.5869 |
| Guinea | 1 310 | 329 | 216 | 545 | 2.40 | 7249558 | | 0 | #DIV/0! | #DIV/0! |
| Guinea-Bissau | 952 | 286 | 207 | 493 | 1.93 | 1103003 | 87.1826 | 168.4353608 | 128.5097 | 248.2786 |
| Guyana | 350 | 124 | 115 | 239 | 1.46 | 726552 | 2169.6615 | 3175.521418 | 3471.152 | 5080.386 |
| Haiti | 1 470 | 393 | 277 | 670 | 2.19 | 7724690 | 18.161 | 39.85560667 | 28.60248 | 62.77018 |
| Honduras | 298 | 133 | 96 | 229 | 1.30 | 5440691 | 487.3005 | 634.7016747 | 837.4317 | 1090.742 |
| Hungary | 41 | 31 | 24 | 55 | 0.74 | 10342427 | | 0 | #DIV/0! | #DIV/0! |
| Iceland | 4 | 4.4 | 3.7 | 8.1 | 0.50 | 264909 | | 0 | #DIV/0! | #DIV/0! |
| India | 726 | 383 | 212 | 595 | 1.22 | 946373316 | 44.5227 | 54.31456733 | 111.4199 | 135.9245 |
| Indonesia | 1 167 | 370 | 201 | 571 | 2.04 | 196488446 | 196.7636 | 402.1400916 | 379.7913 | 776.2071 |

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|---|---|---|---|---|---|---|---|---|---|---|
| Iran (Islamic Republic of) | 84 | 32 | 21 | 53 | 1.59 | 58808655 | 59.4036 | 94.63038897 | 126.8188 | 202.0233 |
| Iraq | 314 | 68 | 49 | 117 | 2.68 | 19633844 | | 0 | #DIV/0! | #DIV/0! |
| Ireland | 8 | 14 | 11 | 25 | 0.33 | 3586685 | | 0 | #DIV/0! | #DIV/0! |
| Israel | 7 | 9.6 | 7.7 | 17.3 | 0.43 | 5164345 | | 0 | #DIV/0! | #DIV/0! |
| Italy | 5 | 9.5 | 7.7 | 17.2 | 0.27 | 56965197 | | 0 | #DIV/0! | #DIV/0! |
| Jamaica | 20 | 8.4 | 6.5 | 14.9 | 1.34 | 2439337 | 134.205 | 179.9076925 | 170.1972 | 228.1568 |
| Japan | 16 | 34 | 27 | 61 | 0.27 | 124097649 | | 0 | #DIV/0! | #DIV/0! |
| Jordan | 15 | 9.2 | 7.2 | 16.4 | 0.91 | 4216536 | 3363.6363 | 3070.542797 | 4183.891 | 3819.324 |
| Kazakhstan | 452 | 366 | 247 | 613 | 0.74 | 16120117 | | 0 | #DIV/0! | #DIV/0! |
| Kenya | 2 577 | 334 | 357 | 691 | 3.73 | 26642887 | 172.346 | 642.7311529 | 250.6111 | 934.6057 |
| Kiribati | 141 | 689 | 448 | 1137 | 0.12 | 76188 | 275.6205 | 34.1676224 | 488.7805 | 60.59225 |
| Kuwait | 41 | 38 | 30 | 68 | 0.61 | 1687552 | | 0 | #DIV/0! | #DIV/0! |
| Kyrgyzstan | 481 | 386 | 226 | 612 | 0.79 | 4542747 | | 0 | #DIV/0! | #DIV/0! |
| Lao People's Democratic Republic | 778 | 782 | 281 | 1063 | 0.73 | 4677981 | 358.091 | 262.2097581 | 769.3386 | 563.3431 |
| Latvia | 149 | 113 | 84 | 197 | 0.76 | 2528893 | | 0 | #DIV/0! | #DIV/0! |
| Lebanon | 29 | 14 | 12 | 26 | 1.10 | 3364891 | 840 | 921.9041237 | 1143.778 | 1255.302 |
| Lesotho | | 415 | 643 | 1058 | | 1761558 | 193.75 | 175.511452 | 381.1072 | 345.2319 |

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|---|---|---|---|---|---|---|---|---|---|---|
| | 958 | | | | 0.91 | | | 1 | | |
| Liberia | 1 684 | 443 | 261 | 704 | 2.39 | 2039922 | 87.5674 | 209.4212289 | 168.1252 | 402.0787 |
| Libya | 42 | 53 | 40 | 93 | 0.45 | 4687106 | | 0 | #DIV/0! | #DIV/0! |
| Lithuania | 157 | 98 | 77 | 175 | 0.90 | 3652438 | | 0 | #DIV/0! | #DIV/0! |
| Luxembourg | 6 | 12 | 9.4 | 21.4 | 0.28 | 401804 | | 0 | #DIV/0! | #DIV/0! |
| Madagascar | 1 248 | 512 | 268 | 780 | 1.60 | 12728117 | 152.4593 | 243.9281038 | 275.5454 | 440.8604 |
| Malawi | 1 563 | 284 | 378 | 662 | 2.36 | 9772164 | 153.3289 | 362.0917645 | 316.1826 | 746.6767 |
| Malaysia | 423 | 125 | 87 | 212 | 2.00 | 20205446 | 29.0697 | 58.0252983 | 45.23463 | 90.29171 |
| Maldives | 141 | 80 | 56 | 136 | 1.03 | 243256 | 787.9856 | 814.7232279 | 916.0959 | 947.1805 |
| Mali | 2 123 | 107 | 71 | 178 | 11.93 | 9564231 | 205.7761 | 2454.534107 | 311.9557 | 3721.063 |
| Malta | 3 | 7.2 | 5.8 | 13 | 0.20 | 383314 | | 0 | #DIV/0! | #DIV/0! |
| Marshall Islands | 206 | 598 | 340 | 938 | 0.22 | 50565 | | 0 | #DIV/0! | #DIV/0! |
| Mauritania | 1 783 | 563 | 300 | 863 | 2.07 | 2228453 | 149.1446 | 308.1547906 | 254.7963 | 526.4468 |
| Mauritius | 53 | 43 | 23 | 66 | 0.80 | 1122040 | | 0 | #DIV/0! | #DIV/0! |
| Mexico | 59 | 35 | 23 | 58 | 1.01 | 90691331 | 91.5204 | 92.45519387 | 123.5525 | 124.8145 |
| Micronesia (Federated States of) | 250 | 476 | 247 | 723 | 0.35 | 105825 | | 0 | #DIV/0! | #DIV/0! |
| Monaco | 4 | 1 | 0.78 | 1.78 | 2.36 | 32574 | | 0 | #DIV/0! | #DIV/0! |

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|---|---|---|---|---|---|---|---|---|---|---|
| Mongolia | 534 | 331 | 228 | 559 | 0.96 | 2288370 | 310.0646 | 296.2766851 | 575.7542 | 550.1516 |
| Montenegro | | 41 | 34 | 75 | - | 10707 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Montserrat | | 4.7 | 10 | 14.7 | - | 26523600 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Morocco | 213 | 131 | 103 | 234 | 0.91 | 15409381 | 27.9314 | 25.45905405 | 38.50031 | 35.09246 |
| Mozambique | 1 872 | 490 | 520 | 1010 | 1.85 | 41552659 | 321.3893 | 595.6103604 | 544.1064 | 1008.358 |
| Myanmar | 487 | 677 | 406 | 1083 | 0.45 | 1603865 | 102.7053 | 46.16912925 | 249.3781 | 112.103 |
| Namibia | 1 048 | 1622 | 1720 | 3342 | 0.31 | 9863 | 53.3333 | 16.72111618 | 72.76991 | 22.8149 |
| Nauru | 66 | 94 | 74 | 168 | 0.39 | 21064150 | | 0 | #DIV/0! | #DIV/0! |
| Nepal | 686 | 236 | 163 | 399 | 1.72 | 30485798 | 37.6492 | 64.75775557 | 80.81318 | 139.0011 |
| Netherlands | 5 | 11 | 8.6 | 19.6 | 0.25 | 15320112 | | 0 | #DIV/0! | #DIV/0! |
| New Caledonia | | 34 | 26 | 60 | - | 186358 | | #DIV/0! | #DIV/0! | #DIV/0! |
| New Zealand | 7 | 13 | 9.9 | 22.9 | 0.31 | 3623421 | | 0 | #DIV/0! | #DIV/0! |
| Nicaragua | 234 | 83 | 56 | 139 | 1.68 | 4535802 | 65.8333 | 110.9159269 | 132.5836 | 223.3768 |
| Niger | 1 124 | 272 | 150 | 422 | 2.66 | 8871631 | | 0 | #DIV/0! | #DIV/0! |
| Nigeria | 1 847 | 300 | 180 | 480 | 3.85 | 107452627 | 242.1602 | 932.0279386 | 314.4452 | 1210.239 |
| Niue | 57 | 48 | 38 | 86 | 0.66 | 2204 | | 0 | #DIV/0! | #DIV/0! |
| Northern Mariana Islands | | 108 | 84 | 192 | - | 54852 | | #DIV/0! | | #DIV/0! |

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|---|---|---|---|---|---|---|---|---|---|---|
| Norway | 4 | 8.9 | 7 | 15.9 | 0.24 | 4333931 | | 0 | #DIV/0! | #DIV/0! |
| Oman | 31 | 17 | 14 | 31 | 1.02 | 2182619 | | 0 | #DIV/0! | #DIV/0! |
| Pakistan | 1 118 | 488 | 231 | 719 | 1.55 | 124121817 | 132.1347 | 205.4233881 | 355.7163 | 553.0148 |
| Palau | 162 | 56 | 34 | 90 | 1.80 | 16804 | | 0 | #DIV/0! | #DIV/0! |
| Panama | 75 | 50 | 47 | 97 | 0.78 | 2622903 | 746.3093 | 579.0816264 | 1166.108 | 904.8148 |
| Papua New Guinea | 1 318 | 544 | 355 | 899 | 1.47 | 4595463 | 199.8906 | 293.1322737 | 307.9001 | 451.5243 |
| Paraguay | 304 | 69 | 49 | 118 | 2.58 | 4685320 | 162.0019 | 417.6702821 | 278.9296 | 719.1311 |
| Peru | 439 | 195 | 148 | 343 | 1.28 | 23404523 | | 0 | #DIV/0! | #DIV/0! |
| Philippines | 1 429 | 662 | 306 | 968 | 1.48 | 67703053 | 74.057 | 109.3082958 | 127.7074 | 188.4964 |
| Poland | 33 | 34 | 26 | 60 | 0.56 | 38364540 | | 0 | #DIV/0! | #DIV/0! |
| Portugal | 40 | 43 | 40 | 83 | 0.48 | 10077548 | | 0 | #DIV/0! | #DIV/0! |
| Puerto Rico | | 3.4 | 3.4 | 6.8 | - | 3668794 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Qatar | 153 | 60 | 47 | 107 | 1.43 | 495126 | | 0 | #DIV/0! | #DIV/0! |
| Republic of Korea | 111 | 170 | 86 | 256 | 0.43 | 44365820 | | 0 | #DIV/0! | #DIV/0! |
| Republic of Moldova | 437 | 264 | 174 | 438 | 1.00 | 4361061 | 1009.7572 | 1007.459276 | 1665.615 | 1661.825 |
| Romania | 201 | 205 | 154 | 359 | 0.56 | 22810195 | 582.5 | 326.5404906 | 754.5337 | 422.9799 |
| Russian Federation | 593 | 216 | 139 | 355 | 1.67 | 148866314 | 4202.8952 | 7015.587313 | 6931.291 | 11569.9 |

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|---|---|---|---|---|---|---|---|---|---|---|
| Rwanda | 2 613 | 230 | 176 | 406 | 6.44 | 5648306 | 140.7065 | 905.7282048 | 262.8331 | 1691.858 |
| Saint Kitts and Nevis | 42 | 3.6 | 2.8 | 6.4 | 6.55 | 42511 | | 0 | #DIV/0! | #DIV/0! |
| Saint Lucia | 17 | 13 | 10 | 23 | 0.74 | 145255 | | 0 | #DIV/0! | #DIV/0! |
| Saint Vincent and the Grenadines | 56 | 41 | 25 | 66 | 0.85 | 108089 | | 0 | #DIV/0! | #DIV/0! |
| Samoa | 97 | 24 | 18 | 42 | 2.31 | 166662 | | 0 | #DIV/0! | #DIV/0! |
| San Marino | 2 | 2.6 | 2 | 4.6 | 0.37 | 25406 | | 0 | #DIV/0! | #DIV/0! |
| Sao Tome and Principe | 1 308 | 123 | 106 | 229 | 5.71 | 125488 | 269.6106 | 1539.696806 | 350.919 | 2004.034 |
| Saudi Arabia | 143 | 22 | 17 | 39 | 3.66 | 18117969 | | 0 | #DIV/0! | #DIV/0! |
| Senegal | 1 584 | 225 | 144 | 369 | 4.29 | 8143140 | 240.7377 | 1033.532861 | 348.5668 | 1496.464 |
| Serbia | 46 | 41 | 34 | 75 | 0.62 | 10753700 | 2140.5652 | 1317.263506 | 3400.898 | 2092.849 |
| Seychelles | 34 | 58 | 34 | 92 | 0.37 | 74016 | | 0 | #DIV/0! | #DIV/0! |
| Sierra Leone | 2 863 | 946 | 479 | 1425 | 2.01 | 3915066 | | 0 | #DIV/0! | #DIV/0! |
| Singapore | 36 | 48 | 39 | 87 | 0.41 | 3385486 | | 0 | #DIV/0! | #DIV/0! |
| Sint Maarten (Dutch part) | | | | 0 | #DIV/0! | | | #DIV/0! | | #DIV/0! |
| Slovakia | 17 | 21 | 17 | 38 | 0.44 | 5353767 | | 0 | #DIV/0! | #DIV/0! |
| Slovenia | 11 | 20 | 15 | 35 | 0.32 | 1959752 | | 0 | #DIV/0! | #DIV/0! |
| Solomon | | 274 | 150 | 424 | | 346599 | 234.4359 | 380.483345 | 378.8794 | 614.9114 |

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|---|---|---|---|---|---|---|---|---|---|---|
| Islands | 688 | | | | 1.62 | | | | | |
| Somalia | 1 441 | 494 | 285 | 779 | 1.85 | 6484228 | 34.0004 | 62.90615422 | #DIV/0! | #DIV/0! |
| South Africa | 2 484 | 785 | 898 | 1683 | 1.48 | 40542036 | 274.0589 | 404.455542 | 421.0137 | 621.3311 |
| South Sudan | | 267 | 146 | 413 | - | | | #DIV/0! | #DIV/0! | #DIV/0! |
| Spain | 13 | 23 | 19 | 42 | 0.31 | 39318577 | | 0 | #DIV/0! | #DIV/0! |
| Sri Lanka | 236 | 102 | 66 | 168 | 1.41 | 18089720 | 727.932 | 1024.110769 | 1390.038 | 1955.612 |
| Sudan | 1 576 | 225 | 135 | 360 | 4.38 | 29367076 | 223.1417 | 976.7135992 | 316.62 | 1385.877 |
| Suriname | 58 | 107 | 67 | 174 | 0.34 | 430102 | | 0 | #DIV/0! | #DIV/0! |
| Swaziland | 2 216 | 672 | 1120 | 1792 | 1.24 | 944404 | 58.4776 | 72.30700612 | 104.6655 | 129.4179 |
| Sweden | 4 | 7 | 5.5 | 12.5 | 0.29 | 8789976 | | 0 | #DIV/0! | #DIV/0! |
| Switzerland | 3 | 9.9 | 7.9 | 17.8 | 0.17 | 6961228 | | 0 | #DIV/0! | #DIV/0! |
| Syrian Arab Republic | 142 | 34 | 28 | 62 | 2.28 | 13809349 | | 0 | #DIV/0! | #DIV/0! |
| Tajikistan | 996 | 408 | 208 | 616 | 1.62 | 5691845 | | 0 | #DIV/0! | #DIV/0! |
| Thailand | 479 | 248 | 164 | 412 | 1.16 | 59126690 | 822.8734 | 956.3890893 | 1536.614 | 1785.938 |
| The Former Yugoslav Republic of Macedonia | 65 | 36 | 32 | 68 | 0.95 | 1953874 | | 0 | #DIV/0! | #DIV/0! |
| Timor-Leste | 2 449 | 741 | 498 | 1239 | 1.98 | | 46.5503 | 92.01133848 | 83.12554 | 164.306 |

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|---|---|---|---|---|---|---|---|---|---|---|
| Togo | 2 476 | 117 | 81 | 198 | 12.50 | 3982804 | 338.1159 | 4227.361362 | 527.2362 | 6591.876 |
| Tokelau | | 1.3 | 0.53 | 1.83 | - | 1524 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Tonga | 87 | 34 | 24 | 58 | 1.50 | 95691 | 3109.3333 | 4667.955035 | 4004.317 | 6011.569 |
| Trinidad and Tobago | 39 | 17 | 15 | 32 | 1.22 | 1253000 | | 0 | #DIV/0! | #DIV/0! |
| Tunisia | 72 | 29 | 23 | 52 | 1.39 | 8808669 | 391.2 | 541.9648791 | 657.9767 | 911.5549 |
| Turkey | 108 | 30 | 31 | 61 | 1.76 | 57911273 | 2545.6496 | 4488.371197 | 3106.4 | 5477.06 |
| Turkmenistan | 296 | 367 | 189 | 556 | 0.53 | 4095512 | | 0 | #DIV/0! | #DIV/0! |
| Turks and Caicos Islands | | 27 | 21 | 48 | - | 14644 | | #DIV/0! | | #DIV/0! |
| Tuvalu | 119 | 511 | 303 | 814 | 0.15 | 9188 | 2800 | 409.2320548 | #DIV/0! | #DIV/0! |
| Uganda | 2 213 | 338 | 326 | 664 | 3.33 | 20193432 | 210.5723 | 701.7294892 | 405.0557 | 1349.843 |
| Ukraine | 502 | 163 | 119 | 282 | 1.78 | 51377434 | | 0 | #DIV/0! | #DIV/0! |
| United Arab Emirates | 77 | 3.7 | 2 | 5.7 | 13.47 | 2232980 | | 0 | #DIV/0! | #DIV/0! |
| United Kingdom of Great Britain and Northern Ireland | 9 | 16 | 13 | 29 | 0.31 | 57838596 | | 0 | #DIV/0! | #DIV/0! |
| United Republic of Tanzania | 1 606 | 233 | 225 | 458 | 3.51 | 29064223 | | 0 | #DIV/0! | #DIV/0! |
| United States of America | 3 | 6.5 | 5.6 | 12.1 | 0.22 | 263468980 | | 0 | #DIV/0! | #DIV/0! |

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|---|---|---|---|---|---|---|---|---|---|---|
| Uruguay | 342 | 28 | 23 | 51 | 6.70 | 3200342 | | 0 | #DIV/0! | #DIV/0! |
| US Virgin Islands | | 9.9 | 7.7 | 17.6 | - | 106260 | | #DIV/0! | #DIV/0! | #DIV/0! |
| Uzbekistan | 449 | 522 | 255 | 777 | 0.58 | 22466866 | 968.4528 | 559.6581339 | 3391.529 | 1959.927 |
| Vanuatu | 372 | 138 | 86 | 224 | 1.66 | 164254 | 646.874 | 1074.324977 | 582.5191 | 967.4447 |
| Venezuela (Bolivarian Republic of) | 61 | 46 | 34 | 80 | 0.76 | 21569680 | 122.0891 | 92.88576327 | 209.7002 | 159.5406 |
| Viet Nam | 533 | 335 | 205 | 540 | 0.99 | 72769366 | 72.1895 | 71.30576741 | 155.372 | 153.47 |
| Wallis and Futuna Islands | | 93 | 72 | 165 | - | 14077 | | #DIV/0! | | #DIV/0! |
| West Bank and Gaza Strip | | 7.3 | 3.6 | 10.9 | - | 2479672 | | #DIV/0! | | #DIV/0! |
| Yemen | 363 | 145 | 87 | 232 | 1.57 | 14530275 | 9.1323 | 14.2931169 | 15.5204 | 24.29124 |
| Zambia | 1 972 | 427 | 591 | 1018 | 1.94 | 8692599 | 164.5421 | 318.8069679 | 165.9756 | 321.5844 |
| Zimbabwe | 1 911 | 409 | 807 | 1216 | 1.57 | 11469872 | 171.2814 | 269.1761782 | #DIV/0! | #DIV/0! |

1- Mathers C, Boerma T, Ma Fat D: The Global Burden of Disease 2004. 2004.

2- World Health Organisation: Global Tuberculosis Control - Surveillance, Planning, Financing. 2004.

Appendix 2: Disease Burden Estimates

| **Data Type** | Prevalence Only | | Incidence Only | | Prevalence + Incidence | |
|---|---|---|---|---|---|---|
| | **Value** | **Country** | **Value** | **Country** | **Value** | **Country** |
| **DALY Data** | | | | | | |
| DALYs PP | 3.16 | SA | 2.77 | SA | 1.48 | SA |
| Best DALYs PP | 0.20 | Kiribati | 0.31 | Kiribati | 0.12 | Kiribati |
| Worst DALYs PP | 21.16 | Togo | 38.38 | UAE | 13.47 | UAE |
| **Disease Burden Data** | | | | | | |
| DB / 100000 | 785.00 | SA | 898.00 | SA | 1683.00 | SA |
| Disease Burden | 318254.98 | | 364067.48 | | 682322.47 | |
| Best DB /100000 | 1.00 | Monaco | 0.53 | Tokelau | 1.78 | Monaco |
| Best DB | 405.42 | | 214.87 | | 721.65 | |
| Worst DB/100000 | 1622.00 | Namibia | 1720.00 | Namibia | 3342.00 | Namibia |
| Worst DB | 657591.82 | | 697323.02 | | 1354914.84 | |
| 2nd Worst DB/10000 | 1318.00 | Cambodia | 1120.00 | Swaziland | 1844.00 | Cambodia |
| 2nd Worst DB | 534344.03 | | 454070.80 | | 747595.14 | |

# JOURNAL:

Health Research Policy and Systems

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Manuscripts for Research Articles submitted to ***Health Research Policy and Systems*** should be divided into the following sections (in this order):

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- Keywords
- Background
- Methods
- Results and discussion
- Conclusions
- List of abbreviations used (if any)
- Competing interests
- Authors' contributions
- Authors' information
- Acknowledgements
- Endnotes
- References
- Illustrations and figures (if any)
- Tables and captions
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- indicate the corresponding author

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The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: **Background,** the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your research reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. **Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

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***Book chapter, or article within a book***

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***Whole issue of journal***

Ponder B, Johnston S, Chodosh L (Eds): **Innovative oncology.** In ***Breast Cancer Res*** 1998, **10:**1-72.

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Smith Y (Ed): ***Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore.*** Stoneham: Butterworth-Heinemann; 1996.

***Complete book***

Margulis L: ***Origin of Eukaryotic Cells.*** New Haven: Yale University Press; 1970.

***Monograph or book in a series***

Hunninghake GW, Gadek JE: **The alveolar macrophage.** In ***Cultured Human Cells and Tissues.***Edited by Harris TJR. New York: Academic Press; 1995:54-56. [Stoner G (Series Editor): ***Methods and Perspectives in Cell Biology,*** vol 1.]

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Advisory Committee on Genetic Modification: ***Annual Report.*** London; 1999.

***PhD thesis***

Kohavi R: **Wrappers for performance enhancement and oblivious decision graphs. *PhD thesis.*** Stanford University, Computer Science Department; 1995.

***Link / URL***

**The Mouse Tumor Biology Database** [http://tumor.informatics.jax.org/mtbwi/index.do]

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Corpas M: **The Crowdfunding Genome Project: a personal genomics community with open source values** [http://blogs.biomedcentral.com/bmcblog/2012/07/16/the-crowdfunding-genome-project-a-personal-genomics-community-with-open-source-values/]

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***Clinical trial registration record with persistent identifier***

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SI units should be used throughout (liter and molar are permitted, however).

# Can a quantitative model be developed to rank priorities in health research?

## Executive Summary

- The use of a quantitative model for ranking research priorities is needed to overcome biases and increase transparency and consistency in ranking
- The WHO proposed a model in 1996 which has seen little use in its current state. However, amendments to the model can increase its validity and functionality, allowing it to be constructed using widely available data
- Quantitative models are still in their infancy, and due to other factors of interest (e.g. equity) should be used in conjunction with other priority setting processes
- Quantitative models can also serve as a useful tool for data presentation and interpretation

## Recommendations

- A quantitative model should be incorporated into all priority setting exercises
- This model should be used to assist stakeholders with interpreting complex datasets
- Research areas should be considered when setting priorities, in addition to issues such as equity and feasibility.
- Further development and refinement of quantitative methodologies is required
- Data sources which feed into such methodologies also need to be interrogated for accuracy,
- More thorough understanding of the costs of research needs to be gained

## Introduction

### Why rank?

Ranking of priorities in health research is important as there are limited financial, human and infrastructural resources available, especially in developing countries. Therefore it is important that these resources be utilised to maximum effect. Selection of priorities on an ad-hoc basis often results in stagnation of research, misalignment of collaborative efforts and biases from certain parties, such as researchers. **Undertaking a formal ranking procedure allows for transparency and consistency in decision making, reduces the potential for biased or irrational decision making, focuses research efforts, improves collaboration and research efficiency, and allows for participation in research prioritisation by various stakeholders, including civil society.**

### How to rank?

Priorities can be ranked by disease, feasibility of research, equity, research area, impact on disease burden, and other criteria. There are various frameworks available to guide the ranking process, although no gold standard currently exists. There are, however, some key principles that almost all frameworks have in common, as well as some glaring challenges faced by all. Any ranking exercise should be informed by relevant data, allow for a broad stakeholder composition in decision making and be tailored to the specific contextual background it is being performed in. Relevant criteria must be defined prior to ranking, and consistently applied by all parties. Some of the common pitfalls

**Priority setting in South Africa at a glance**

South Africa's National Health Research Committee (NHRC) held a priority setting summit in 2011, which loosely followed the Essential National Health Research framework of priority setting. Seven experts, as well as sub-committees of the NHRC presented evidence and SWOT (strength, weakness, opportunity and threat) analysis for seven areas of health research. The research areas were : HIV and TB; Maternal and child health; Non-communicable diseases; Violence and injury; Basic; Health systems; and National service delivery. A broader stakeholder constituent then divided into subcommittees and identified specific research questions for each of these areas. These research questions were then collated, and a shortlist of future recommendations was compiled (although no attempt was made to rank these questions in order of importance).

For more information see: *http://www.doh.gov.za/docs/reports/2012/summitreport.pdf*

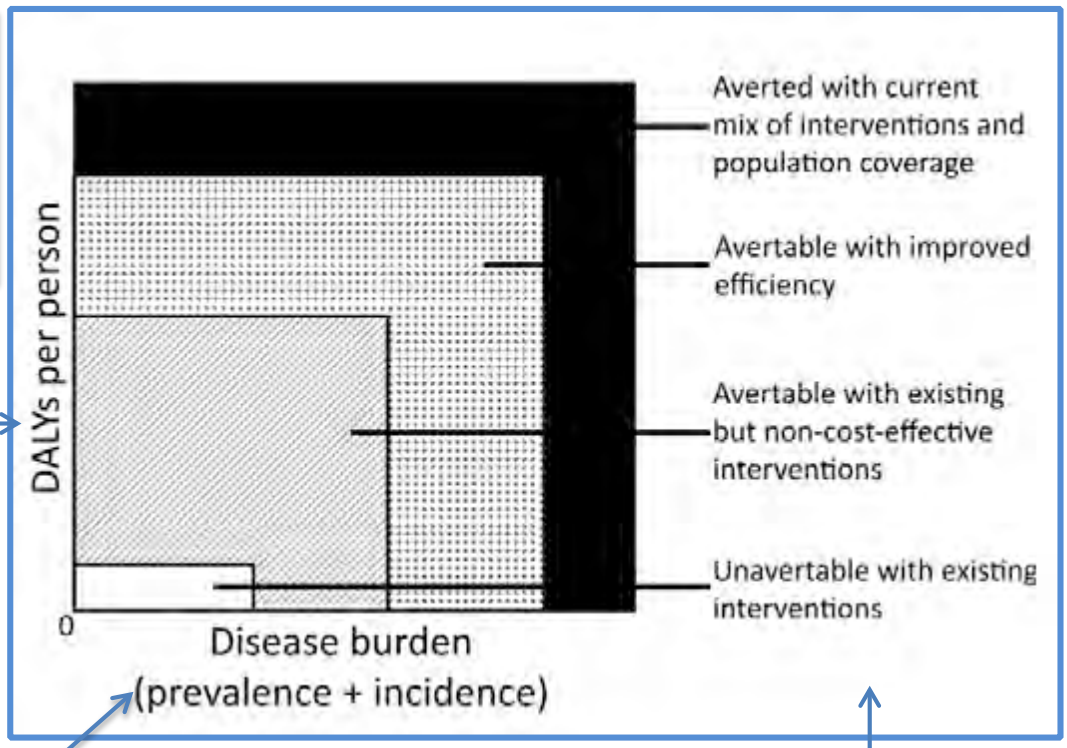

experienced in such processes include: deciding who is a relevant stakeholder, the uncertainty of health research outcomes, defining and deciding upon relevant criteria for ranking, limiting stakeholder biases, and defining a valid and transparent ranking process. It has thus been suggested that **a simple quantitative way to rank competing research priorities is required**. This policy document reports on the development and feasibility of using such a quantitative model via an adaptation of a framework proposed by the World Health Organisation. While policy makers at different levels may have different primary goals, they all have at some level a desire to reduce morbidity and mortality through their research priorities, and hence this methodology is of relevance to them all.

## The Proposed Model

The development of a quantitative model to rank priorities by research area was based on the WHO model (see *The World Health Organisation Model* insert for more details), which is the only quantitative model previously described for ranking of priorities. The model is outlined below:

The model represents disease as total DALYs, which are a product of the severity of the disease, and the size of the population inflicted.

**DALYs:** A Disability Adjusted Life Year is a measurement of the severity of disease that looks at both years of life lost due to fatality, as well as converting reductions in quality of life (due to a disease) to a hypothetical amount of years of life lost




**Prevalence** is an estimate of the number of people in the population with a disease at a given time.
**Incidence** is an estimate of the number of new or recurring cases occurring over a time period.
Some diseases have high incidence but could have a low prevalence depending on when the prevalence is measured (e.g. seasonal diarrhoeal diseases), or vice versa (e.g. chronic diseases). Therefore it is important that both measures are included in the analysis

The overall DALYs from a disease are subdivided into four sections which inform the areas of research required.

The model represents the severity of a disease as a combination of the impact it has on an individual who contracts it **(DALYs per person)** and the amount of people who contract the disease **(Disease burden)**. It then divides the disease into four sections, three of which represent different targets for research:

- **Unavertable with existing interventions** – This proportion of the disease can be combated with **basic research**
- **Avertable with existing but non-cost-effective interventions** – This proportion of the disease can be combated with **biomedical research** to reduce the cost of interventions
- **Avertable with improved efficiency** – This proportion of the disease can be combated with **health systems research**

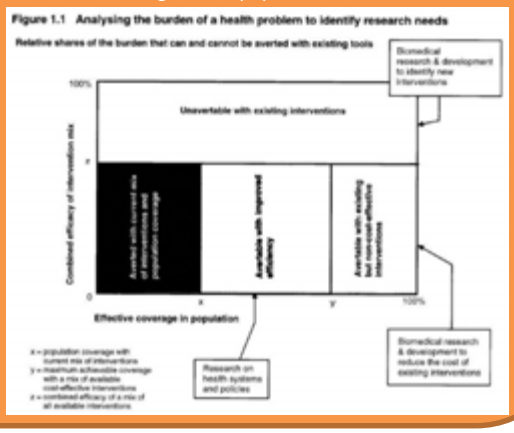
## Benefits of the model

- ✓ It is **objective**. Provided the data is reliable, then there is no opportunity for personal biases to influence the results.
- ✓ It is **transparent.** Unlike personal decision making, the methodology used to construct the model is entirely transparent.
- ✓ The model is **easy to construct**. Minimal data inputs are required for construction of this model, which allows it to be used in many developing world setting where data is scarce.
- ✓ Comparisons can be made between diseases as the figures used to construct the model are **standardised across diseases**.
- ✓ The model guides the direction of research by area, but leaves the specific topics in that area up to researchers. This **allows for some academic freedom and room for innovation.**
- ✓ The model **can easily be incorporated into a broader priority setting framework/exercise.**

## Limitations of the model

- × There is a high possibility of **confounding variables** influencing the results.
- × There are still issues that need to be addressed before it can have any practical worth, such as determining the **costs of different types of research**, as well as **defining research endeavours by research area**.
- × This model does not take into account issues such as **equity**, and so needs to be part of a broader process.

**The World Health Organisation Model:** The WHO model was developed in 1996, as part of the *Investing in Research for Health* report. It is a Disability Adjusted Life Year (DALY) based model with a focus on research areas as the unit of priority setting. Briefly, it conceptualises the ability to reduce DALYs as either through increases in the efficacy of interventions or increases in coverage of the population, as illustrated in figure 1.1.




This model has remained largely unused as no formal methodology for its construction has been developed. Furthermore, there are some issues of the model that need to be addressed: The model assumes mutual exclusivity of the three forms of research, and that combined they contribute to 100% efficacy and coverage. The model also assumes that basic research can only improve intervention efficacy, and health systems and biomedical research only population coverage, but these latter two could also improve intervention efficacy. Finally, data on efficacy of interventions and coverage in populations is not readily available, so it is not clear that these are the best axes to use for this model. For these reasons an adaptation of the model was developed that addresses some of these issues, whilst still retaining the core principles of the model.

## Worked example: Tuberculosis

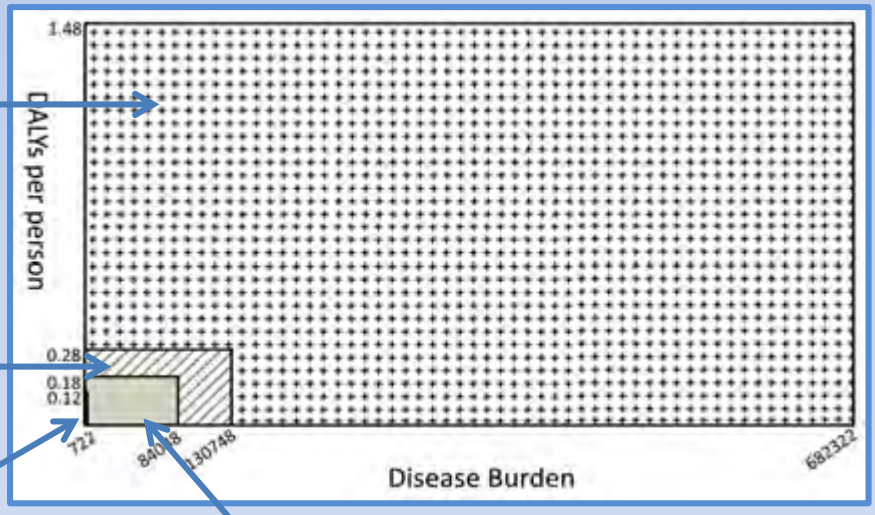
Tuberculosis is the number one cause of death in South Africa, accounting for 11.6% of all deaths in 2010. In order to construct the model to determine what research would best tackle this problem, DALY data from the WHO Burden of Disease database was used, as well as data from the WHO Global TB and the Disease Control Priorities Project reports, as detailed in the table on the right. Comparisons were made between South Africa and the best and worst performing countries in terms of DALYs per person, Disease Burden and Cost per patient treated. Efficacy of intervention data was also used to examine the efficacy of existing but non-cost effective interventions  Using this data it was determined that the burden of TB in South Africa is approximately 1 009 837 DALYs. These results are represented in the figure below. The unavertable portion is almost invisible at this scale, whilst that which is currently being averted is almost 10 times larger than the current DALY burden and hence was not depicted. It was also decided to apply gains due to increases in healthy systems efficiency prior to gains by use of non-cost-effective interventions, as South Africa is a developing country with limited resources and therefore is more likely to first implement more efficient measures, as opposed to more expensive measures.

| | Value | Country |
|---|---|---|
| **DALYs per person (pp)** | 1.48 | SA |
| Best | 0.12 | Kiribati |
| Worst | 13.47 | UAE |
| **Disease Burden  (per 100 000)** | 1683 | SA |
| Best | 1.78 | Monaco |
| Worst | 1844 | Cambodia |
| **Cost per patient** | 621.33 | SA |
| Best | 22.81 | Namibia |
| **Efficacy of Interventions** | 0.33 | |
| Irrespective of cost | 0.71 | |

South Africa's current disease burden could be reduced significantly with improvements in health systems efficiency

This could be further reduced with use of non-cost-effective interventions, or research to reduce the cost of drugs

Unavertable DALYs comprise a very small fraction of the DALY burden




1.52% of South Africa's DALY burden is unaccounted for.

From this it was determined that:

- 87 DALYs are unavertable no matter what (**basic research**)
- 9 060 270 DALYs are currently being averted with South Africa's intervention mix
- 96% of DALYs could be averted with improvements in efficiency (**health systems research**)
- 54% of the remaining DALYs could be averted with reductions in cost of existing Interventions  (**biomedical research**)

**Interrogating the data: Why does UAE (United Arab Emirates) have such high DALY pp levels even in the desert?**

It has long been known that drier climates speed TB recovery, and so it is surprising that the UAE would have such a high DALY per person rate. Some possible explanations include a large contribution from Southeast Asian migrants, and a particularly virulent strain of TB unique to the region. This serves to highlight the potential of confounding factors that limit the generalizability of cross country comparisons.

For more information please see: *Setting priorities in health research using the World Health Organisation model: Development of a quantitative methodology using tuberculosis in South Africa as a worked example,* or contact the author: Mr Damian Hacking (damianuct@gmail.com)