Economic evaluation of disease elimination: an extension to the net-benefit framework and application to human African trypanosomiasis

Marina Antillon[a,b,*], Ching-I Huang[c,d], Kat S Rock[c,d,‡], and Fabrizio Tediosi[a,b,‡]

[a]Swiss Tropical and Public Health Institute, Basel, Switzerland; [b]University of Basel, Basel, Switzerland; [c]Zeeman Institute, University of Warwick, Coventry, UK; [d]Mathematics Institute, University of Warwick, Coventry, UK

The global health community has earmarked a number of diseases for elimination or eradication, and these goals have often been praised on the premise of long-run cost-savings. However, decision-makers must contend with a multitude of demands on health budgets in the short- or medium-term, and costs-per-case often rise as the burden of a disease falls, rendering such efforts beyond the cost-effective use of scarce resources. In addition, these decisions must be made in the presence of substantial uncertainty regarding the feasibility and costs of elimination or eradication efforts. Therefore, analytical frameworks are necessary to consider the additional effort for reaching global goals, like elimination or eradication, that are beyond the cost-effective use of country resources. We propose a modification to the net-benefit framework to consider the implications of switching from an optimal strategy, in terms of cost-per-burden-averted, to a strategy with a higher likelihood of meeting the global target of elimination or eradication. We illustrate the properties of our framework by considering the economic case of efforts to eliminate the transmission of *gambiense* human African trypanosomiasis (gHAT), a vector-borne parasitic disease in West and Central Africa, by 2030.

eradication | elimination | economic evaluation | mathematical modeling

The successful eradication campaigns of smallpox and rinderpest have curried political support for the elimination or eradication of transmission (EEOT) of other diseases. While the health economic implications of EEOT have been discussed before, one important topic remains unexplored: uncertainty and its consideration within extant cost-effectiveness frameworks. The funding for these efforts comes in part from global health stakeholders with large portfolios (i.e. the Bill and Melinda Gates Foundation, the Global Fund, the World Health Organization) working alongside country-level ministries of health, and therefore resources dedicated to the "last mile" of EEOT could potentially be diverted to cost-effective programs targeting other diseases.

Salient questions exist around the economic implications of disease "control" – the disease reduction that occurs when other opportunity costs are taken into account. While a few studies have tried to grapple with questions around the economic implications of EEOT by employing game-theoretic approaches (1–3), frameworks with multiple objectives (efficiency and EEOT) are exceedingly rare ((4, 5)), and such approaches have never been developed for analyses taking into account CEA and EEOT objectives. The absence of probabilistic thinking in previous literature fails to capture a key component of the decision-making process.

Here we develop a framework that can handle 1) strategies that have different probabilities of EEOT, 2) where activities are not easily classified as exclusively "control" or "elimination" activities, 3) and where multiple objectives – specifically disease burden reduction and EEOT – are transparently considered. We extend the net-benefit framework, useful for decision-analysis in the presence of uncertainty, in order to evaluate cost-effectiveness of public health strategies while explicitly outlining the 'premium' of elimination, or the additional resources that are necessary to bring a country's activities in line with global goals. We then apply our new framework to the analysis of campaigns against *gambiense* human African trypanosomiasis (gHAT) in three distinct regions of the Democratic Republic of Congo (DRC).

Economic framework

The metric of efficiency within the net benefits framework is the net monetary benefit (NMB):

$$\text{NMB}(\lambda^{\text{WTP}}) = \lambda^{\text{WTP}} \times \Delta E - \Delta C$$

The NMB captures the justifiable cost of a strategy minus the actual cost of the strategy. The justifiable cost is the product of the disease burden averted, denominated as Disability-Adjusted Life-Years (DALYs), and the willingness-to-pay (WTP)[*] for a marginal gain in a unit of health. The

[*]Note on willingness-to-pay (WTP) values: The WTP is not a metric equivalent to the total cost of

Significance Statement

While the health economic implications of disease elimination have been discussed before, the combination of uncertainty, cost-effectiveness, and elimination has not been tackled before. We propose a modification to the net-benefit framework to explicitly consider the implications of switching from an optimal strategy, in terms of cost-per-burden-averted, to a strategy with a higher likelihood of meeting the global target of elimination. The modification proposed yields a methodology to quantify the efficiency of elimination, and to aid discussions among stakeholders with different objectives. We apply our method to strategies against human African trypanosomiasis in three settings, but this method is flexible enough that it can be applied directly to any simulation-based studies of disease elimination efforts.

M.A. performed the formal analysis, created visualizations. M.A., K.S.R. and F.T. conceptualized the study and wrote the original draft. K.S.R. and F.T. acquired funding and supervised the study. C.H. performed simulations. All authors reviewed and edited the final draft.

The authors declare no conflict of interest.

‡ K.S.R. and F.T. contributed equally to this work.

* To whom correspondence should be addressed. E-mail: marina.antillon@swisstph.ch.

strategy whose justifiable cost surpasses the actual cost by the largest margin is the strategy that yields the largest net monetary cost, and hence, the most efficient strategy.

We propose the following adjustment for the NMB, distinguishing between the cost of an intervention justifiable by disease averted (e.g. DALYs) the cost justifiable by an objective of elimination of transmission (EOT), above and beyond the disease objective.

$$\text{NMB}(\lambda^{\text{WTP}}_{\text{DALY}}, \lambda^{\text{WTP}}_{\text{EOT}}) = \lambda^{\text{WTP}}_{\text{DALY}} \times \Delta\text{DALYs} + \lambda^{\text{WTP}}_{\text{EOT}} \times \Delta\mathbb{I}_{\text{EOT}} - \Delta C$$

The analysis incorporating uncertainty and the implications of this new framework are discussed in the Methods section of the paper and SI Section 1A.

We used disease model projections and cost model from previous studies (6–8) to apply our framework to the analysis of end-game interventions in three illustrative settings in the Democratic Republic of Congo (DRC). The strategies analyzed are in table 1.

For the purpose of this summary, we present Region 1 (Kwamouth) and Region 3 (Sia).

Table 1. Strategies for control and elimination of gHAT in a typical endemic health district.

Component Interventions	Strategy: Mean AS[‡]	Max AS	Mean AS & VC	Max AS & VC
Mean active screening	✓	✓	✓	✓
Additional active screening		✓		✓
Passive surveillance	✓	✓	✓	✓
Vector control			✓	✓
Treatment of cases	✓	✓	✓	✓

[‡] Status quo strategy.

Results

Net Monetary Elimination Benefits: Region 1, where success and failure of EOT by 2030 are certain. For Region 1, where success and failure of EOT by 2030 is certain, the probability of EOT is shown in 1A and the results of our decision analysis under the traditional net benefits framework are shown in Figure 1B. At the low $\lambda^{\text{WTP}}_{\text{DALY}}$=\$0, our analysis shows that Mean AS has an 80% probability of being the only cost-neutral or cost-saving strategy. The expected $\text{Premium}_{\text{EOT}}$, is shown in 1C. In a policy environment of low $\lambda^{\text{WTP}}_{\text{DALY}}$, any health planner must be able to justify the entire \$710,000 in additional economic resource on the basis of EOT alone.

We show the optimal choice of strategy for a range of $\lambda^{\text{WTP}}_{\text{DALY}}$ and $\lambda^{\text{WTP}}_{\text{EOT}}$ values in Figure 1D. In a policy environment where $\lambda^{\text{WTP}}_{\text{DALY}}$=0 and $\lambda^{\text{WTP}}_{\text{EOT}}$=7,098, the optimal strategy guarantees elimination, as that is the $\lambda^{\text{WTP}}_{\text{EOT}}$ that justifies the \$710,000 (\$0-\$2,765,000) premium of elimination (see figure 1 and Table S2).

However, as the policy environment becomes more generous, for instance if $\lambda^{\text{WTP}}_{\text{DALY}}$=\$300, the strategy Mean AS & VC has between a 47%-55% probability of being optimal, which is the strategy that reaches EOT. Therefore, EOT is entirely justifiable on the health gains achieved (DALYs averted), and the $\text{Premium}_{\text{EOT}}$ is therefore \$0.

Net Monetary Elimination Benefits: Region 3, where success and failure are uncertain. Our most complex setting, Region 3, is shown in Figure 2. Under the traditional net benefits framework, either the Mean AS or Max AS strategy are cost-effective at $\lambda^{\text{WTP}}_{\text{DALY}}$ values consistent with historical investment levels in low-income countries (Fig 2C), but these strategies have only a 42% and 54% probability of EOT respectively (inset Fig 2B). Without an investment justifiable by an EOT objective, EOT will remain uncertain; at $\lambda^{\text{WTP}}_{\text{DALY}}$=0; any external partners intent on EOT must be willing to contribute at least \$11,210 per per percentage point of EOT to bolster the chances of elimination from 45% to >99%, representing a $\text{Premium}_{\text{EOT}}$ of \$651,000 (\$16,000-\$1,613,000)[†] (see figure 3 and Table S4).

Discussion

We have extended the net benefits framework to inform decisions that contain an elimination objective that may stand at odds with concerns about efficient resource allocation. The illustrative analysis shows that in Region 1 elimination is nearly impossible with the comparator strategy, but elimination is cost-effective at a relatively low $\lambda^{\text{WTP}}_{\text{DALY}}$>290. The other region presents a more complicated policy prescription: elimination is likely in Region 3 (42%) even with the comparator strategy (Mean AS), but the value-for-money in terms of EOT is lower, needing a higher $\lambda^{\text{WTP}}_{\text{EOT}}$ than in Region 1 (11,210 vs 7,098). However, raising the probability of EOT to >99% has a lower Premium of Elimination but is less efficient in Region 3 than in Region 1.

Data availability and code

The data and the code to reproduce the analysis are available at https://osf.io/fh6ca/. The full paper is available at https://doi.org/10.1073/pnas.2026797118.

References

1. S Barrett, Economic considerations for the eradication endgame. *Philos. Transactions Royal Soc. B: Biol. Sci.* **368**, 20120149–20120149 (2013).
2. P Klepac, R Laxminarayan, BT Grenfell, Synthesizing epidemiological and economic optima for control of immunizing infections. *Proc. Natl. Acad. Sci.* **108**, 14366–14370 (2011).
3. P Klepac, I Megiddo, BT Grenfell, R Laxminarayan, Self-enforcing regional vaccination agreements. *J. Royal Soc. Interface* **13** (2016).
4. WJ Probert, et al., Decision-making for foot-and-mouth disease control: Objectives matter. *Epidemics* **15**, 10–19 (2016).
5. S Verguet, DT Jamison, Health Policy Analysis: Applications of Extended Cost-Effectiveness Analysis Methodology in Disease Control Priorities, Third Edition in *Disease Control Priorities: Improving Health and Reducing Poverty.* pp. 157–166 (2017).
6. RE Crump, et al., Quantifying epidemiological drivers of gambiense human African Trypanosomiasis across the Democratic Republic of Congo. *PLOS Comput. Biol.* **17**, e1008532 (2021).
7. CI Huang, et al., Identifying regions for enhanced control of gambiense sleeping sickness in the Democratic Republic of Congo (2020).
8. M Antillon, et al., Cost-effectiveness of sleeping sickness elimination campaigns in five settings of the Democratic Republic of Congo (2020).

the program, it is a metric of comparative efficiency, considering incremental costs and incremental effects between two or more strategies. In general, it is difficult to take the previous policy behaviour as a guide of what current WTP might be, unless similar cost-effectiveness analyses were done at the time. Moreover, incremental costs are expected to rise when there are other efforts in place to address the burden of that disease. Because we aim to provide guidance rather than prescription, we adhere to recent WHO recommendations to show a variety of WTP values in cost-effectiveness analyses. There are no recommendations for the WTP values for elimination, $\lambda^{\text{WTP}}_{\text{EOT}}$.

[†] Note that the strategy "Mean AS & VC" is what is termed "dominated", which means that the next best strategy "Max AS & VC" has a lower cost per DALY averted.

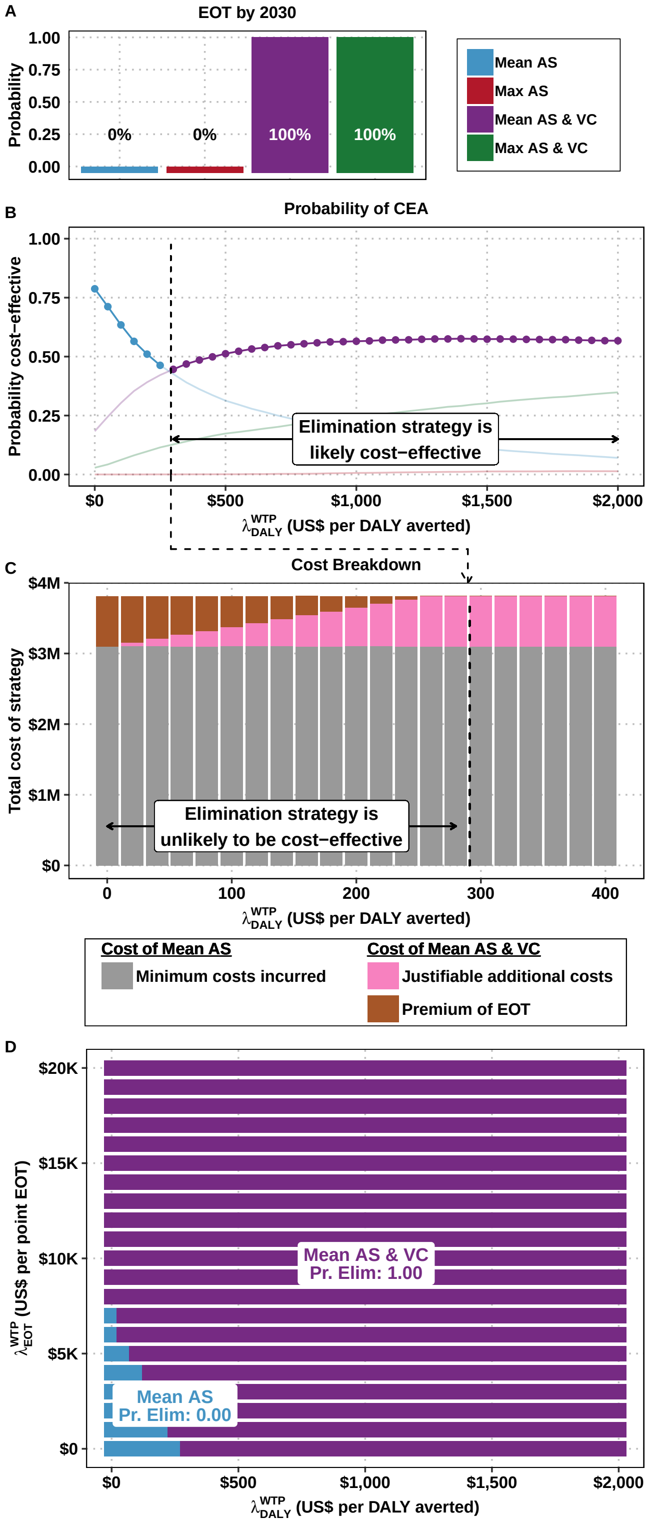

Fig. 1. Cost-effectiveness acceptability curves and cost breakdown for Region 1.

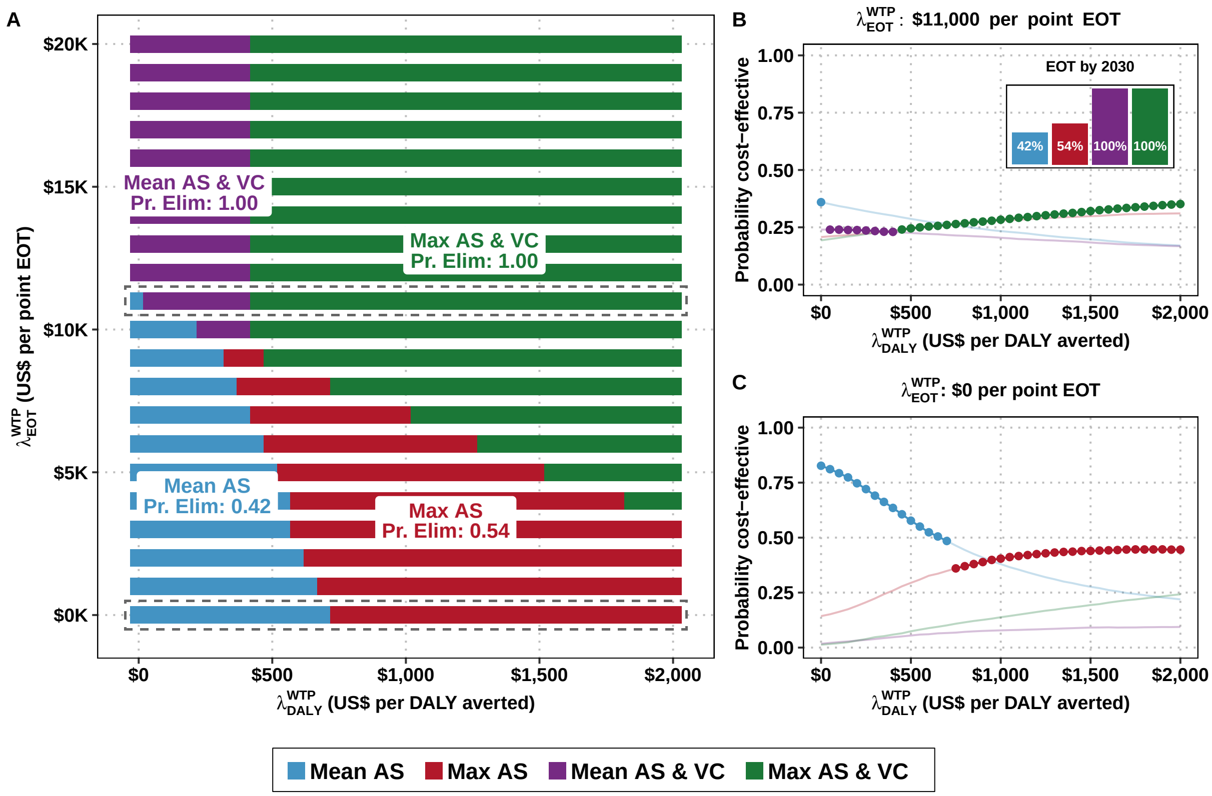

Fig. 2. Cost-effectiveness acceptability heatmaps for Region 3. On the left is the cost-effectiveness acceptability heatmap (CEAH). Along the x-axis is the willingness-to-pay (WTP) for control (to avert disability-adjusted life-years (DALYs), and along y-axis are the WTP for elimination of transmission (EOT); the resources available above and beyond those dedicated to averting DALYs. On the right are the more traditional cost-effectiveness acceptability frontiers (CEAFs). The inset in the top-right graph is the probability of each strategy's EOT by 2030.

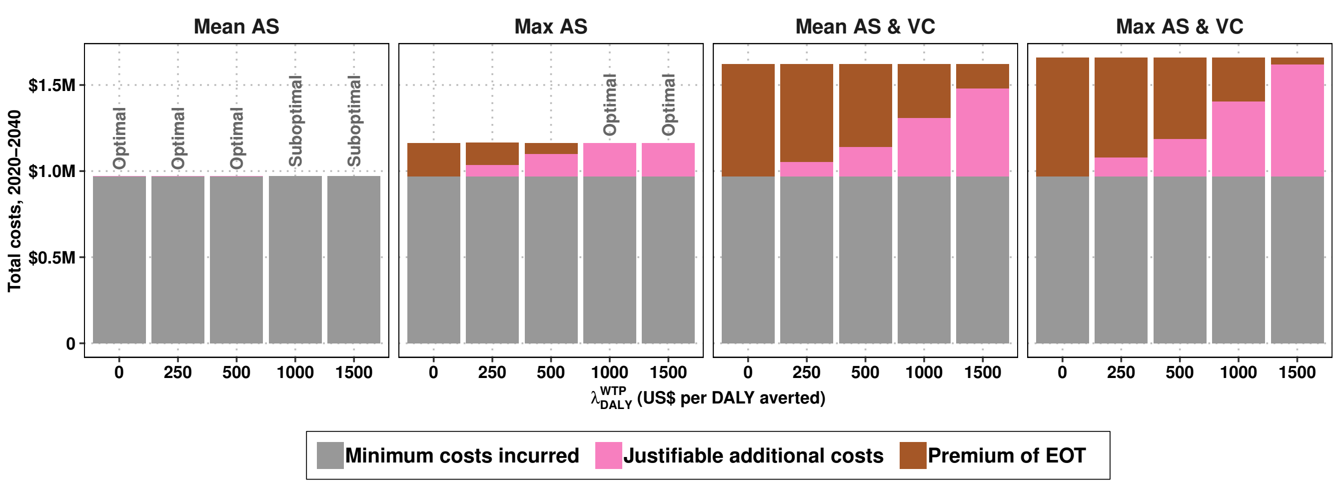

Fig. 3. Premium of elimination in Region 3, across different values of λ_{DALY}^{WTP}, contextualized in table 1.