Summary: Cost-effectiveness analysis of targeted end-game interventions against *gambiense* human African trypanosomiasis in the Democratic Republic of Congo

Marina Antillon[1,2], Ching-I Huang[3,4], Ronald E. Crump[3,4], Samuel A. Sutherland[3,5], Rian Snijders[1,2,6], Paul E. Brown[3,4], Emily H. Crowley[3,4], Andrew Hope[7], Paul Bessell[8], Iñaki Tirados[8], Chancy Shampa[9], Junior Lebuki[9], Erick Mwamba Miaka[9], Fabrizio Tediosi[1,2], Kat S. Rock[3,4]

1. Swiss Tropical and Public Health Institute, Basel, Switzerland
2. University of Basel, Basel, Switzerland
3. Zeeman Institute, University of Warwick, Coventry, UK
4. Mathematics Institute, University of Warwick, Coventry, UK
5. Warwick Medical School, University of Warwick, Coventry, UK
6. Institute of Tropical Medicine, Antwerp, Belgium
7. Liverpool School of Tropical Medicine, Liverpool, UK
8. Independent consultant, Edinburgh, UK
9. Programme National de Lutte contre la Trypanosomie Humaine Africaine, Kinshasa, Democratic Republic of Congo

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Abstract

Gambiense *human African trypanosomiasis (gHAT) is marked for elimination of transmission (EoT) by 2030. We examined the cost-effectiveness (CE) of EoT in the Democratic Republic of Congo (DRC), which has the highest global gHAT burden. In 166 health zones (HZs), we modelled the transmission dynamics, health outcomes, and economic costs of six strategies during 2024–40, including the cessation of activities after case reporting reduces to zero. Uncertainty in CE was assessed within the net monetary framework, presented as the optimal strategies at a range of willingness-to-pay values (WTP), denominated in costs per disability-adjusted life-year averted. Status quo strategies, CE strategies (WTP=$500), and strategies with a high probability of EoT by 2030 are predicted to yield EoT by 2030 in 117 HZs, 130 HZs, and 138 HZs respectively, at a cost by 2040 of $159M (82M–266M), $175M (98M–285M), $206M (114M–339M). A more lenient timeline of EoT by 2040 could lead to EoT in 153 HZs at a cost of $189M (105M–311M), leaving 12 HZs shy of the goal. Investing in EoT by 2030 is predicted to reduce gHAT deaths from 34,770 (14,113–71,118) to 8,214 (3,284–18,507).*

E1 Introduction

This study focuses on the health economic impact of implementing six plausible gHAT control and elimination strategies for the whole of the DRC at the health zone level and under a variety of funding and elimination targets. This is an expansion of previous work described above (see [1]) that focused on five low- to high-risk health zones but scaled up to 166 health zones across the DRC. Model fits and projections are also refined from previous work through the use of an extra four years of gHAT case and screening data (see [2, 3]). Using a modelling framework we examined the interplay of epidemiological, economic and temporal factors in effective decision-making around gHAT strategies for EoT. The objective of this piece is to estimate future resource needs including the resource implications of pursuing gHAT EoT by 2030 and which of the strategies under consideration has the highest probability of being cost-effective in these different settings.

E2 Methods

E2.1 Data

Historical case data was acquired from the WHO HAT Atlas project, which also includes records of the number of people tested in active screening activities [4]. For cost purposes, populations screened during passive screening were

deduced from two data sources: the historical records of clinics capable of screening with serological tests (RDT or CATT) [5], and records acquired from the PNLTHA for the years 2019–2020. Cost data was acquired from the literature and conversations with program staff ([6, 7], among others).

E2.2 Transmission model fit to data

For this study, we used the previously published Warwick gHAT model [2] consisting of a mechanistic modelling framework to explicitly simulate transmission between humans via tsetse vectors (see Supplementary Figure E6A). The model parameterisation has recently been updated by fitting to WHO HAT Atlas data from 2000–2020 for health zones in the DRC that had sufficient data (at least 10 data points, where any year with active screening and any year with non-zero passive case detection count as individual data points). Furthermore, the modelling framework has been updated to capture stochastic dynamics and is better able to estimate the time until EoT. Moreover, we fit also the data to an animal model variant which considers the possibility that animals can acquire and transmit infections to and from tsetse (as per [8] but with an extra four years of data). Our final projections will consist of an "ensemble" of samples of projections from both models – with and without animals. The proportion of samples from both models will be determined by the statistical support of each model based on the data. The health zones included in the analysis are described in Table E2.

E2.3 Epidemiological projections

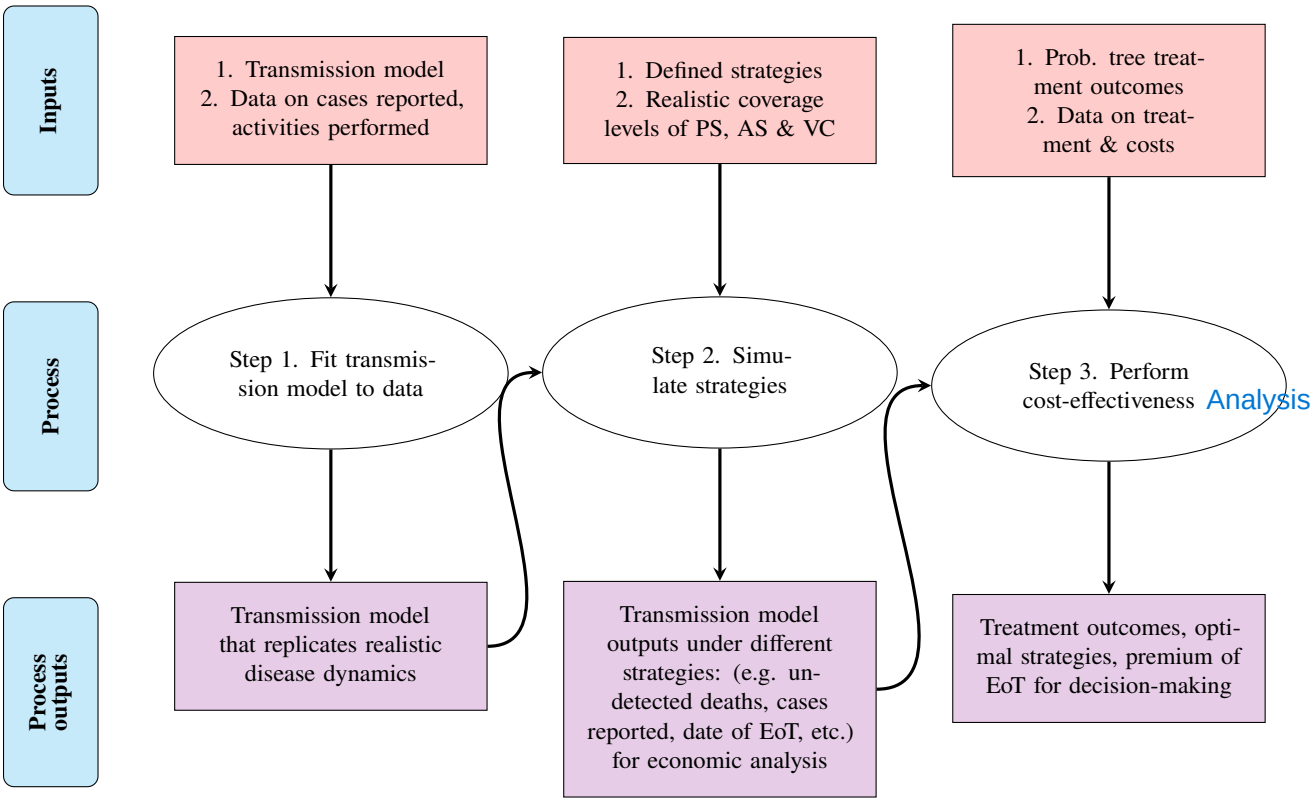
Projections under six plausible gHAT control and intervention strategies were simulated from 2024–2050 and are displayed in Figure E1; three health zones in the Bas Uéle region – Ango, Ganga, and Doruma – have alternative strategies due to the special situations in these health zones. Each activity is further explained in Table E1. The *Targeted VC* strategy uses an adapted algorithm based on that previously used by LSTM to identify large rivers with recent nearby high case density at which to focus Tiny Target deployment. The *Full VC* strategy, by contrast, involves an expansion of VC interventions, considering the deployment of Tiny Targets throughout all large rivers in a health zone. All strategies feature the continuation of the current PS. All strategies assume that AS will cease after 3 years of AS with zero cases in either AS or PS, followed by another AS in year 5 with no cases. RS is triggered if a case is found in PS and stops using the same 3+1 algorithm. VC stops after 3 years of no cases. PS is stopped 5 years after AS and RS have ceased. PS is assumed to remain constant for the duration of our simulations, even after cessation of AS and VC and presumed EoT. Fexinidazole is simulated as being available immediately, but acoziborole is not included in this analysis.

E2.4 Economic evaluation and investment horizon

We adopted the net-benefits framework, which expresses the probability that an intervention is optimal at a range of thresholds, known as the willingness-to-pay (WTP) thresholds. We computed net monetary benefits by taking the mean difference in costs and monetised health effects (DALYs $\times$ willingness-to-pay value). As per recent recommendations from the WHO, we refrained from selecting a specific ICER that would be considered "cost-effective", and we aimed to make recommendations after accounting for uncertainty.

We examined health and cost impacts in the long term (2024–2040) to assess the returns on investments in both augmented disease control and elimination. Costs are presented in their undiscounted version for pragmatic reasons but for the selection of cost-effectiveness, both costs and health outcomes are discounted at a yearly rate of 3%.
A glossary of epidemiology and health economic terms is found in the Appendix, Box 1.

(a) Process of analysis



(b) General set of strategies.

Strategies	Interventions				
	Mean AS (2016–20)	Intensified AS	Passive screening	Realistic VC	Full VC
Mean AS (status quo)	■		■		
Int. AS		■	■		
Mean AS & realistic VC	■		■	■	
Int. AS & realistic VC		■	■	■	
Mean AS & full VC	■		■		■
Int. AS & full VC		■	■		■

(c) Special set of strategies.

Strategies	Interventions		
	Mean AS (2010–14)	Passive screening	VC*
No PS, AS, nor VC (status quo)			
Int. AS & no PS	■		
Restart PS		■	
Int. AS & Restart PS	■	■	
Restart PS & VC		■	■
Int. AS & Restart PS & VC	■	■	■

Figure E1: a) Process of analysis. b) Future strategies simulated in most health zones. *Mean AS* is equal to the mean coverage of AS between 2016–2020, *Int. AS* is 30% or the historical maximum coverage between 2000–2020, whichever is higher. c) Future strategies simulated in Ango, Ganga, and Doruma health zones of the Bas-Uélé region. We do not mean AS from 2016–2020 in these health zones as there was no AS during this period, hence *Restart PS* is effectively equivalent to this strategy. In these health zones, we take *Int. AS* to be the mean of 2010–2014 when MSF was operating in the region. In all health zones, the *Targeted VC* strategy only simulates VC along rivers in regions with high case density, and because the cases may be diffuse in some health zones, this strategy is not present in some health zones. Whereas the *Full VC* strategy involves the deployment of Tiny Targets throughout all large rivers in a health zone, regardless of the density of the cases. *Intervention cessation:* All strategies assume that AS will cease after 3 years of AS with zero cases in either AS or PS, followed by another AS in year 5 with no cases. RS is triggered if a case is found in PS and stops using the same 3+1 algorithm. VC stops after 3 years of no cases. PS is stopped 5 years after AS and RS have ceased. See the glossary and Table 9 for details of abbreviations.

E3 Results

Figure E2 summarises the optimal strategy for each of the 166 health zones included in this analysis at each WTP threshold (status quo, minimum cost, WTP=$250 and WTP=$500) and the strategy necessary to maximise the probability of EoT by 2030 and a more lenient goal date of 2040. For strategies in health zones that yield ¡90% probability of EoT by either date, then the strategy with the maximum probability of EoT is selected. Modelling suggests that 95 health zones could switch strategies to maximize their probability of EoT by 2030. For the 71 health zones that are predicted to be on track to achieve EoT by 2030, the optimal strategy in the first column (status quo) remains the same as that in the second-to-last column (EoT by 2030). For a more lenient goal of EoT by 2040, 72 health zones need to change strategies from their status quo strategies.

National-level results are summarised in Figure E3. Although 95 health zones should switch strategies to maximise the probability of EoT by 2030 – leaving 71 health zones with the same strategy – we expected that 117 health zones out of 166 health zones will reach the goal with their current strategies. With a switch of the 95 health zones to EoT-aligned strategies, only 21 more health zones will be seen to reach the goal. The low expectation (out of 166 health zones) is since 48 health zones have a probability of EoT by 2030 < 90% even under the strategy that maximises EoT.

Costs and effects at different levels of investment In terms of total investments, by 2040, the Status Quo strategy will cost $159M, the Minimum Cost will cost $151M, cost-effective strategies at a WTP of $250/DALYS and $500/DALY will cost $166M and $175M and EoT will cost $206M (Figure E5). We further show that a lot of our uncertainty is due to the lack of screening in Bas Uélé in recent years, so if nothing were necessary in that region, EoT by 2030 would cost $193M. Although the increase in costs is 30% from the status quo to EoT by 2030 over 17 years, the increase in resources in 2024 to reach EOT would need to increase by almost 60% (from $15M to $24M in 2024) (Figure F4). The EoT 2030 strategies will begin to cost less than status quo interventions in 2035 if we look at estimates including Bas Uéle, and by 2033, if we look at estimates excluding Bas Uélé. Delaying the goal until 2040 saves only $16M-$17M (if we exclude/include Bas Uélé) compared to putting into place activities aimed at EoT by 2030.

The status quo strategies will bring an expected 35K deaths of 765K DALYs by 2040 and minimum cost strategies would bring about 33K deaths or 731K DALYs including Bas Uélé. However, the majority of those deaths and DALYs are in Bas Uélé. Without Bas Uéle, status quo interventions would bring about 8256 deaths and 189K DALYs, and minimum cost interventions would bring about 6696 deaths and 155K DALYs (Figure E5).

The largest portion of the costs at any level of investment will go to screening and vector control activities (see Figure E16). Although the cost of treatment is quite small in relative terms, timely access to treatment is pivotal for strategies to remain effective.

All results are available stratified by coordination in Figures E7–E17.

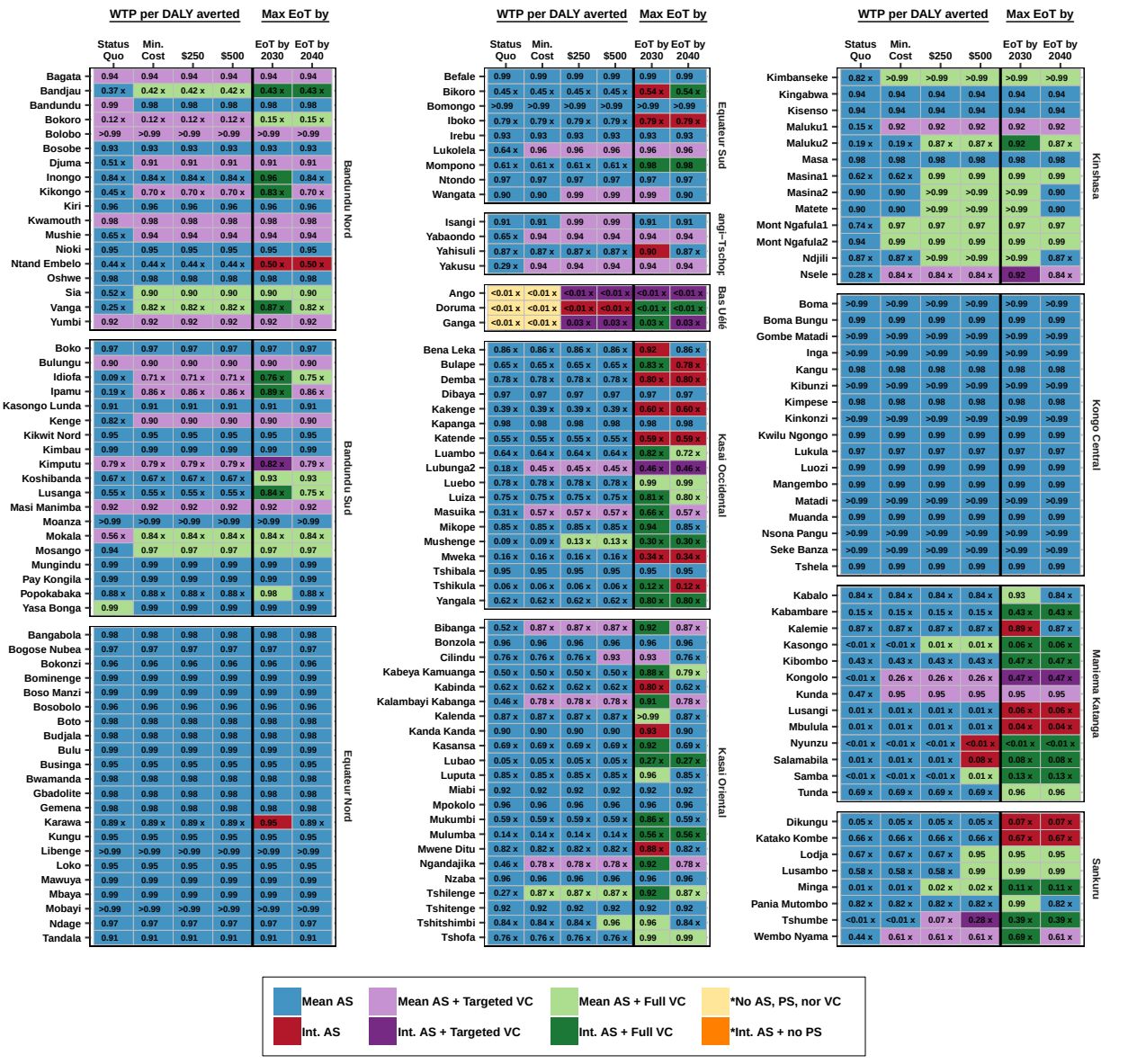
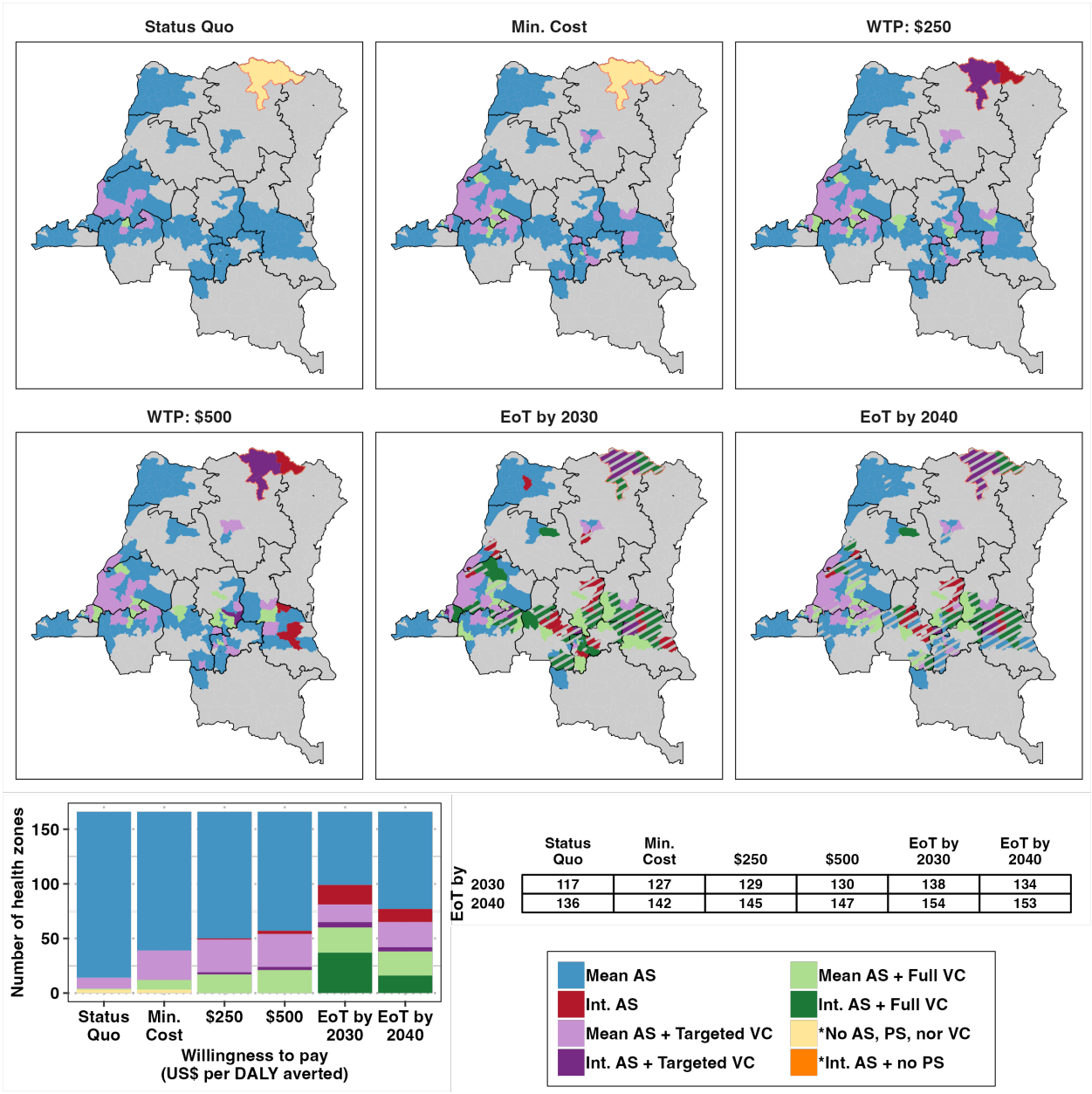


Figure E2: Table indicating optimal strategies according to economic or elimination goals for the whole of the DRC, (time horizon 2024–2040 and 3% discounting). Optimal strategies in each health zone of DRC compared to the status quo strategy (first column) depending on the level of investment (denominated by USD per DALYs averted, or by the date by which EOT is intended.



EoT by	Status Quo	Min. Cost	$250	$500	EoT by 2030	EoT by 2040
2030	117	127	129	130	138	134
2040	136	142	145	147	154	153

Figure E3: **Maps of optimal strategies according to economic or elimination goals for the whole of the DRC (time horizon 2024–2040 and 3% discounting, based on fits to 2000–2020 data).**

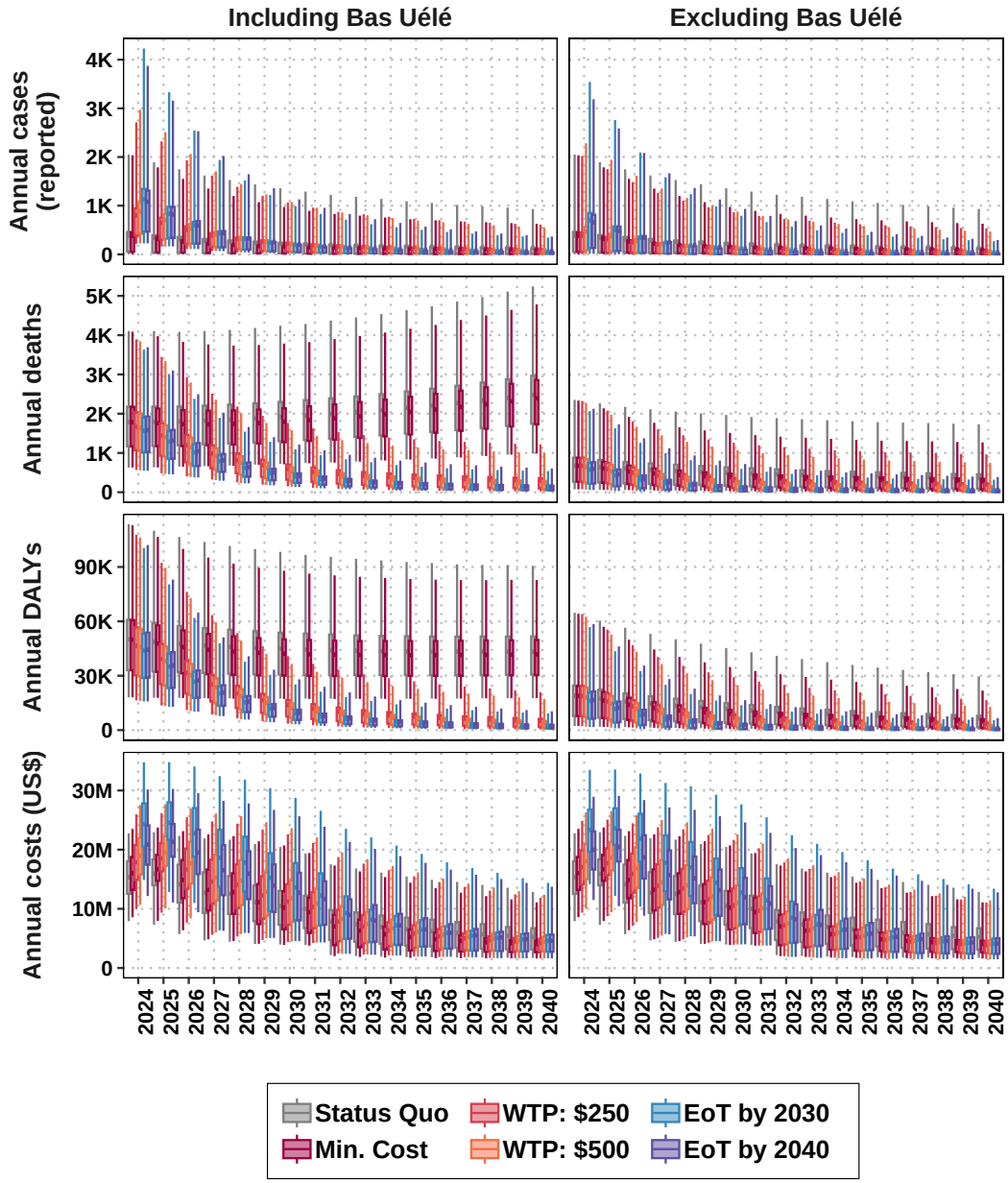


Figure E4: **Total Deaths, DALYs and Costs in all the DRC with optimal strategies with 3% discounting over the time horizon 2024–2040 based on fits to 2000–2020 data.**

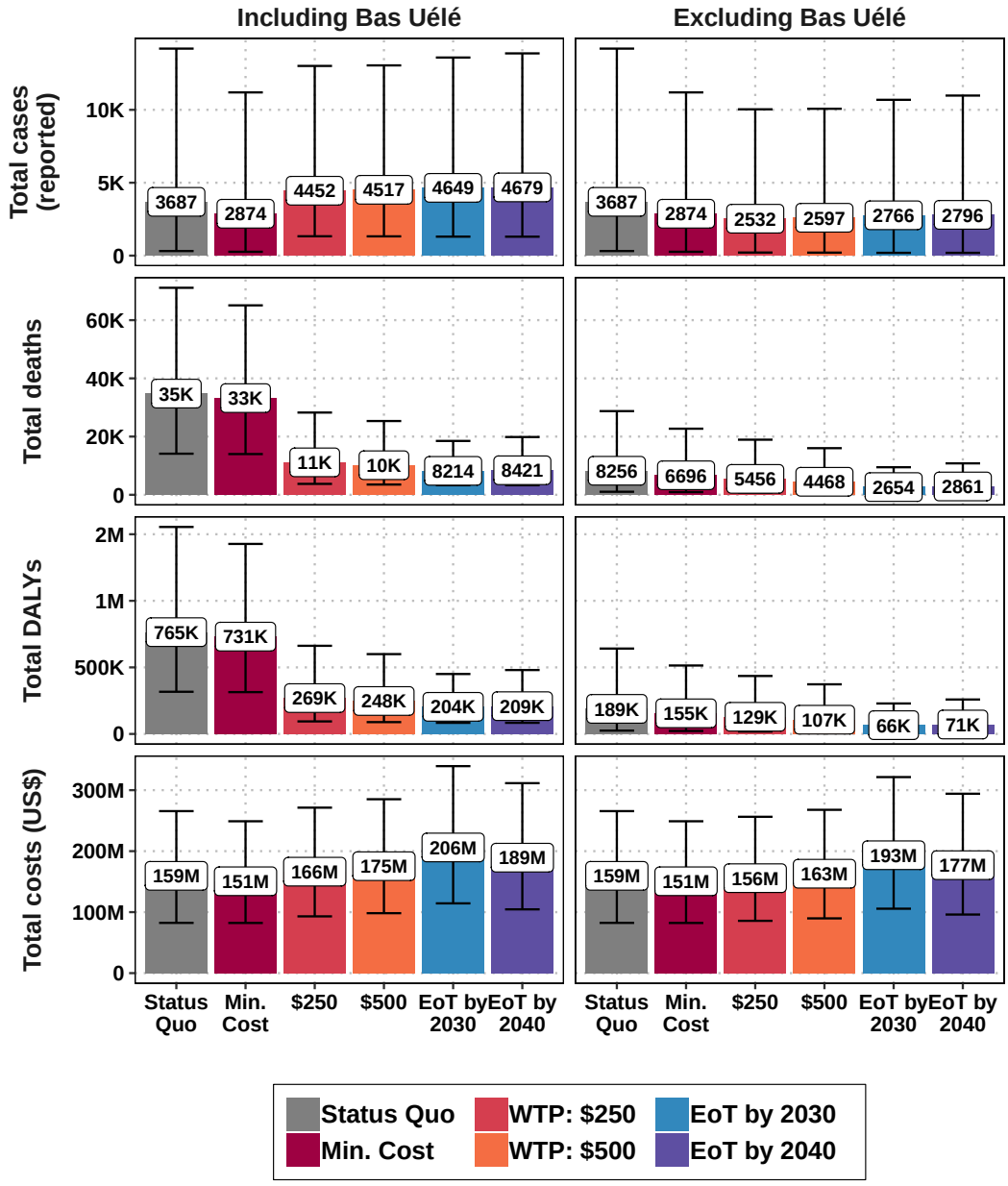


Figure E5: **Total Deaths, DALYs and Costs in all the DRC with optimal strategies with 3% discounting over the time horizon 2024–2040 based on fits to 2000–2020 data.**

E4 Discussion

E4.1 Conclusion

Financial resources will have to increase for a short period to reach EoT by 2030, but EoT strategies will begin to give returns to investments by 2033–35. Expanded strategies will be necessary in some health zones, particularly in the East where uncertainty makes the analysis favour more intense strategies. In Kongo Central and Equateur Nord, current strategies appear to be on track for EoT by 2030.

Future analysis for the DRC, which is currently outside the scope of this study, will look at 1. the potential impact of strategies that use acoziborole as a single-dose treatment and 2. the premium paid for EoT above and beyond what would be considered a cost-effective use of resources compared to other health programmes using our new "net monetary and elimination benefits" framework [9].

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E5 Glossary of epidemiologic and health economic terms

Box 1: Glossary (adapted from Antillon et. al 2022 [1] under a CC-BY 4.0 license.)

Epidemiology Terms

Intervention Interventions are separate activities to address a health need (e.g. active screening (AS) or vector control (VC)).

Strategy A strategy is a combination of interventions, carried out with a specific coverage, and in parallel. In this paper, we simulate strategies with and without an improvement in AS and with and without VC (e.g. strategy 1 is passive surveillance (PS) and mean AS, and strategy 4 is PS, maximum AS and VC).

Elimination of transmission (EoT) Globally this is the 2030 goal for gHAT; here we also consider local EOT for health zones. The feasibility of EOT is expressed as a probability equal to the proportion of our simulations in which new infections is zero before a given year (usually 2030).

Disability-adjusted life-year (DALY) In order to present the burden of disease in one common metric across diseases, DALYs are calculated in cost-effectiveness analyses. This is the sum of the years lived with disability due to the disease and the years of life lost by fatal cases.

Health Economics Terms

Parameter uncertainty Uncertainty in the level of transmission or in the costs of interventions and treatment due to unknown underlying parameters (see supplementary section F for an explanation of our parameterization of the health outcomes and cost model).

Willingness-to-pay (WTP) or cost-effectiveness threshold The amount of money that payers would pay to avert one DALY arising from the disease in the analysis (gHAT). No specific threshold is recommended, but a recent analysis shows that the WTP in DRC is between 5–230 USD per DALY averted [10–12].

Incremental cost-effectiveness ratio A ratio of marginal cost for a marginal benefit, calculated as follows:

$$\text{ICER} = \frac{\Delta\text{Costs}}{\Delta\text{DALYs}} = \frac{\text{Costs}_{\text{strategy}} - \text{Costs}_{\text{next best}}}{\text{Effects}_{\text{strategy}} - \text{Effects}_{\text{next best}}}$$

Cost-effective strategy The strategy where the ICER is less than the WTP (or cost-effectiveness threshold). We say that the cost-effective strategy is "conditional" on the WTP.

Dominated strategy A strategy that costs more than the minimum cost intervention while reducing the burden by a smaller degree. This strategy ought not to be implemented.

Weakly dominated strategy (or strategies under extended dominance) A strategy in which the ICER is higher that the next more expensive strategy. This is a strategy that is less efficient than the next more expensive strategy and ought not be implemented. For further illustration of weak dominance, see Supplementary Section, page 46 of Antillon et. al 2022 [1].

Net monetary benefit The net benefits (NMB) framework is derived from ICERs, but also takes uncertainty into account.

$$\text{NMB}|\text{WTP} : \text{WTP} \times \Delta\text{DALYs} - \Delta\text{Costs}$$

The optimal strategy at a given WTP is the strategy with the highest mean NMB at that value of WTP.

Optimal strategy Analogous to the cost-effective strategy when no uncertainty is assumed, this is the strategy that is recommended by the NMB framework.

E6 Supplementary Tables and Figures

Term	Description
Active screening (AS)	Mobile teams travelling to at-risk villages to test any person willing to participate
High risk	Individuals with greatest risk of gHAT infection
Intensified (Int.) active screening (Int. AS)	Screening coverage (% people) at either the historic maximum or at 30% if the historic maximum is lower than this value
Intervention	Tools, treatments or approaches used to prevent or treat the infection
Low risk	Individuals with lowest risk of gHAT infection
Mean active screening (Mean AS)	Screening coverage (% people) at the mean of the last five years for a region
Passive screening (PS)	Testing self-presenting individuals for gHAT at fixed health facilities
Reactive screening (RS)	Testing in specific locations in response to cases detected through passive screening
Treatment	Treatment of confirmed cases with either fexinidazole (oral drug course) if eligible, or pentamidine or NECT. Acoziborole (oral single-dose cure) may be used in the future if approved but is not considered in this analysis.
Vector control (VC)	Methods used to reduce or eradicate the vector, e.g. tsetse, that transmits infection
Targeted vector control (Targeted VC)	An adapted method based on that previously used by LSTM to identify areas with high case density at which to focus Tiny Target deployment efforts along waterways
Full vector control (Full VC)	Considers the deployment of Tiny Targets throughout all waterways in a health zone

Table E1: **Terms used to describe the interventions and the strategies**

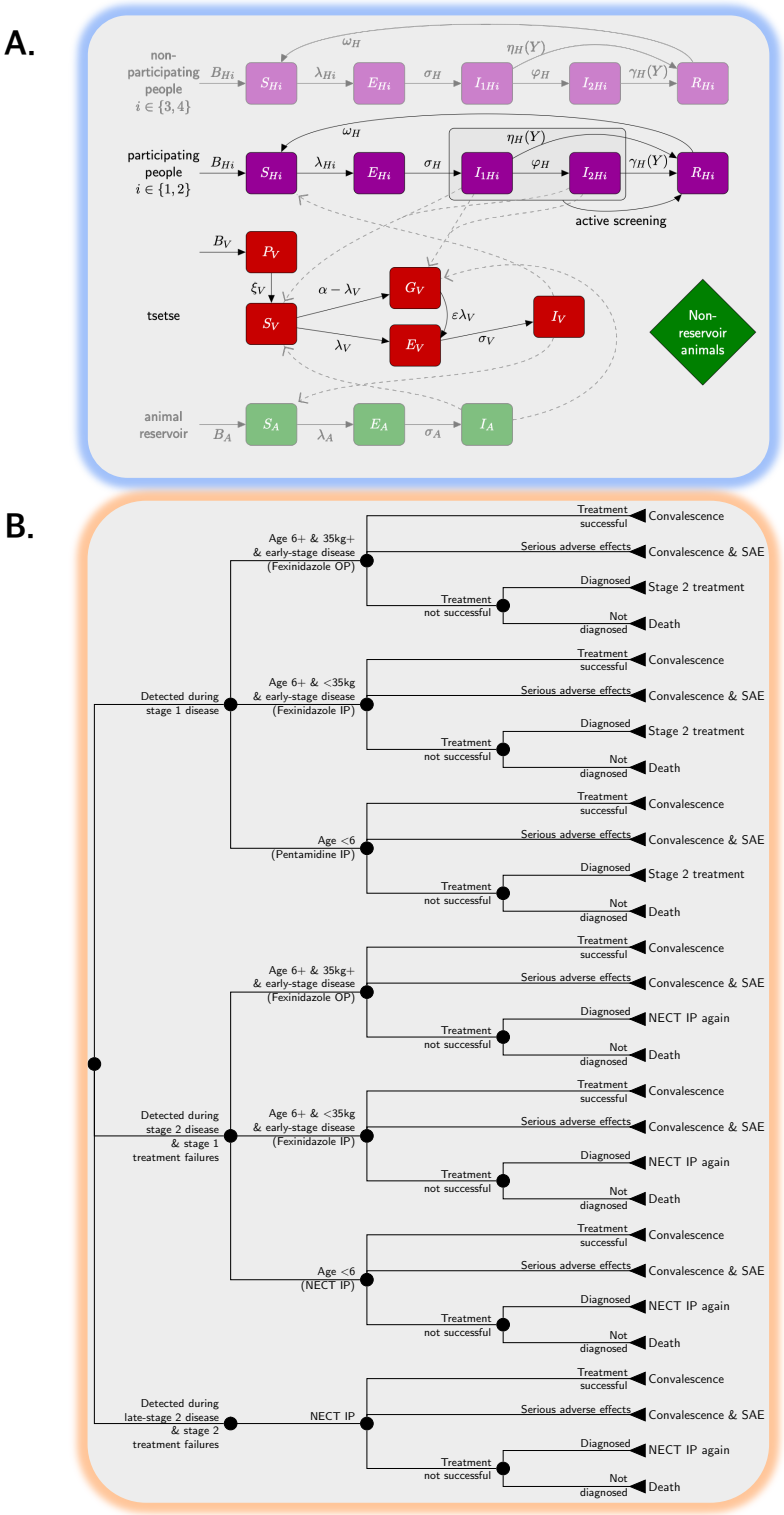

Figure E6: Disease suppression and prevention strategies and treatment model. A) Strategies against gHAT, including active screening (AS) by mobile teams, passive surveillance (PS) in fixed health facilities, and vector control (VC). In two strategies ('Mean AS' and 'Mean AS & VC') the proportion screened equalled the mean number screened during 2014–2018. In two other strategies ('Max AS' and 'Max AS & VC'), the coverage is the maximum number screened during 2000–2018. In strategies 3 and 4, vector control (VC) is simulated assuming an 80% tsetse density reduction in 1 year. PS is in place under all strategies. B) Treatment for diagnosed gHAT patients is modeled as a branching tree process of possible health outcomes including eligibility for novel fexinidazole. Abbreviations: SAE: Serious adverse events, IP: inpatient care, OP: outpatient care.

Coordination	Total No. HZ	Included			Excluded - insufficient data			Excluded - urban locale		
		No. HZ	Cases 2000-2020	Populatio (millions)	No. HZ	Cases 2000-2020	Populatio (millions)	No. HZ	Cases 2000-2020	Populatio (millions)
Bandundu Nord	20	18	36369	3.6	2	6	0.2	0	0	0.0
Bandundu Sud	32	19	30458	4.8	12	27	2.3	1	64	0.3
Equateur Nord	39	22	19340	4.7	17	21	3.6	0	0	0.0
Equateur Sud	30	9	1622	1.3	21	55	4.0	0	0	0.0
Isangi - Bas-Uélé	6	3	6370	0.4	3	222	0.3	0	0	0.0
Isangi - Tschopo	29	4	2792	0.7	25	55	3.9	0	0	0.0
Kasai Occidental	45	18	6314	4.4	26	66	6.5	1	172	0.3
Kasai Oriental	35	22	17415	6.4	5	31	1	8	2874	3.1
Kinshasa	36	13	3032	4.2	9	108	1.8	14	1107	5.0
Kongo Central	30	17	4681	2.6	13	41	1.9	0	0	0.0
Maniema Katanga	29	13	4583	3.3	16	30	3.3	0	0	0.0
Sankuru	16	8	2053	1.3	8	17	1.1	0	0	0.0
No Coordination	172	0	0	0.0	172	58	41.3	0	0	0.0
Total	**519**	**166**	**135029**	**37.7**	**329**	**737**	**71.2**	**24**	**4217**	**8.7**

Table E2: Summary of demographics characteristics and HAT case burden of health zones that were included compared to those excluded from the analysis. Health zones were omitted if there were fewer than 10 data points: in other words the number of years in which AS activity was reported available plus the number of years in which cases were found through PS totalled to less than 10, or if we did not believe that transmission could take place in the health zone because it was urban. Around 0.5 percent of cases occurred in health zones with insufficient data to fit, and a further 3 percent occurred in health zones with enough data points, but that we have deliberately excluded because of their urban locale, where we believe there is no transmission. All populations are estimates of the 2023 population.

Coordination	No. HZ	Pop. per HZ (thousands)	Pop. subtotal (millions)	2000-2020 Cases per HZ[a]	2000-2020 Sum cases	2016-2020 Cases per HZ[a]	2016-2020 Sum cases
Bandundu Nord	18	180 [110-367]	3.60	1748 [37-7186]	36369	66 [3-210]	1278
Bandundu Sud	19	249 [154-358]	4.80	592 [10-6827]	30456	36 [1-183]	1194
Equateur Nord	22	188 [84-427]	4.70	474 [25-4298]	19340	2 [0-29]	113
Equateur Sud	9	171 [45-212]	1.30	92 [19-550]	1622	2 [0-15]	34
Isangi - Bas-Uélé[b]	3	133 [88-159]	0.40	1907 [1387-3076]	6370	0 [0-0]	0
Isangi - Tschopo[b]	4	198 [106-208]	0.70	579 [41-1593]	2792	23 [0-55]	101
Kasai Occidental	18	230 [117-420]	4.40	180 [9-1982]	6314	12 [0-85]	446
Kasai Oriental	22	265 [153-543]	6.40	472 [56-4567]	17415	8 [1-58]	307
Kinshasa	13	338 [90-594]	4.20	98 [35-858]	3027	5 [0-43]	143
Kongo Central	17	133 [83-251]	2.60	249 [15-912]	4673	4 [0-51]	169
Maniema	13	237 [107-417]	3.30	391 [31-691]	4583	14 [0-74]	309
Katanga							
Sankuru	8	150 [95-239]	1.30	218 [13-773]	2053	20 [1-104]	331
Total	**166**	**210 [45-594]**	**37.74**	**350 [9-7186]**	**135014**	**9 [0-210]**	**4425**

[a] Cases are shown per health zone: median [minimum-maximum].

[b] Isangi coordination has been separated into two subregions in this analysis. Bas-Uélé is constituted of Ango and Ganga health zones in Bas-Uélé Province and Doruma health zone in Haut-Uélé Province. Tshopo is constituted of Isangi, Yabaondo, Yahisuli, and Yakusu health zones in Tschopo province.

Table E3: Summary of the demographic characteristics and recent vs complete case burden in health zones in the analysis, stratified by the coordinations delineated the programme national de lutte contre la Trypanosomiase humaine africaine (PNLTHA-RDC). Abbreviation: HZ: health zone.

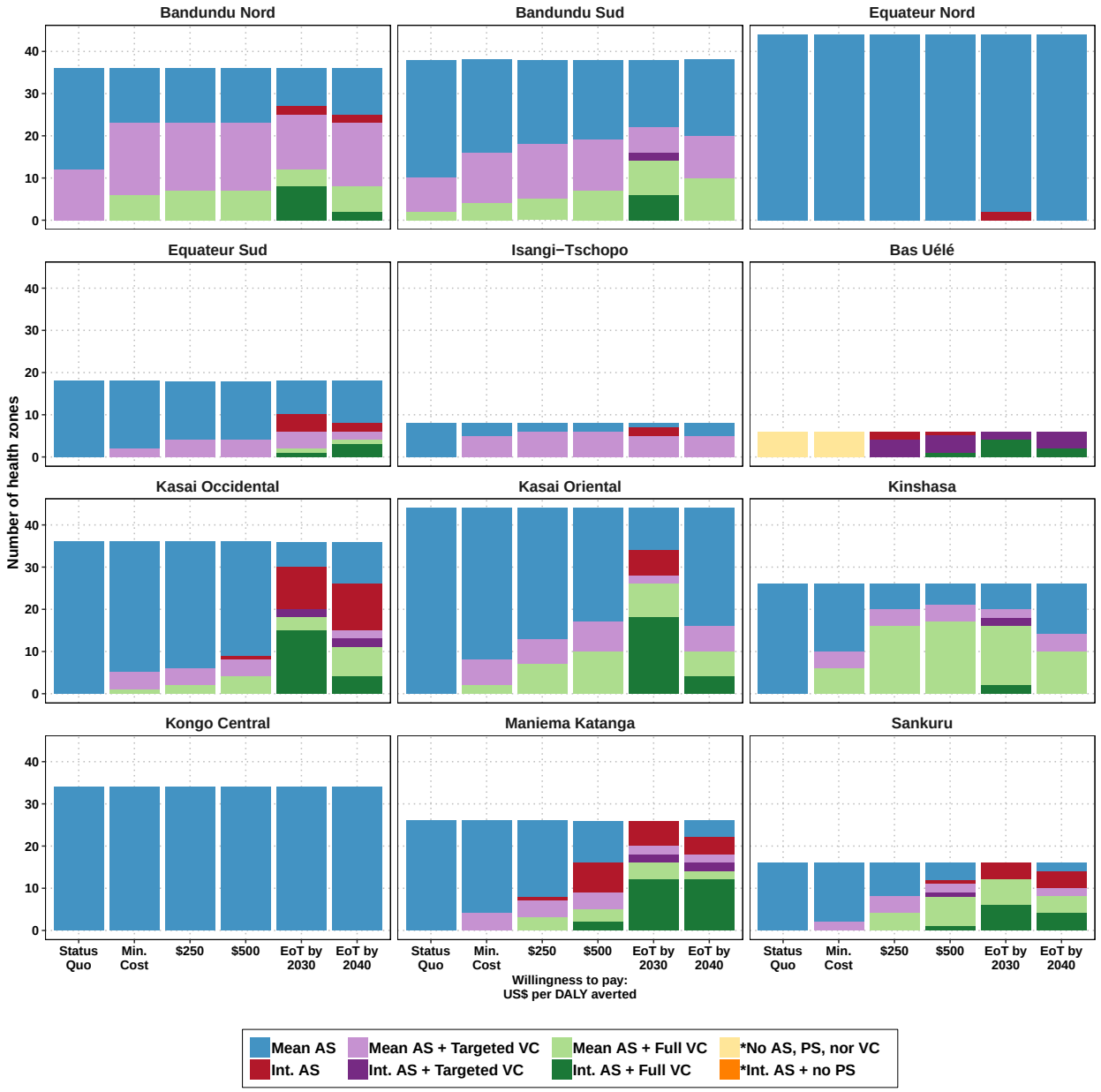

Figure E7: **Histrogram of optimal strategies by coordination**

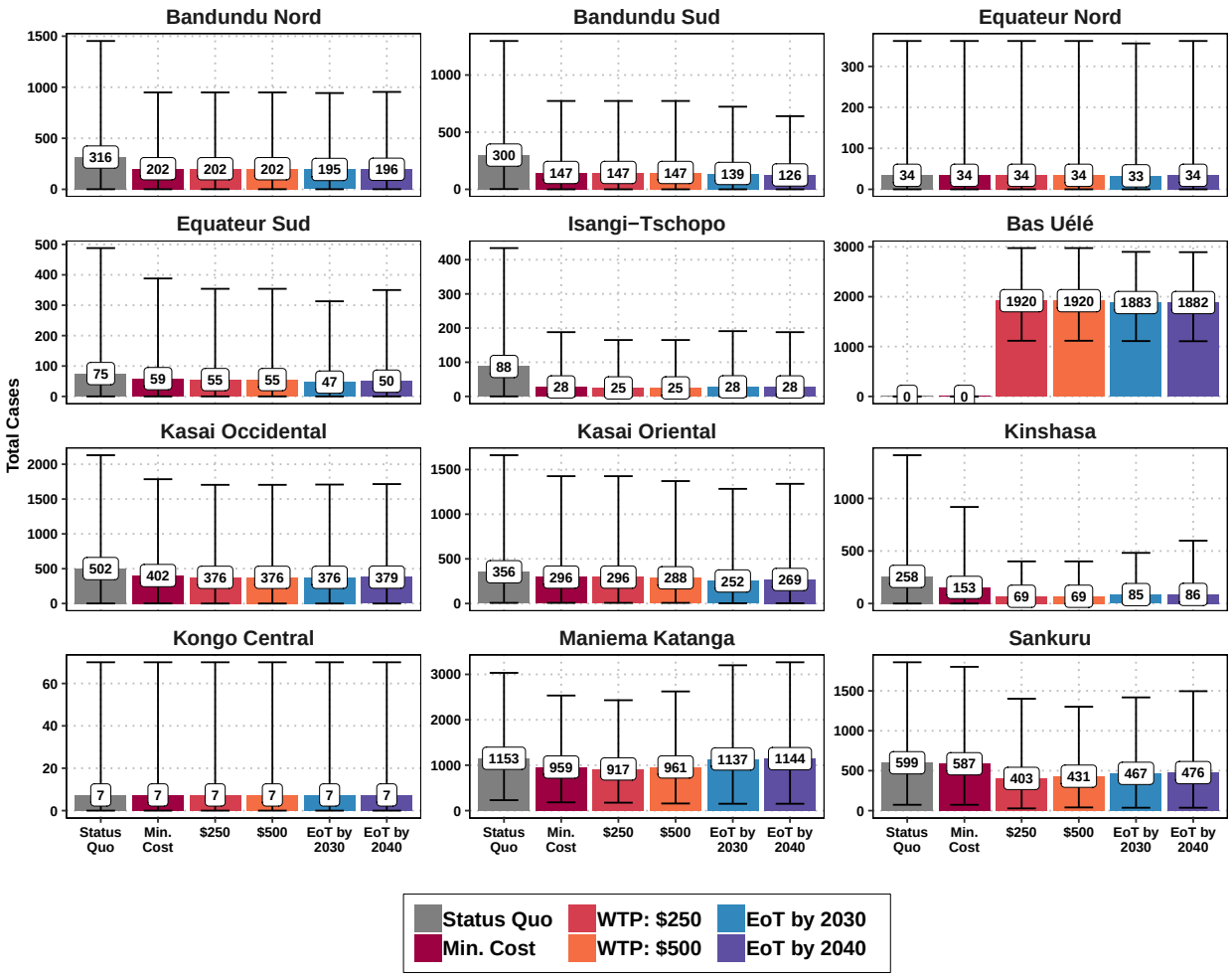

Figure E8: **Total cases 2024-2040 across different levels of investment.**

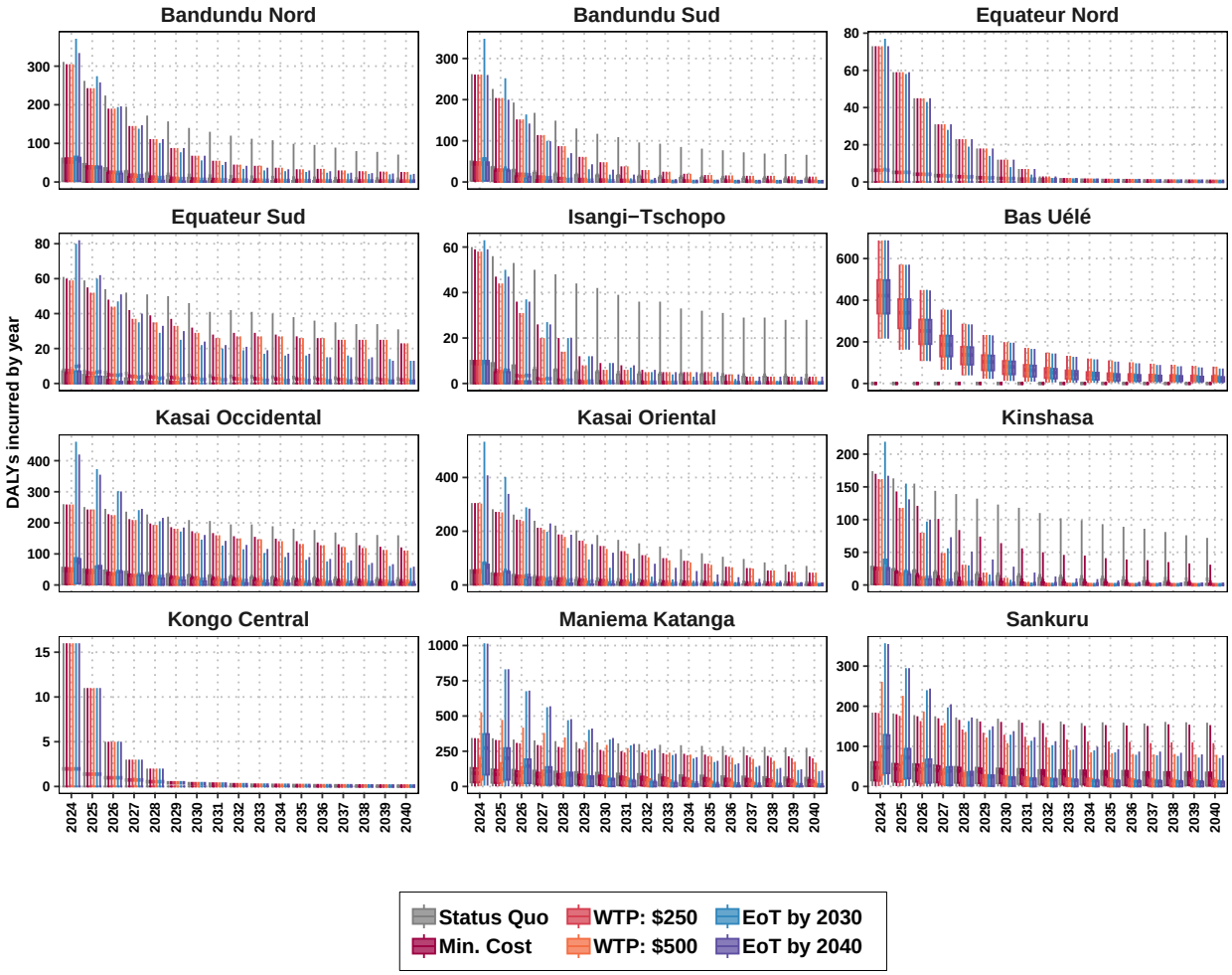

Figure E9: **Cases by year 2024-2040 across different levels of investment.**

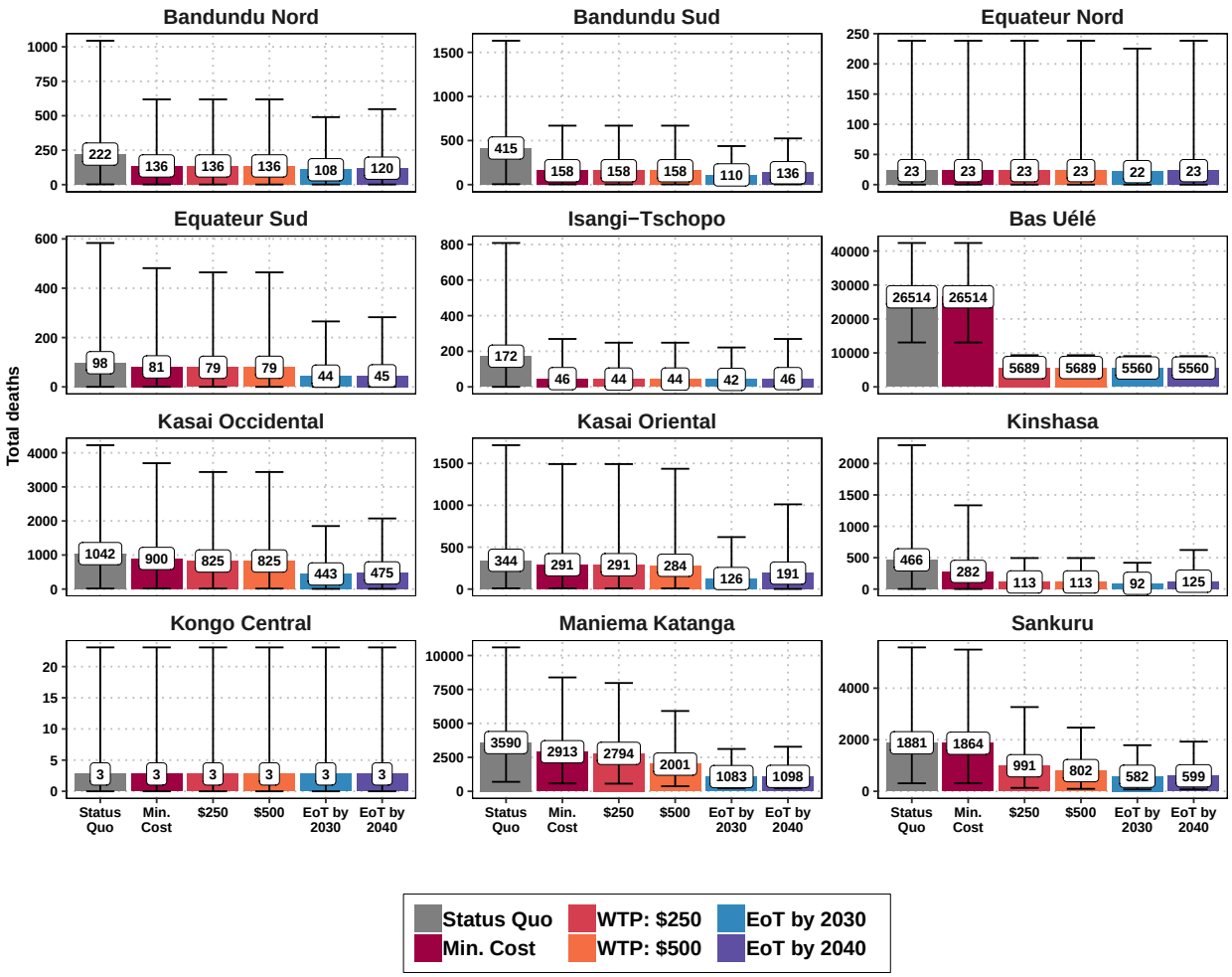

Figure E10: **Total deaths 2024-2040 across different levels of investment.**

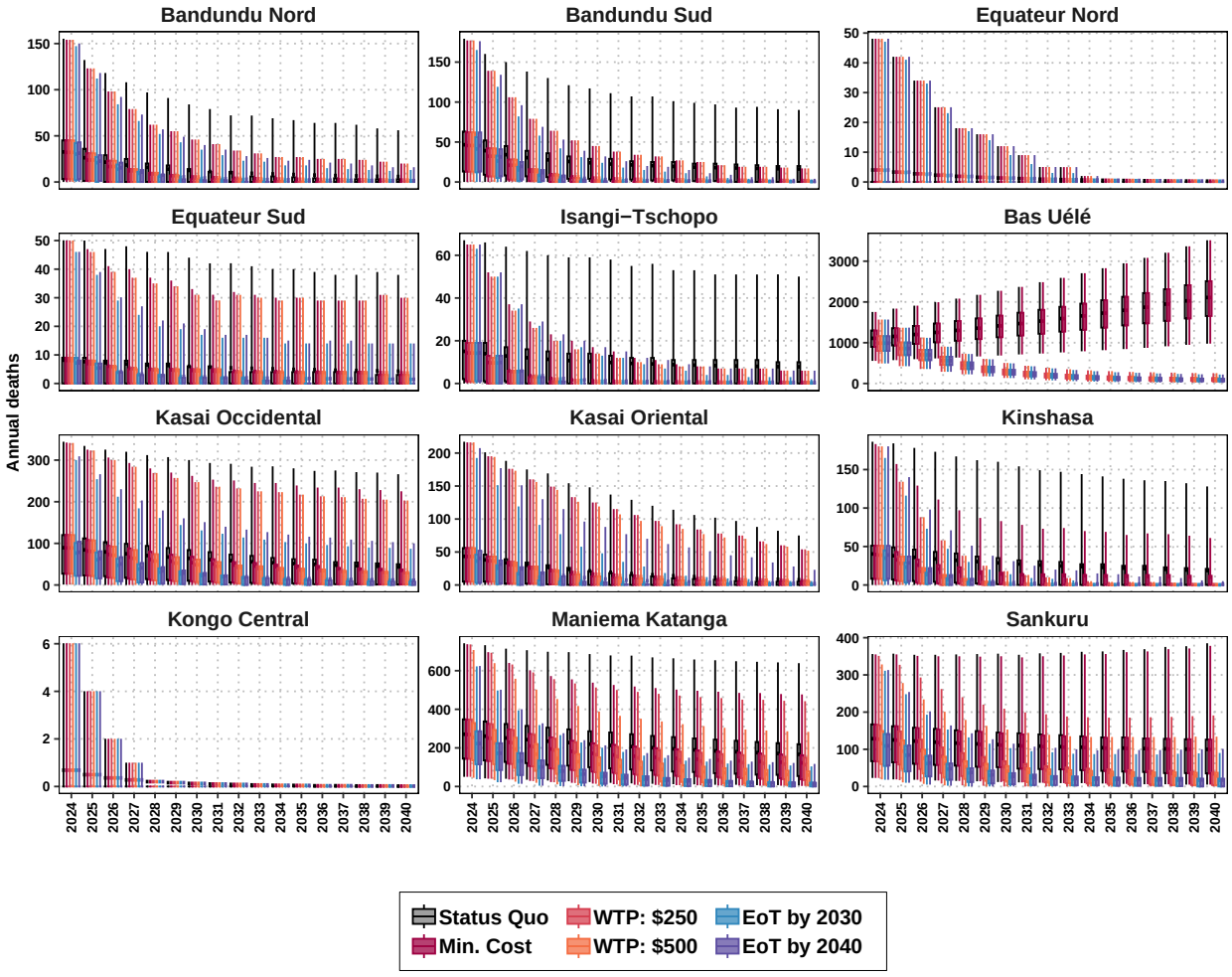

Figure E11: **Deaths by year 2024-2040 across different levels of investment.**

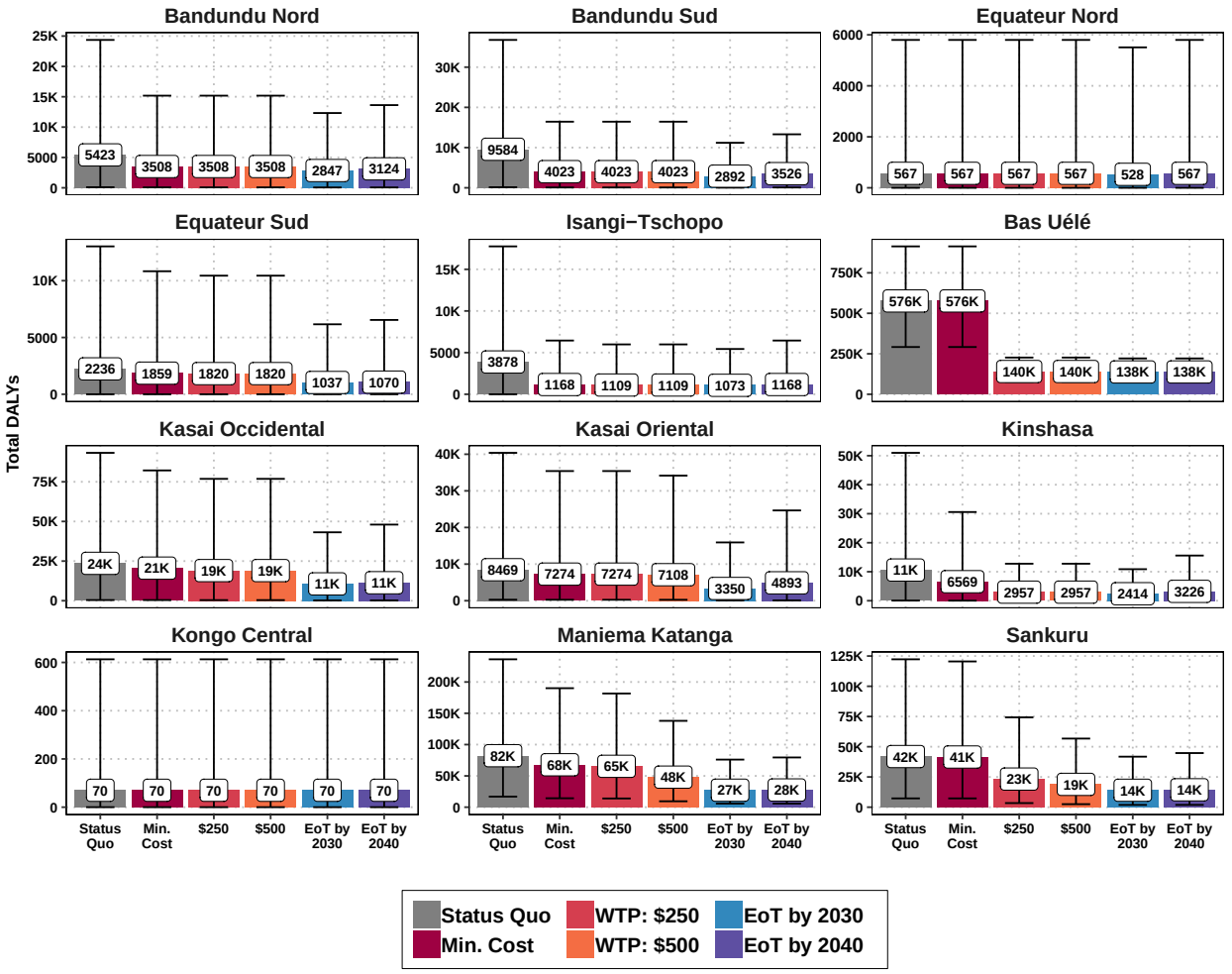

Figure E12: **Total DALYs 2024-2040 across different levels of investment. Abbreviations: DALYs: disability-adjusted life-years.**

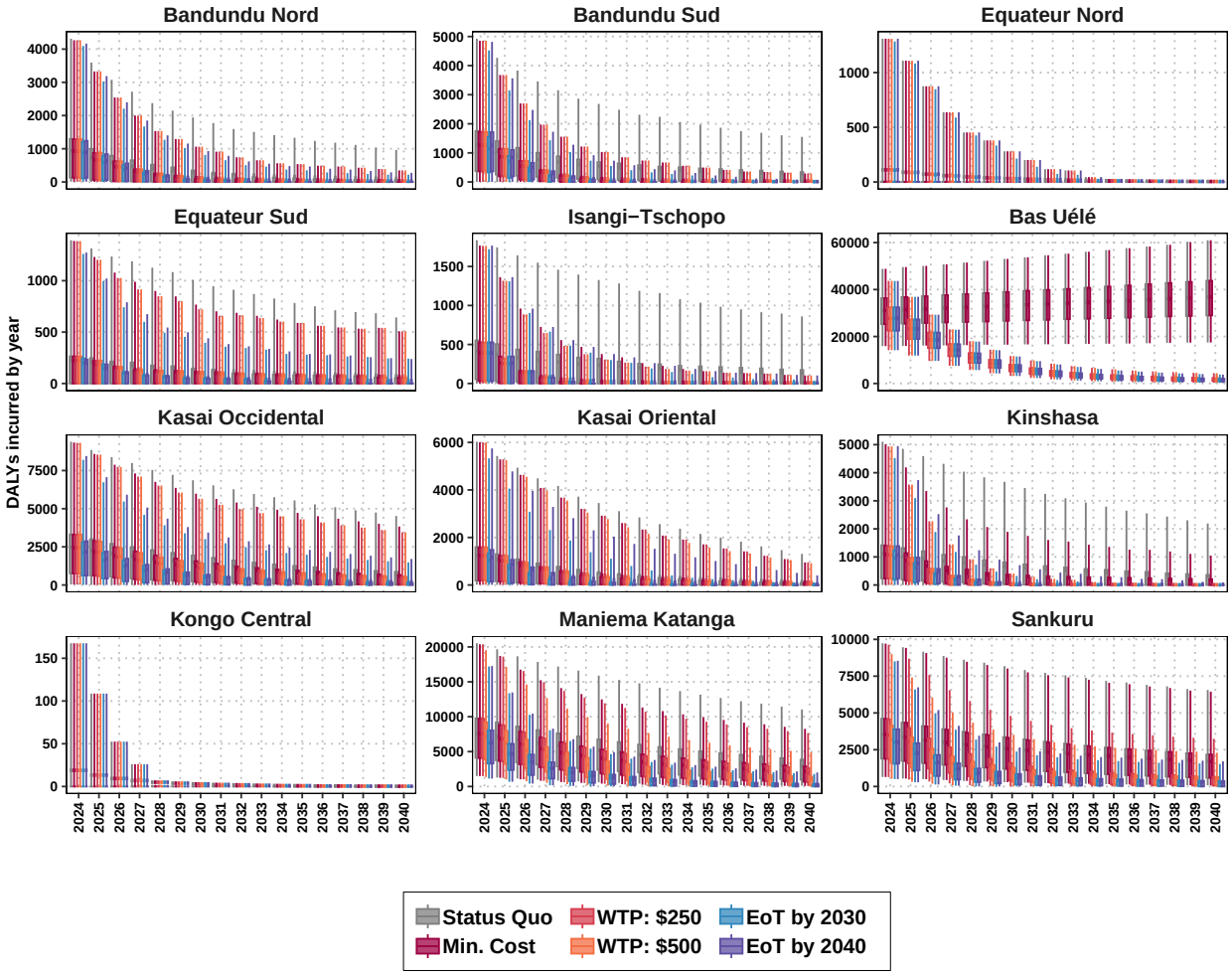

Figure E13: **DALYs by year 2024-2040 across different levels of investment.**

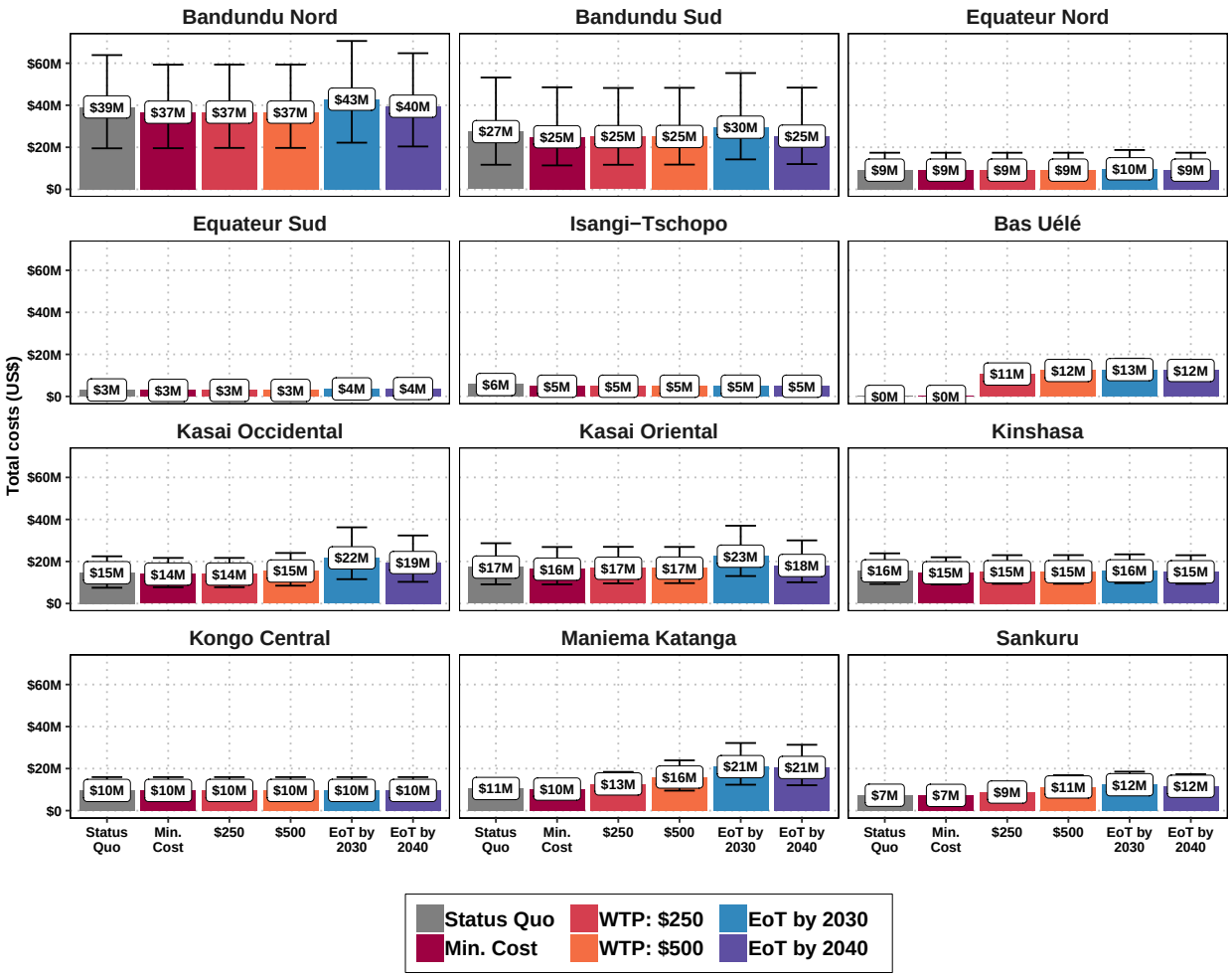

Figure E14: **Total costs 2024-2040 across different levels of investment.**

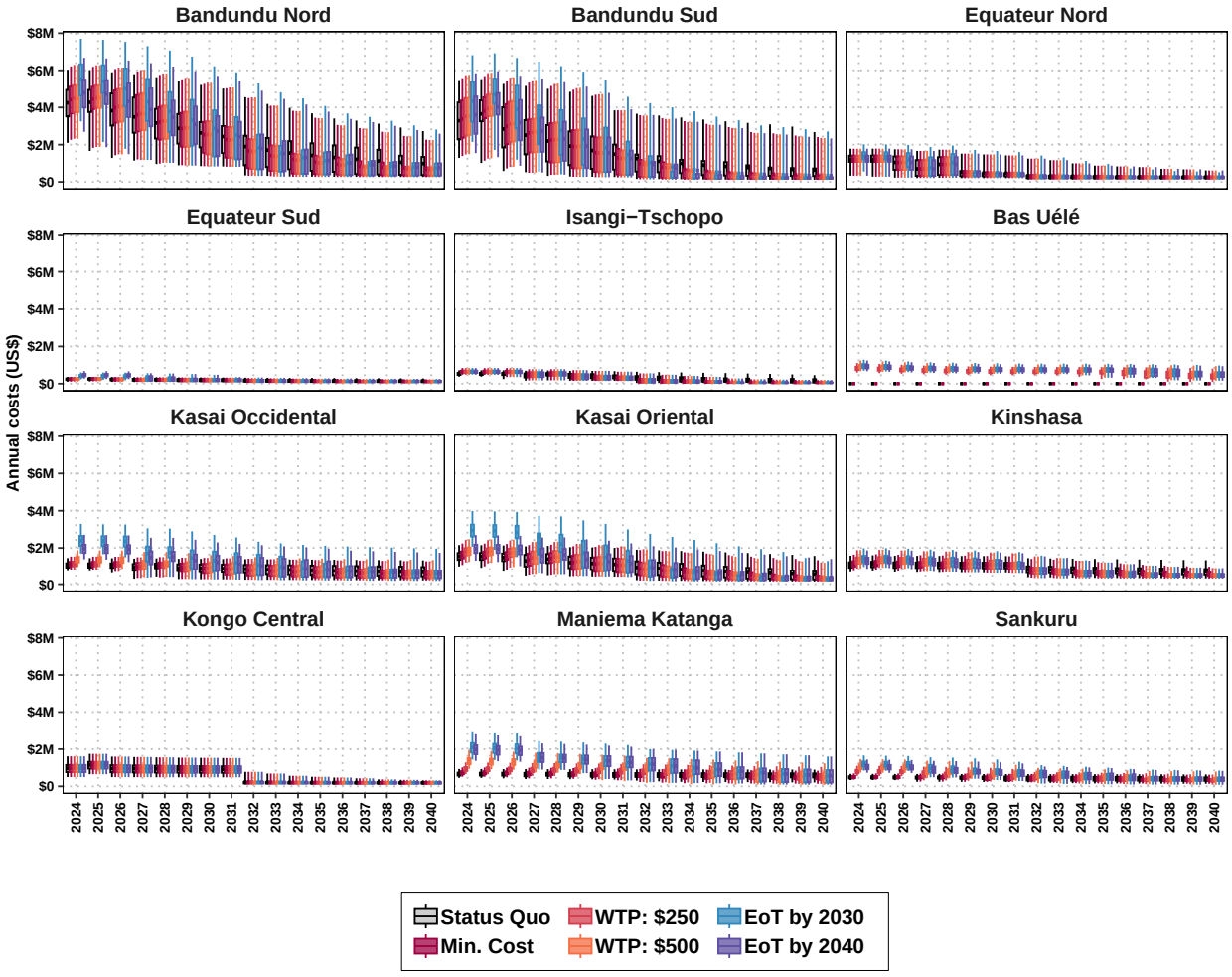

Figure E15: **Total costs 2024-2040 across different levels of investment.**

E6.1 Resource forecasts

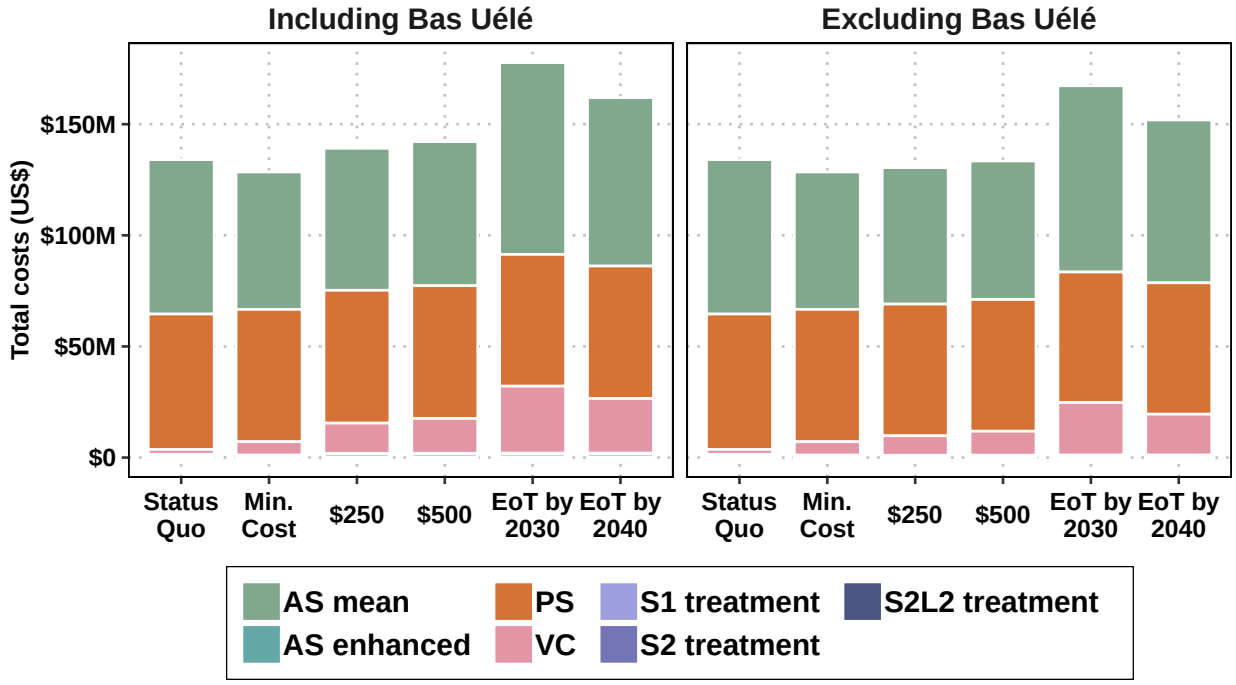

Figure E16: **Costs allocated to different activities across different levels of investment.**

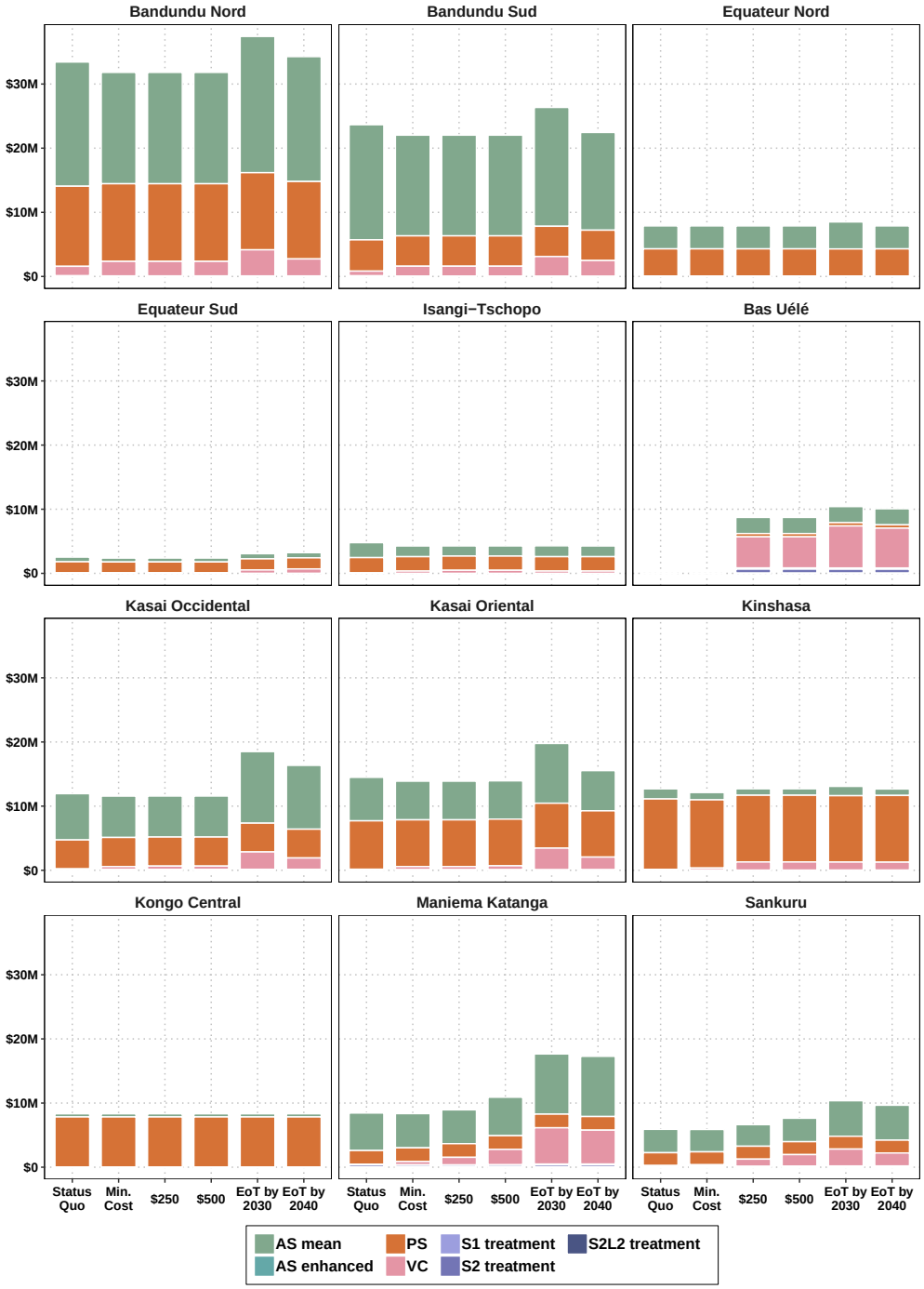

Figure E17: **Costs allocated to different activities across different levels of investment by coordination.**

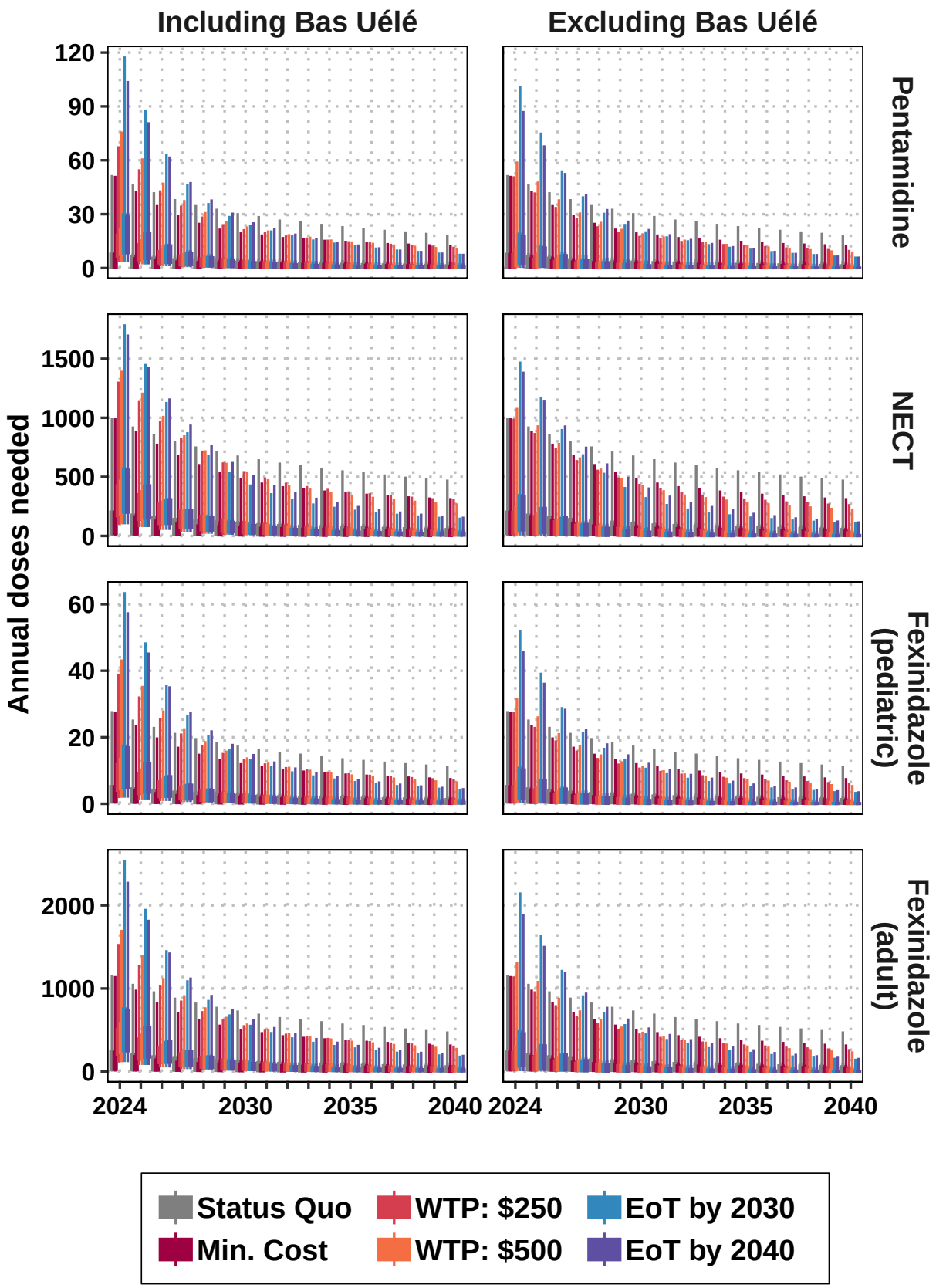

Figure E18: **Drugs used by year from 2024-2040 across different levels of investment.**

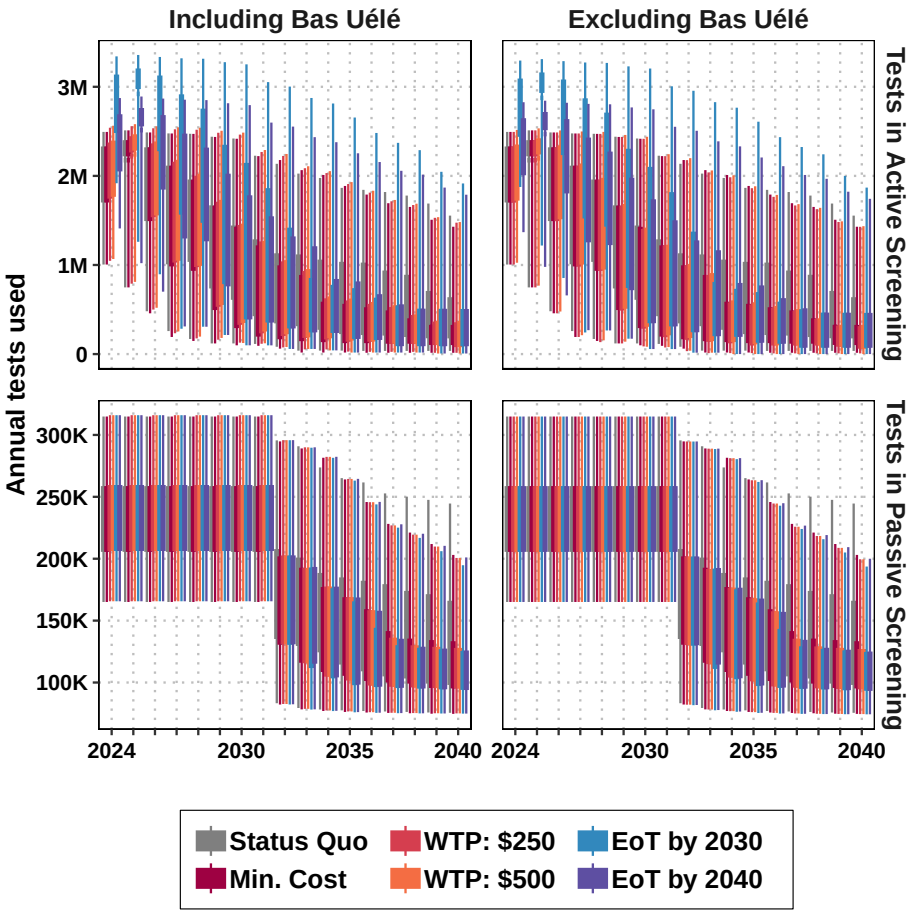

Figure E19: **Tests used by year from 2024-2040 across different levels of investment.**