

RESEARCH ARTICLE

Cost-Effectiveness of Antivenoms for Snakebite Envenoming in 16 Countries in West Africa

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Abstract

Background

Snakebite poisoning is a significant medical problem in agricultural societies in Sub Saharan Africa. Antivenom (AV) is the standard treatment, and we assessed the cost-effectiveness of making it available in 16 countries in West Africa.

Methods

We determined the cost-effectiveness of AV based on a decision-tree model from a public payer perspective. Specific AVs included in the model were Antivipmyn, FAV Afrique, Echi-Tab-G and EchiTab-Plus. We derived inputs from the literature which included: type of snakes causing bites (carpet viper (*Echis* species)/non-carpet viper), AV effectiveness against death, mortality without AV, probability of Early Adverse Reactions (EAR), likelihood of death from EAR, average age at envenomation in years, anticipated remaining life span and likelihood of amputation. Costs incurred by the victims include: costs of confirming and evaluating envenomation, AV acquisition, routine care, AV transportation logistics, hospital admission and related transportation costs, management of AV EAR compared to the alternative of free snakebite care with ineffective or no AV. Incremental Cost Effectiveness Ratios (ICERs) were assessed as the cost per death averted and the cost per Disability-Adjusted-Life-Years (DALY) averted. Probabilistic Sensitivity Analyses (PSA) using Monte Carlo simulations were used to obtain 95% Confidence Intervals of ICERs.

Results

The cost/death averted for the 16 countries of interest ranged from \$1,997 in Guinea Bissau to \$6,205 for Liberia and Sierra Leone. The cost/DALY averted ranged from \$83 (95% Confidence Interval: \$36-\$240) for Benin Republic to \$281 (\$159–457) for Sierra-Leone. In all cases, the base-case cost/DALY averted estimate fell below the commonly accepted

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threshold of one time per capita GDP, suggesting that AV is highly cost-effective for the treatment of snakebite in all 16 WA countries. The findings were consistent even with variations of inputs in 1—way sensitivity analyses. In addition, the PSA showed that in the majority of iterations ranging from 97.3% in Liberia to 100% in Cameroun, Guinea Bissau, Mali, Nigeria and Senegal, our model results yielded an ICER that fell below the threshold of one time per capita GDP, thus, indicating a high degree of confidence in our results.

Conclusions

Therapy for SBE with AV in countries of WA is highly cost-effective at commonly accepted thresholds. Broadening access to effective AVs in rural communities in West Africa is a priority.

Author Summary

Antivenom is the main intervention against snakebite poisoning but is relatively scarce, unaffordable and the situation has been compounded further by the recent cessation of production of effective antivenoms and marketing of inappropriate products. Given this crisis, we assessed the cost effectiveness of providing antivenoms in West Africa by comparing costs associated with antivenom treatment against their health benefits in decreasing mortality. In the most comprehensive analyses ever conducted, it was observed the incremental cost effectiveness ratio of providing antivenom ranged from \$1,997 in Guinea Bissau to \$6,205 for Liberia and Sierra-Leone per death averted while cost per Disability Adjusted Life Year (DALY) averted ranged from \$83 for Benin Republic to \$281 for Sierra-Leone. There is probability of 97.3–100% that antivenoms are very cost-effective in the analyses. These demonstrate antivenom is highly cost-effective and compares favorably to other commonly funded healthcare interventions. Providing and broadening antivenom access throughout areas at risk in rural West Africa should be prioritized given the considerable reduction in deaths and DALYs that could be derived at a relatively small cost.

Introduction

Snakebite poisoning is a significant cause of death and disability in rural West Africa [1,2,3,4,5,6,7]. The exact burden of snakebite is difficult to ascertain and is often underreported. A study by Jean-Philippe Chippaux reported an estimate of over 314,000 envenomations, 7300 mortality and nearly 6000 amputations occurring yearly in sub-Saharan Africa (SSA) [7]. However, even in West Africa alone, a range of 1504 to 18,654 annual mortality from snakebite envenoming has been made [8]. This is further compounded by the variability in snakebite incidence with estimates of as high as 500 bites per 100,000 persons per year in parts of northern Nigeria [9].

Vipers (*Echis ocellatus*, *E. leucogaster* and *E. jogeri*) are a major cause of snakebite envenoming throughout the sub-region mainly in Benin republic, Burkina Faso, Cameroun, Chad, Gambia, Ghana, Mali, Niger, Nigeria, Togo and Senegal [1,2,3,4,5,6,7]. In the sub-region, envenoming from snakes other than vipers mostly results from African spitting cobras (*Naja nigricollis*, *N. katiensis*), puff-adder (*Bitis arietans*), mambas (*Dendroaspis viridis*, *D. polylepis*),

burrowing asps or stiletto snakes (*Atractaspis* species), night adders (*Causus maculatus*, *C. rhombeatus*, *C. resimus*, *C. lichtensteinii*) and very rarely boomslang (*Dispholidus typus*). Joger's carpet viper (*E. jogeri*) is confined to Mali. Romane's carpet viper (*Echis leucogaster*) and Egyptian cobras (*Naja haje* and *N. senegalensis*) are causes of snakebite envenoming in the Sahelian and drier parts of West Africa while the forest cobra (*Naja melanoleuca*) and the Gaboon viper (*Bitis gabonica*) cause occasional bites in the rain forest and South-eastern parts of the sub-region [1,5,7].

In West Africa, carpet vipers may account for as many as two thirds of all snakebite envenoming although their range is limited to the savannah region [1,9,10,11]. Envenoming from carpet vipers leads to swelling and tissue damage at the site of bite, local and systematic bleeding, anaemia and shock. Often death results from cerebral haemorrhage, bleeding elsewhere or haemorrhagic shock [1,10,11]. The bleeding abnormality results from a prothrombin activating metalloprotease "Ecarin" and a FX activating component, an anticoagulant, platelet activator/inhibitor and haemorrhagins in the snake's venom [1,10,11]. Non-clotting blood detected by the 20minute Whole Blood Clotting Test [20WBCT] virtually confirms carpet viper envenoming in the northern third of Africa (roughly north of the equator) and is utilized to assess adequacy of treatment [1,10,11]. Most non-carpet viper bites lead to local swelling and tissue damage. The colubrids, boomslangs and twig snake (*Thelotornis kirtlandii*), are back fanged snakes that rarely envenom but can cause severe bleeding and acute kidney injury. Neurotoxic features may result from *Naja haje*, *Naja melanoleuca* and *Dendroaspis* spp bites with deaths often resulting from respiratory muscle paralysis [12]. The risk of death from snakebites other than viper envenoming is lower [9,13,14,15,16,17], but cobra spits may lead to blindness and bites to cancerous ulcers, abortions, scarring, arthrodeses, contractures and psychological impairment leading to permanent disability and productivity loss following hospitalization and incapacitation [7,18,19,20,21]. Cessation of bleeding abnormalities and restoration of clotting following administration of effective antivenom usually occurs promptly in carpet viper envenoming. Antivenom is efficacious in decreasing the likelihood of dying and is the main treatment for snakebite envenoming [1,11,22,23]. However, its administration is associated with early adverse reactions (EAR) which rarely results in fatality. [24,25,26]. Specific interventions may be required to either prevent EAR with administration of premedication prior to antivenom or to treat it once developed following antivenom administration [25,26]. Antivenoms are formulated as either liquid agents that needs to conveyed and stored at low temperature with a life span of about three years [27,28] or as freeze dried substances that are more stable with extended shelf life. Both types of formulations have been produced for the sub-region [6,27,28]. The average cost per treatment of antivenom was reported as US\$124 (range US\$55–\$640) although a median price of US\$153 was also reported for Sub-Saharan Africa [29,30,31]. The few effective antivenoms in the sub-region generally have been scarce, locally unaffordable and inaccessible where they are most needed. Partly for these reasons antivenom utilization has drastically declined to a very small fraction of indicated need. The situation has been compounded further by the recent announcement by Sanofi-Pasteur that production and distribution of FAV Afrique, currently the most widely distributed and most dependable antivenom in the sub-region, will be discontinued by 2016. Its loss will exacerbate an already serious public health crisis and makes the management of snakebite even more challenging [32]. It is therefore extremely important within the context of other competing public health priorities to assess the health economics of antivenoms to guide policy. Before the recent publication of our work focusing on Nigeria [33], few economic evaluations of preliminary nature had been conducted on antivenoms [34,35]. Here, we evaluated the cost-effectiveness of antivenom utility in the treatment of snakebite envenomation by computing incremental cost effectiveness ratios (ICERs) of the cost per death averted and the cost per DALY averted by adapting a previously

published model for Nigeria to 16 countries in WA. We performed the analysis from health-care system perspective to provide policy makers with evidence towards broadening access to antivenoms given their importance in preventing loss of lives and limbs among poor vulnerable communities in West Africa.

Materials and Methods

Model Overview

A decision analytic model ([Fig 1](#)) was adapted to estimate health outcomes and costs associated with the availability and use of geographically appropriate and effective antivenoms for snakebite poisoning in West Africa [[33](#)]. Details of the model structure are described elsewhere [[33](#)]. Briefly, the model assessed the availability of effective antivenoms relative to no availability in the decision node. The model differentiated snakebite envenoming by carpet viper and non-carpet viper and distinction was made on the basis of the 20WBCT in the treatment arm of the model. Evidence of coagulopathy would lead to the administration of mono-specific antivenom that neutralizes carpet viper venom only, whereas absence of coagulopathy triggers the administration of a polyspecific antivenom that neutralizes venoms from several snakes, including the carpet viper. In the first chance node, the model included EARs associated with antivenom use, which are more likely to occur with polyspecific rather than the monospecific antivenom [[23,27,28,36,37](#)]. Symptoms of EAR were diverse and death could happen in about 1% of cases [[24,25,26](#)]. Survivors of snakebite may recover completely or remain with significant sequela (e.g. amputation) that was considered in the model. Treatment outcomes were converted into DALYs on the basis of local life expectancy. Tree Age Pro Suite Healthcare 2014 software was used for analyses.

Model Inputs

Antivenom effectiveness and Early Adverse Reactions (EAR) data. The likelihood of death from carpet viper and other snakebites among untreated victims was previously reported at 8.1–15.83% and 5–27.3% respectively [[9,10,38,39,40,41,42](#)] although these were varied in sensitivity analyses. When data on antivenom effectiveness was available for a given country, it was applied for that country. It ranged from 56.43% to 92% against carpet viper deaths. A meta-analysis estimate was applied for countries without data ([Table 1](#)) [[38,39,40](#)]. There hasn't been placebo-controlled randomized controlled trials (RCT) ever conducted for antivenom assessment and the estimates of effectiveness derived from the meta-analysis that exclusively only included observational studies from Chad, Ghana and Nigeria [[10,22,37,38,39](#)] were applied in the model. Results from the meta-analysis suggested that an effective antivenom has a 75% (95% confidence interval: 55–86%) effectiveness in averting mortality from carpet viper bites [[22](#)]. Since the meta-analysis included studies wherein polyspecific antivenoms were used, these estimates of effectiveness were applied against non-carpet viper deaths except in Benin and Guinea-Conakry, where country-level effectiveness data exists for Antivipmyn antivenom against non-carpet viper (elapid) deaths, reported at 43.6% (0–80.5%) ([Table 1](#)) [[42](#)]. However, in a scenario analysis antivenoms were assumed to be ineffective (0%) against non-carpet viper envenoming. Estimates of EAR for the corresponding antivenoms were Antivipmyn 3.3% and FAV Afrique 4.3% as obtained in observational studies while it was EchiTab-G 19% and EchiTab-Plus 26% [[23,36,37](#)]. For countries where none of the antivenoms have been in use, the EAR risk median estimate of 4.3% was used in the model [[36](#)]. The EAR estimates were varied from 0% to 30% in sensitivity analyses. The risk for disability (limb amputation) among survivors was approximated to 3% from studies in sub-Saharan Africa and the tropics [[7,43,44](#)]. In base-case analysis antivenom administration had no effect on amputation, however,

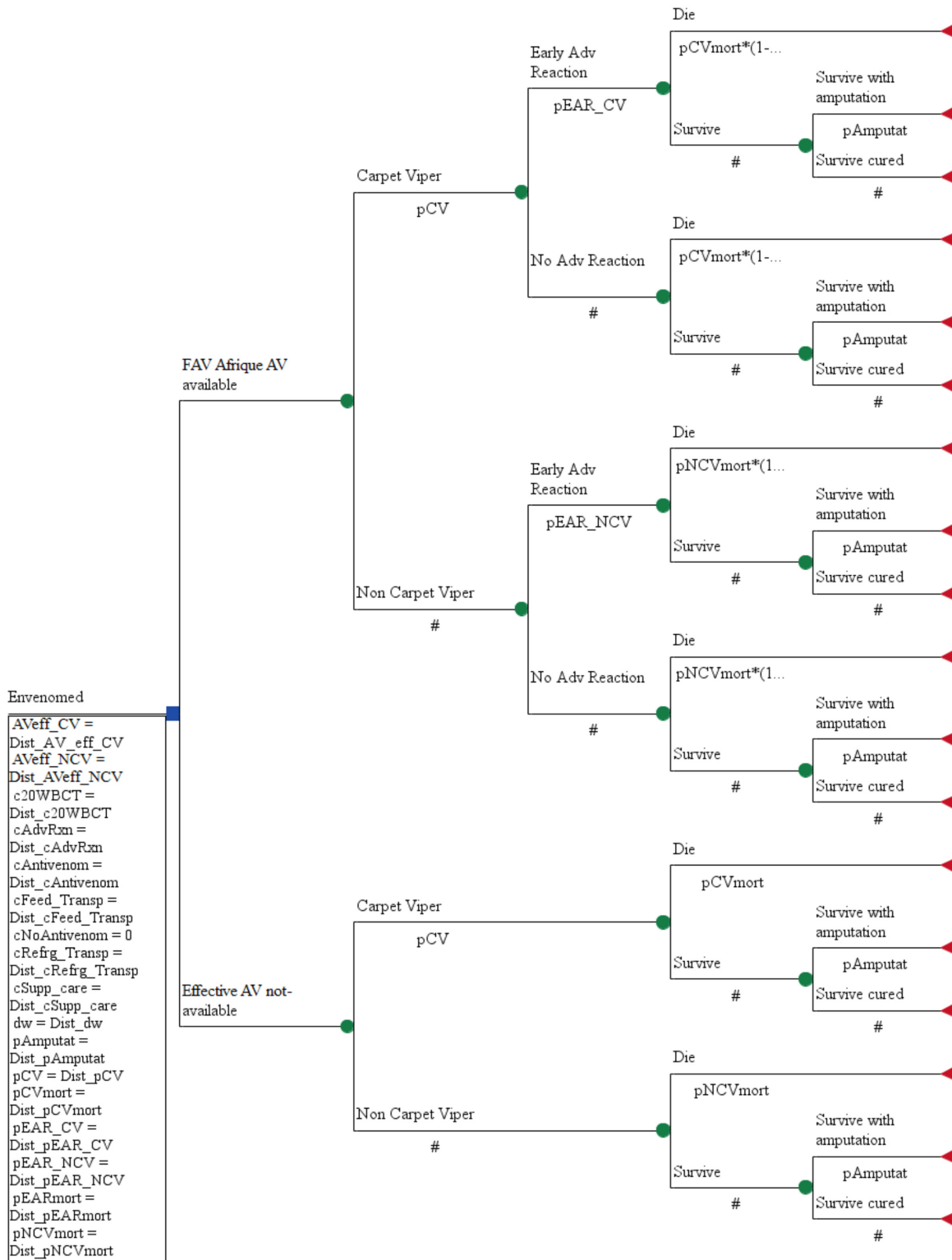


Fig 1. Decision tree model for managing snakebite envenoming with or without FAV Afrique antivenom in Cameroun (each of the 16 countries has a similar model with its data input). Model parameter definitions: c20WBCT = cost of 20 minutes Whole Blood Clotting Test on 10 occasions over 7 days at diagnoses and monitoring; cAdvReaction = Cost of managing early adverse reactions; cAntivenom = Cost of Antivenom; cFeed_Transp = Cost of transportation and stay in Hospital for 7days; cRefrg_Transp = Cost of shipping and refrigeration; cNoAntivenom = Cost of management without effective antivenoms either traditional/herbal care or other alternatives; cSupp_care = Cost of supportive care. All costs are in US\$. antivenomeff = Effectiveness of

antivenom to prevent death; pEARmono = probability of early adverse reactions with monospecific antivenom; pEARpoly = probability of early adverse reactions with polyspecific antivenom; pEARmort = probability of dying following effective antivenom and early adverse reactions; pCVmort = probability of dying following carpet viper envenoming; pNCVMort = probability of dying following non-carpet viper envenoming; pCV = proportion of envenoming due to carpet viper; pDisabl = probability of disability; dw = disability weighting of consequences of snakebite envenoming; x = effect of adrenaline premedication reduction of risk of early adverse reactions.

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effectiveness was applied in sensitivity analyses. The mean ages of snakebite envenomed victims were reported for Chad 25.2 years, Niger 29 years, Nigeria 26 years and Mali 28 years [38,39,41,45,46]. So, since snakebite envenoming occurs among persons with average age in the 25–29 year age group, we determined the remaining local life expectancies in this age group for the 16 countries ranged from 37 years in Sierra-Leone to 45 years in Ghana and Senegal (Table 1) [47]. The base-case analysis on disability was restricted to extremity amputation although blindness from venom-ophthalmia and Post Traumatic Stress Disorder (PTSD) from encountering snake with respective disability weights of 0.552 and 0.105 [48] were also explored in scenario analyses. An annual discount rate of 3% was applied on the health outcomes (mortality and amputation) and the associated amputation-related disability weight used was 0.102 [48]. The model was adapted to 3 types of antivenoms used in WA: Antivipmyn in Benin and Guinea Conakry; EchiTab-G and EchiTab-Plus in Burkina Faso and Nigeria; FAV Afrique in Cameroun, Chad, Ghana and Mali. For the remaining 8 countries without evidence of effectiveness data for a particular antivenom, the meta-analytic estimates were used [22]. Where other required data item was unavailable, data from adjacent or neighboring countries were used to input a model with mixed data sources. These parameters for the respective models were obtained in the literature and imputed to the antivenom-defined models and was run for each of the 16 countries.

Cost data. The cost of the full antivenom treatment regimen was modeled as US\$153 [29,30,31]. The cost of care, ten 20WBCT measurements in 7 days, transportation to-and-from hospital and feeding for 7 days, shipping and freezing of antivenom, management of EAR, supportive care (such as pain relief, blood transfusion, medications, fluid replacement and wound management) were obtained from series of envenomed patients admitted to Kaltungo General Hospital in Nigeria Table 2 [33]. All costs were expressed in US\$. Given snakebite is a short term condition and costs occur during a brief period of time (2 to 10 days), costs were not discounted to adjust for time elapsed between expenditure and outcome during Incremental Cost Effectiveness Ratio (ICER) calculations [49,50]. As a conservative analysis the alternative of no antivenom therapy carried a cost of zero as no treatment, care, test and EAR management was provided. However, in a scenario analysis cost of \$65.63 was added/incurred for the alternative of no antivenom therapy, comprising of supportive care \$18.75, feeding and transportation \$43.75, and for 20WBCT \$3.125. The ICER was computed by dividing total cost by the difference in DALYs (e.g., cost/DALY averted) [49,50].

Sensitivity analysis. One-way sensitivity analysis was performed for select input variables to test robustness and determine the most important variables influencing cost-effectiveness of an antivenom programme. Each base-case model input was varied independently according to the upper and lower limits obtained from literature and according to low and high value scenarios.

In addition, Probabilistic Sensitivity Analyses (PSA) were performed using Monte Carlo simulation by running 10,000 iterations of the model while randomly selecting the values for 16 key model inputs from a probability distribution that was defined for each of the parameters (Table 2). This process enabled us to estimate the 95% confidence interval around the base case ICER estimates for each of the 16 countries included in the analysis, and it also allowed us to estimate the probability that antivenom therapy is cost-effective by calculating the proportion

Table 1. Data estimates used in the model by country.

	(a) Mean age at bite (+remaining life expectancy [2012]), years	(b) Proportion of envenoming due to CV or vipers (%)	(c) Untreated Mortality (CV; Non-CV)	(d) Mortality post AV (CV; Non-CV)	AV effectiveness against mortality (e) = [1-RR] or alternatively = (c-d)/c (for CV; Non-CV)	Risk of Early Adverse Reactions with CV (mono) and NCV(poly)[(%)	Comments	References
Model 1: Antivipmyn Antivenom								
Benin Republic	25–29 (44)	85%	15%; 9/33 (27.3%)	3.11%; 4/26(15.4%)	79.3%; (NA) 43.6% (0–80.5%)	3.3%	Used NCV data from Guinea	Fayomi et al 2002 [4]; Chippaux et al 2007 [6]; Balde et al 2012 [37]; Balde et al 2013 [42];
Guinea-Conakry	25–29 (43)	83%	15%; 9/33 (27.3%)	3.11%; 4/26(15.4%)	79.3%; (NA) 43.6% (0–80.5%)	3.3%	Used CV data from Benin	Fayomi et al 2002 [4]; Chippaux et al 2007 [6]; Balde et al 2012 [37]; Balde et al 2013 [42]; Adehossi et al 2011 [45];
Model 2: EchiTab-G and EchiTab-Plus Antivenom								
Nigeria	26 (41)	66%	19/120 (15.83%); 5%	78/6137 (1.27%)	92% (87–95%)	ET-19%; ETPlus-26%		Warrell et al 1977 [10]; Abubakar et al 2010[23]; Habib & Abubakar 2011 [38]; Pugh et al 1980 [13]
Burkina Faso	25–29 (43)	85%	12.1%; 5%	NA	92% (87–95%)	ET-19%; ETPlus-26%	Used AV effect from Nigeria; Ghana mortality	Warrell et al 1977 [10]; Abubakar et al 2010[23]; Habib & Abubakar 2011 [38]; Visser et al 2008 [40]; Pugh et al 1980 [13]
Model 3: FAV Afrique Antivenom								
Cameroon	25–29 (41)	85%	15/98 (15.3%)	NA	85.2%(56.1–95%);	4.3%	Used (c) & (e) from Chad/Ghana	Chippaux et al 1999 [36]; Bregani et al 2006 [39]; Visser et al 2008 [40];
Chad	25.2 (38)	85%	15/98 (15.3%)	4/60 (6.67%)	56.43% (0–85.2%);	4.3%		Chippaux et al 1999 [36]; Bregani et al 2006 [39];
Ghana	25–29 (45)	85%	8/66 (12.1%); -	5/278 (1.8%)	85.2%(56.1–95%);	4.3%		Chippaux et al 1999 [36]; Visser et al 2008 [40];
Mali	28 (43)	85%	8.1%; 5%	1.5%	81.48% (NA)	4.3%		Chippaux et al 1999 [36]; Drame et al 2012 [41]
Other/Multiple Antivenoms								
Cote d'Ivoire	25–29 (39)	83%	12.1%;-		75%(55–86%)-	4.3%	AV efficacy from meta-analysis	Habib & Warrell 2013 [22]; Chippaux et al 1999 [36]; Visser et al 2008 [40];

(Continued)

Table 1. (Continued)

	(a) Mean age at bite (+remaining life expectancy [2012]), years	(b) Proportion of envenoming due to CV or vipers (%)	(c) Untreated Mortality (CV; Non-CV)	(d) Mortality post AV (CV; Non-CV)	AV effectiveness against mortality (e) = [1-RR] or alternatively = (c-d)/c (for CV; Non-CV)	Risk of Early Adverse Reactions with CV (mono) and NCV(poly)(%)	Comments	References
Gambia	25–29 (44)	40%	14.3%		75%(55–86%)	4.3%		Enwere et al 2000 [3]; Habib & Warrell 2013 [22]; Chippaux et al 1999 [36];
Guinea-Bissau	25–29 (41)	40%	15%; 27.3%		75%(55–86%); 43.6% (0–80.5%)	4.3%		Habib & Warrell 2013 [22]; Balde et al 2013 [42]; Adehossi et al 2011 [45];
Liberia	25–29 (44)	0% (*1%)	0% (*15%);5%		75%(55–86%)	4.3%		Pugh et al 1980 [13] Habib & Warrell 2013 [22];
Niger	29 (44)	85%	15%; 5%		75%(55–86%)	4.3%		Habib & Warrell 2013 [22]; Chippaux et al 1999 [36]; Fayomi et al 2002 [4]; Adehossi et al 2011 [45];
Senegal	25–29 (45)	40%	15%;5%		75%(55–86%)	4.3%		Trape et al 2002 [5];Habib & Warrell 2013 [22]; Chippaux et al 1999 [36]; Adehossi et al 2011 [45];
Sierra-Leone	25–29 (37)	0% (*1%)	0% (*15%);5%		75%(55–86%)	4.3%		Pugh et al 1980 [13] Habib & Warrell 2013 [22];
Togo	25–29 (43)	85%	12.1%; 5%		75%(55–86%)—	4.3%		Habib & Warrell 2013 [22]; Visser et al 2008 [40];

CV—carpet viper; RR—Relative Risk

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of 10,000 iterations that resulted in ICERs that fell below commonly accepted cost-effectiveness thresholds of one time per capita Gross Domestic Product (GDP) for each of the 16 countries [51,52].

The study reporting was done consistent to standard guidelines for cost effectiveness analyses and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [49,50,52,53,54].

Results

The cost/death averted for the 16 countries of interest varied. It was as low as \$1,997 in Guinea Bissau to as high as \$6,205 in Liberia and Sierra Leone. The cost/DALY averted ranged from a low of \$83 (95% Confidence Interval: \$36-\$240) for Benin Republic to a high of \$281 (\$159–457) for Sierra-Leone. In all cases, the base-case cost/DALY averted estimate fell below the

Table 2. General assumptions used in Monte Carlo simulations.

Assumption	Base Case Value (BCV)	Range of BCVs	Distribution	Reference
Proportion of envenoming due to CV/ Non-Elapids (%)	Varies by country	1–85%	Beta	1,5,6,7,36
Mortality due to untreated CV envenoming (%)	Varies by country	8.1–15.83%	Beta	3,4,10,39,40,41,45
Mortality due to untreated Non-CV/Elapid envenoming (%)	Varies by country	5–27.3%	Beta	13,14,42
AV effectiveness against CV mortality (%)	Varies by country	56.43–92%	Beta	4,6,10,22,38,39,40,41
AV effectiveness against Non-CV/Elapid mortality (%)	Varies by country	43.6–92%	Beta	10,38,42
Risk of AV EAR for CV envenoming (%)	Varies by country	3.3–19%	Beta	23,36,37
Risk of AV EAR for Non-CV envenoming (%)	Varies by country	3.3–26%	Beta	23,36,37
Risk of AV EAR mortality (%)	1%	Same for each country	Beta	24
Risk of amputation following envenoming (%)	3%	Same for each country	Beta	7,43,44
Disability weight for amputation	0.102	Same for each country	Beta	48
Cost of antivenom (US\$)	\$153	Same for each country	Normal	29,30,31
Cost of 20min Whole Blood Clotting Test	\$3.125	Same for each country	Normal	33
Cost of managing Early Adverse Reactions	\$1.875	Same for each country	Normal	33
Cost of supportive care	\$18.75	Same for each country	Normal	33
Cost of feeding and transportation	\$43.75	Same for each country	Normal	33
Cost of refrigeration and transportation	\$18.75	Same for each country	Normal	33
Cost of no antivenom (US\$)	\$0	Same for each country	Not varied	Our assumption
DALYs averted per death averted (3% discounted)	Varies by country	22.17–24.52	Not varied	Our calculations
DALYs averted per amputation averted (3% discounted)	Varies by country	2.26–2.50	Not varied	Our calculations

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commonly accepted threshold of one time per capita GDP, suggesting that AV is highly cost-effective for the treatment of snakebite in all 16 WA countries [51,52].

The findings from the analyses were also consistent to variations of inputs in 1-way sensitivity and scenario analyses as depicted (Table 3 and Fig 2). The individual countries' model results were most sensitive to effectiveness of antivenom in decreasing mortality, natural (untended) mortality, costs of antivenoms and types of snake causing envenoming (Fig 2). Results were not sensitive to antivenom associated EAR or the cost of managing it. Varying the cost of antivenom from \$125 to two times for victims who may require two doses, i.e. \$306, still yielded ICER estimates that remain cost-effective. The ICERs rose when the frequency of snakebite envenomation due to saw-scaled viper was reduced to 0% except in Benin and Guinea Conakry where Antivipmyn antivenom is used and is effective even against elapids (Table 3) [42].

Moreover, the ICER ranged from \$97.26 in Benin to high levels of \$13,964.26 in Liberia and \$15,278.99 in Sierra Leone even in the worst case scenario where (poly-specific) antivenoms have nil effectiveness (0%) against bites from snakes other than carpet viper. These estimates fall outside the cost-effectiveness thresholds in Liberia and Sierra Leone largely because non-carpet viper accounts for 99% of SBE. Applying a modest reduction of 40% on the probability of EAR with the use of adrenaline premedication [25,26,33] gave a cost per DALY averted slightly lower than base-case ICERs. Similarly, the ICERs were only very slightly altered even when more serious or more frequent disabilities were substituted in the model. This was demonstrated with venom-induced-blindness (0.01%) or Post-Traumatic-Stress-Disorder (20%) with disability-weights of 0.552 and 0.105 respectively [18,21,48].

Furthermore, our PSA confirms the model findings remain consistent to concurrent variation of all model inputs, as the ICERs with their respective 95% confidence limits are far less than the cost-effectiveness thresholds (Table 3). It showed that in majority of simulations (97.3% in Liberia to 100% in Cameroun, Guinea Bissau, Mali, Nigeria and Senegal (Fig 3)) our

Table 3. Results from model outputs by country and scenarios.

Country and GDP/Capita (\$) [49]	Increment Cost Effect Ratio [ICER]/DALY (\$) (95% Conf. Interval)	Cost/Death Averted (\$)	Probability Antivenom is cost-effective (%)	ICER if Antivenom Cost = \$125	ICER if Antivenom Cost = \$306	ICER if proportion of Carpet Viper = 0% (\$)	ICER if Av Effect for Non Carpet Viper = 0% (\$)	ICER if the 'No Antivenom' arm paid for Basic costs of \$65.63*
Benin (751)	82.63 (36.41–240.09)	1997.91	99.99	72.87	135.96	81.75	97.26	59.75
B/Faso (652)	99.44 (40.39–377.40)	2384.81	99.61	87.98	164.05	226.53	107.18	71.94
Cameroun (1220)	86.97 (38.47–240.43)	2030.05	100.00	76.70	143.11	238.39	92.01	62.89
Chad (1035)	136.94 (51.33–704.75)	3070.80	99.13	120.77	225.34	376.61	144.89	99.03
Cote d'Ivoire (1366)	128.24 (51.20–461.64)	2916.02	99.97	113.09	211.04	278.37	139.16	92.73
Gambia (509)	150.08 (72.18–305.49)	3628.88	99.99	132.25	247.47	261.77	229.59	108.30
Ghana (1646)	103.61 (42.04–372.87)	2532.73	99.99	91.38	170.50	227.63	111.21	74.93
Guinea Bissau (576)	87.09 (44.96–171.55)	2032.72	100.00	76.75	143.60	84.76	226.64	62.85
Guinea Conakry (493)	83.54 (36.59–236.35)	1997.41	99.98	73.67	137.49	82.68	100.72	60.40
Liberia (414)	256.61 (147.67–417.68)	6204.95	97.28	226.00	423.92	261.77	13,964.26	184.85
Mali (696)	160.48 (82.21–306.83)	3836.74	100.00	141.52	264.06	243.47	178.09	116.04
Niger (385)	97.23 (39.84–328.02)	2351.06	98.64	85.75	159.99	261.77	102.98	70.31
Nigeria (2742)	92.56 (40.27–242.63)	2160.33	100.00	81.61	152.35	232.04	107.96	66.91
Senegal (1023)	143.81 (67.34–317.76)	3515.25	100.00	126.73	237.14	258.95	216.41	103.78
Sierra Leone (590)	280.77 (158.51–456.68)	6204.95	99.86	247.27	463.83	286.42	15,278.99	202.25
Togo (589)	120.42 (47.62–455.04)	2878.98	98.86	106.19	198.14	264.75	129.25	87.08

*Scenario of Basic costs in the No antivenom arm = Cost of supportive care (\$18.75) + Cost of feeding and transportation (\$43.75) + Cost of 20min Whole Blood Clotting Test (\$3.125) = \$65.63

AV—antivenom; ICER—Incremental Cost Effectiveness Ratio;

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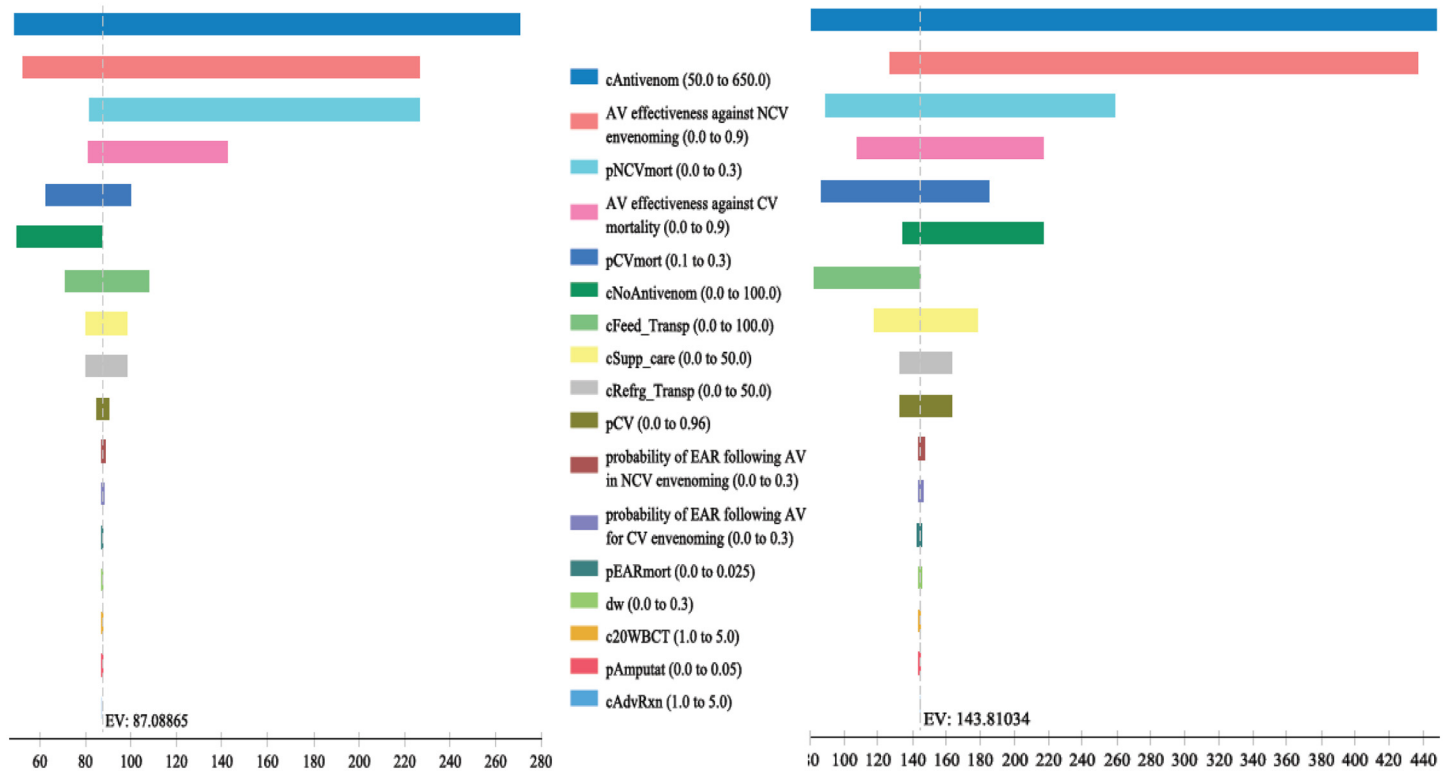


Fig 2. Tornado diagrams assessing the impact of changes in envenoming/antivenom and cost parameters on the incremental cost-effectiveness ratio (ICER) per DALY for antivenom use in Guinea Bissau (L) and Senegal (R). Diagram parameter definitions: c20WBCTest = cost of 20 minutes Whole Blood Clotting Test on 10 occasions over 7 days at diagnoses and monitoring; cAntivenom = Cost of Antivenom; cFeed_Transp = Cost of transportation and stay in Hospital for 7days; cRefrg_Transp = Cost of shipping and refrigeration; cNoAntivenom = Cost of management without effective antivenoms either traditional/herbal care or other alternatives; cSupp_care = Cost of supportive care. All costs are in US\$. Antivenomeff = Effectiveness of antivenom to prevent death; pEARmono = probability of early adverse reactions with monospecific antivenom; pEARpoly = probability of early adverse reactions with polyspecific antivenom; pEARmort = probability of dying following effective antivenom and early adverse reactions; pCVmort = probability of dying following carpet viper envenoming; pNCVmort = probability of dying following non-carpet viper envenoming; pCV = proportion of envenoming due to carpet viper; pDisabl = probability of disability.

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model results yielded an ICER that fell below the threshold of one time per capita GDP, thus, indicating a high degree of confidence in our results [51,52].

Discussion

Economic modeling is very useful in determining the best ways to utilize resources to optimally manage medical conditions where there are competing priorities and limited resources [49]. This is the first extensive assessment of the cost-effectiveness of expanding antivenom access in the 16 countries in West Africa. We find that the cost/death averted for the 16 countries of interest ranged from \$1,997 in Guinea Bissau to \$6,205 for Liberia and Sierra Leone. The cost/DALY averted ranged from \$83 (95% Confidence Interval: \$36-\$240) for Benin Republic to \$281 (\$159-\$457) for Sierra-Leone. The ICER point estimate is <\$100/DALY averted in 7 countries, \$100-\$200/DALY averted in 7 countries and <\$300/DALY averted in 2 countries. The results show that snakebite antivenoms are highly cost-effective in West Africa, as our findings are far less than the one time per capita GDP threshold [51,52]. While it will be worthwhile to repeat the analysis for similar geographic and socioeconomic settings, most of the model inputs such as the antivenom efficacy and cost would largely be similar across many African countries

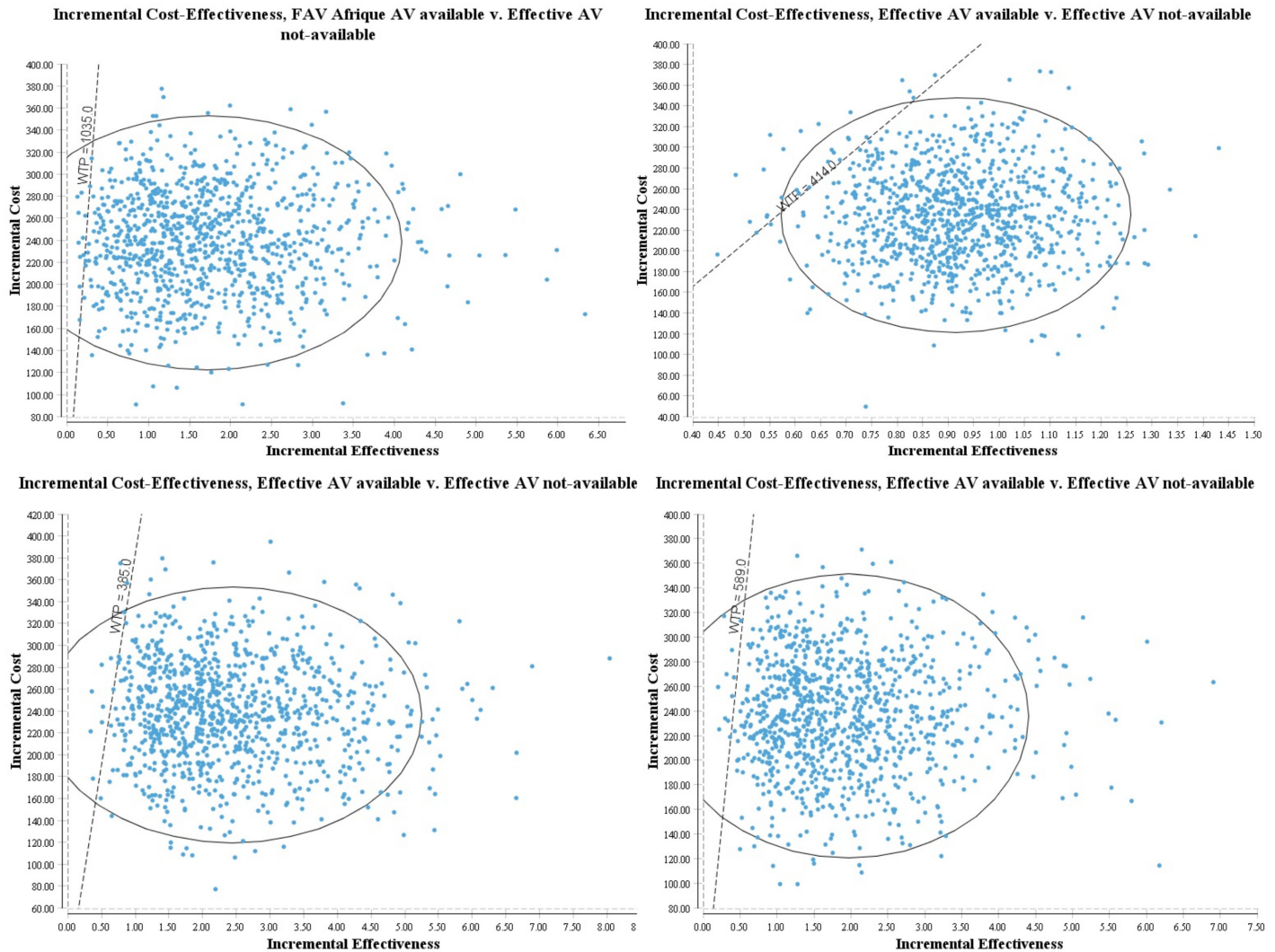


Fig 3. Monte Carlo Simulation showing the probability antivenom is cost-effective in majority of iterations (out of 10,000) for 4 countries with respective Willingness To Pay (GDP/capita) and probabilities: top panel Chad (WTP \$1035; prob-99.13%) [L] and Liberia (WTP \$414; prob-97.28%) [R] and bottom panel Niger (WTP \$385; prob-98.64%) [L] and Togo (WTP \$589; prob-98.86%) [R].

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with similar GDPs where snakebite envenoming occurs. An exception may be the prevalence of carpet viper (*Echis ocellatus*) envenoming, a snake that is confined to West Africa extending eastwards only as far as Chad and Central Africa Republic. However, even in areas without carpet viper bites (0%) our results demonstrate that antivenoms remain highly cost-effective.

The combination of effective and relatively inexpensive antivenoms and the utilization of a cheap, dependable and simple point-of-care test have been instrumental to our results. Antivenom effectiveness is loosely inversely related to the ICER per DALY saved (Fig 2) [33]. With discontinuation of production of geographically appropriate effective antivenoms and marketing of inappropriate ineffective products the cost per DALY saved will substantially soar [32,39,40]. The 20WBCT is discriminatory and will be useful following envenoming from other snakes in the rest of Africa that result in coagulopathy e.g., other species of carpet viper (*Echis leucogaster*, *Echis pyramidum*, *Echis jageri*, *Echis coloratus*) and boomslang. In the

context of differing circumstances where multiple types of snakes with varying manifestations of envenoming or lack of reliable cheap differentiating test, antivenoms may not be as cost-effective. Nevertheless, where patients come along with the dead snakes, decision on antivenom choice is feasible [23] and in such cases the differentiating test becomes not so useful. In the face of competing health needs and constrained-resources, it would be helpful to contextualize our findings in the light of other healthcare initiatives. The cost-effectiveness of Human Immunodeficiency Virus treatment used in similar resource-constrained settings as first-line, second-line or for protecting negative partners among discordant partners ranged from US\$530 to US\$1037 per year of life gained [33,55,56,57]. However, these estimates are still higher than the highest ICERs obtained for two countries in this analysis, i.e., Liberia and Sierra-Leone with \$257/DALY averted and \$281/DALY averted respectively. The antivenom cost effectiveness is comparable to what obtains in other healthcare programmes. For example, the cost/DALY averted obtained in this study ranged from \$100 to \$200 for 7 countries (see Table 3) and is comparable to the cost effectiveness of rotavirus vaccines in other developing countries in Africa and Asia [33,58,59]. Similarly, the cost/DALY averted in the remaining 7 countries was <\$100/DALY averted and is similar to what obtains for preventing Human Papilloma Virus and pneumococcal infections with vaccines in West Africa [33,60,61].

We estimated a cost/DALY averted ranging from \$73 in Benin to \$247 in Sierra Leone if the cost input of antivenom is reduced to \$125 per dose as obtained in Mali [30]. Doubling the cost of antivenom for patients requiring more than a dose still yielded ICERs that remain cost effective ranging from \$136/DALY averted in Benin to \$464/DALY averted in Sierra Leone.

In 8 of the 16 countries with neither indigenous antivenom effectiveness data nor data from adjacent countries, we used efficacy derived from a meta-analysis with data inputs from other countries in the sub-region [22, 38].

The study has a number of limitations. First, the effectiveness of antivenom was derived from observational studies rather than RCTs. Definitive placebo controlled trials of antivenom are considered unethical and RCTs are unlikely to be conducted in the absence of a suitable comparator to antivenom. However, to reduce bias, improve data quality and validity of estimates, three investigators independently searched both English and French literature and extracted data using a checklist for consistency. Secondly, we applied the estimated protection conferred by antivenoms against carpet viper envenoming to the antivenoms used for other than carpet viper envenoming (except in Benin and Guinea Conakry with specific estimates), though this assumption was subsequently dropped in a scenario analysis where antivenoms were assumed to be ineffective (0%) against non-carpet viper envenoming. Thirdly, the analysis mainly considered amputation as the major disability to the exclusion of other anecdotal complications [7, 20, 43, 44]. Fourthly, in our model, antivenoms only conferred protection against death—being a more objective and valid outcome. Fifthly, other benefits of antivenom (e.g. speedier recovery) were not included in the model. Sixth, we used separate EAR risk inputs for EchiTab-G and EchiTab-Plus respectively [23] but could not discern their respective efficacy against mortality so the combined estimate of the two was used in Burkina Faso and Nigeria. Lastly, we did not include the costs incurred for logistics in conveying and preserving antivenoms as we assumed facilities for existing health programmes will be utilized.

Conclusion

The findings from the cost effectiveness analysis demonstrate that providing and broadening antivenom access throughout areas at risk in rural West Africa should be prioritized given the considerable reduction in deaths and disabilities that could be derived at a relatively small cost.

Author Contributions

Conceived and designed the experiments: AGH AK ML MAI MBM MH DAW JPC. Performed the experiments: AGH AK ML. Analyzed the data: AGH AK ML MAI MBM MH DAW JPC. Contributed reagents/materials/analysis tools: AGH AK ML. Wrote the paper: AGH AK ML MAI MBM MH DAW JPC.

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