ECONOMIC BURDEN OF SNAKEBITE AND COST-EFFECTIVENESS OF IMPROVING ACCESS TO SNAKE ANTIVENOM IN ASEAN COUNTRIES

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ภาระทางเศรษฐกิจของแผลงูกัดและความคุ้มทุนของการปรับปรุงการเข้าถึงเซรุ่มพิษงูในกลุ่มประเทศอาเซียน

นายฉันทวัฒน์ ปฏิกรณ์

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ฉันทวัฒน์ ปฏิกรณ์ : ภาระทางเศรษฐกิจของแผลงูกัดและความคุ้มทุนของการปรับปรุงการเข้าถึงเซรุ่มพิษงูในกลุ่มประเทศอาเซียน. (ECONOMIC BURDEN OF SNAKEBITE AND COST-EFFECTIVENESS OF IMPROVING ACCESS TO SNAKE ANTIVENOM IN ASEAN COUNTRIES) อ.ที่ปรึกษาหลัก : ผศ. ภญ. ดร.สุธีรา เตชคุณวุฒิ, อ.ที่ปรึกษาร่วม : ศ. ภก. ดร.ณ ธร ชัยญาคุณาพฤกษ์

กลุ่มประเทศอาเซียนเป็นหนึ่งในภูมิภาคเขตร้อนที่พบอุบัติการณ์ของงูกัดที่สูงมาก ดังนั้นการทำความเข้าใจสถานการณ์ของงูกัดและเซรุ่มพิษงูจึงมีความสำคัญต่อการพัฒนากลยุทธ์ที่ขับเคลื่อนโดยหลักฐานเชิงประจักษ์ เพื่อลดความเจ็บป่วยและการตายจากงูกัดให้ได้ครึ่งหนึ่งภายในปี ค.ศ. 2030 ตามเป้าหมายขององค์การอนามัยโลก การศึกษาแรก ผู้วิจัยได้ทำการทบทวนวรรณกรรมอย่างเป็นระบบโดยทำการสืบค้นการศึกษาเกี่ยวกับภาระทางเศรษฐกิจของงูกัด จำนวน 23 ฉบับ และการประเมินความคุ้มค่าของเซรุ่มพิษงู จำนวน 3 ฉบับ พบว่ามีการประเมินภาระทางเศรษฐกิจของงูกัดมีการวิจัยไม่มาก และส่วนใหญ่ประเมินค่าต่ำกว่าความเป็นจริง การศึกษาส่วนใหญ่วิเคราะห์เพียงต้นทุนทางตรงของคนไข้งูกัดที่เข้ารับการรักษาที่สถานพยาบาล ดังนั้น ควรใช้ข้อมูลของสถานพยาบาลประกอบกับข้อมูลที่ได้จากการลงพื้นที่เก็บข้อมูลในชุมชนเพื่อให้มั่นใจว่าสามารถประเมินภาระทางเศรษฐกิจของงูกัดได้แม่นยำยิ่งขึ้น การศึกษาที่สอง ผู้วิจัยได้ประเมินภาระของงูกัดในกลุ่มประเทศอาเซียน พบว่าภาระโรคและภาระทางเศรษฐกิจของงูกัดมีค่าที่สูงมาก แม้ว่าจะมีการผลิตเซรุ่มพิษงูในภูมิภาคก็ตาม ทั้งนี้พบว่าภาระโรคและภาระทางเศรษฐกิจของงูกัดเกือบทั้งหมดเกิดจากการเสียชีวิตก่อนวัยอันควรจากการถูกงูกัด ซึ่งบ่งชี้ให้เห็นว่าภาระโรคและภาระทางเศรษฐกิจของงูกัดสามารถหลีกเลี่ยงได้ โดยเฉพาะประเทศที่ผู้ถูกงูกัดส่วนใหญ่ไม่ได้รับการรักษาด้วยเซรุ่มพิษงูที่เหมาะสม การศึกษาที่สาม ผู้วิจัยได้ประเมินความคุ้มค่าของการปรับปรุงการเข้าถึงเซรุ่มพิษงูใน 5 ประเทศภายในกลุ่มประเทศอาเซียน พบว่าการปรับปรุงการเข้าถึงเซรุ่มพิษงูสามารถประหยัดงบประมาณได้ ซึ่งบ่งชี้ให้เห็นว่าการปรับปรุงการเข้าถึงเซรุ่มพิษงูโดยให้ผู้ที่ถูกงูกัดทุกรายได้รับเซรุ่มพิษงูสามารถภาระของงูกัดได้และสามารถบรรลุเป้าประสงค์ขององค์การอนามัยโลกในการลดภาระของงูกัด โดยสรุป การปรับปรุงสถานการณ์ของงูกัดและเซรุ่มพิษงูไม่ได้มีเพียงการผลิตเซรุ่มพิษงู แต่ต้องคำนึงถึงระบบทั้งหมดที่เกี่ยวข้องกับการจัดการงูกัดและเซรุ่มพิษงู ทั้งนี้การประเมินสถานการณ์ของงูกัดเซรุ่มพิษงูมีความสำคัญอย่างมากในประเทศ หรือภูมิภาคที่มีความชุกของงูกัดสูง เพื่อที่จะได้เข้าใจจุดยืดในปัจจุบัน และพัฒนากลยุทธ์ที่เหมาะสมสำหรับการจัดการปัญหางูกัดในกลุ่มประเทศอาเซียน

สาขาวิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อนิสิต .....
ปีการศึกษา	2565	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

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KEYWORD: Snakebite, Antivenom, ASEAN, Southeast Asia, Burden of disease, Cost-effectiveness analysis

Chanthawat Patikorn : ECONOMIC BURDEN OF SNAKEBITE AND COST-EFFECTIVENESS OF IMPROVING ACCESS TO SNAKE ANTIVENOM IN ASEAN COUNTRIES. Advisor: Asst. Prof. Suthira Taychakhoonavudh, Ph.D. Co-advisor: Prof. Nathorn Chaiyakunapruk, Pharm.D., Ph.D.

The Association of Southeast Asian Nations (ASEAN) countries are among the tropical regions with disproportionately high incidence of snakebite. Understanding the snakebite and antivenom market situation and burden of snakebite is crucial for developing evidence-based strategies to pursue the goal set by the World Health Organization (WHO) to halve morbidity and mortality of snakebite by 2030. Firstly, we systematically review 23 cost of illness studies and 3 economic evaluations. Economic burdens of snakebite were underestimated and not extensively studied. Majority of studies only provided direct costs of snakebite patients presented to the hospitals. Thus, hospital data should be used to combine with community survey to ensure the accurate estimation of overall economic burdens of snakebite victims. Secondly, we estimated the high economic and disease burden of snakebite in ASEAN, despite the availability of domestically produced antivenoms. Almost all of the estimated economic and disease burdens were attributed to premature deaths from snakebite envenoming which suggested that the remarkably high burden of snakebite could be averted, especially in countries where large proportions of victims who needed antivenom were not treated with geographically appropriate antivenoms. Thirdly, cost-effectiveness analysis demonstrated improving access to snake antivenom from the current to the full level of access in five ASEAN countries was cost-saving. Our findings indicated that the WHO's goal to halve the snakebite burden could be achieved by providing full access to snake antivenoms for all victims in ASEAN. In conclusion, improving the situation of snakebite and antivenom is not only about the availability of antivenom, but the whole landscape of surrounding management and supporting system. The assessment of the situation of snakebite and antivenom is crucial for countries or regions where snakebites are prevalent to recognize their current standpoint to inform the development of strategies to address snakebite problems in ASEAN countries.

Field of Study:	Social and Administrative Pharmacy	Student's Signature .....
Academic Year:	2022	Advisor's Signature .....
		Co-advisor's Signature .....

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Chanthawat Patikorn

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1 INTRODUCTION

This dissertation comprises three studies; (1) the global systematic review of previous economic studies of snakebites conducted to inform the best methodological considerations for (2) estimating the economic burden of snakebites and (3) a cost-effectiveness analysis of improving access to snake antivenom in the Association of Southeast Asian Nations (ASEAN) countries. The input parameters were retrieved from a comprehensive literature review which was validated and complemented by an in-depth interview with country experts in ASEAN countries (**Figure 1**). All of the studies described are part of a dissertation disseminated in partial fulfillment of the requirements for the degree of doctor of philosophy in social and administrative pharmacy.

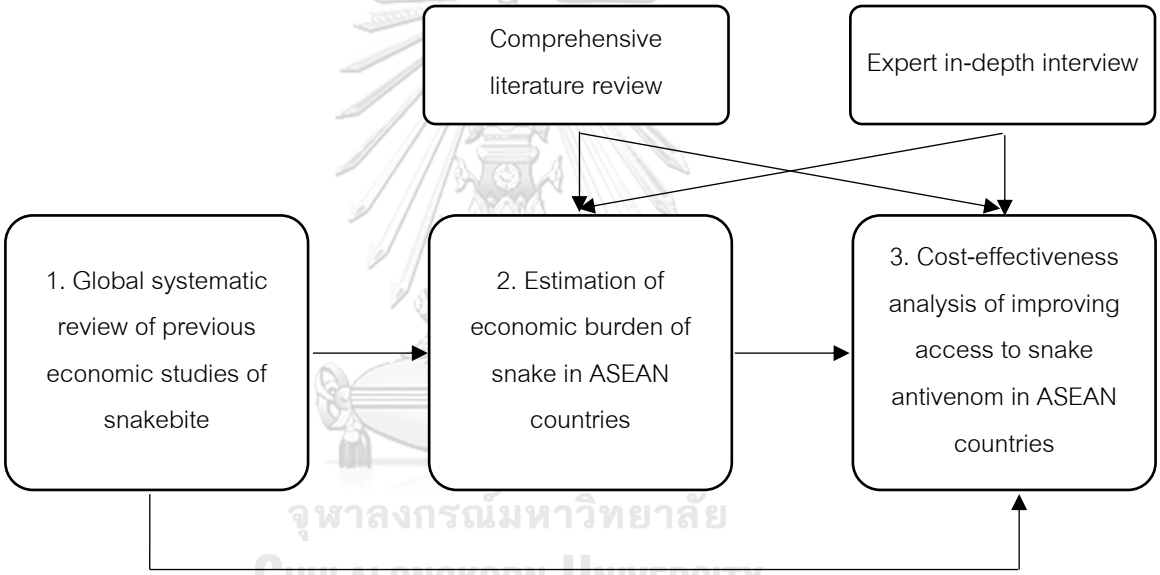

Figure 1 Conceptual framework

Abbreviation: ASEAN – Association of Southeast Asian Nations.

1.1 BACKGROUND AND RATIONALE OF STUDY

Snakebite is an occupational and environmental disease mostly affecting agricultural workers and children, leading to morbidity, disability, and mortality.[1] Approximately 5.4 million people are bitten by snakes, of which 1.8 to 2.7 million cases are snakebite envenoming, and responsible for 81,000 to 138,000 deaths annually. The annual national costs for snakebite victims have been estimated at up to 13.8 million US Dollars (USD) in Sri Lanka.[2,3] Highly venomous snakes can be classified into two groups based on the level of medical significance based on the World Health Organization's (WHO) categorization to guide antivenom production; category 1 - highest medical importance, which are

snakes that commonly cause snakebites with high levels of morbidity, disability, and mortality, and category 2 – secondary medical importance which are snakes capable of causing morbidity, disability, or death, but are less common or lack of exact epidemiological and clinical data.[4]

Snakebite envenoming occurs when a snake injects a toxins into the victim's body which could result in a medical emergency. Snakebite envenoming can be classified based on the effects of snake toxins, including hematotoxicity (bleeding), neurotoxicity (paralysis, unable to breathe), and cytotoxicity (inflammation, wound, necrosis).[5] Consequences of snakebite envenoming range from mild conditions like scarring to severe conditions both physically, such as limb amputation, blindness, and death, and mentally such as chronic anxiety.[6]

Management of snakebite includes first-aid, transportation to a hospital, supportive medical treatments and antivenom treatment specifically for snakebite envenoming.[5] Snake antivenom immunoglobulins are included in the WHO List of Essential Medicines, guidance for countries in prioritizing patient access to essential medicines.[7] However, access to effective antivenom is inadequate to meet the need, especially in sub-Saharan and Asia.[8] Lack of access to antivenom is one of the factors that has driven snakebite victims to seek care outside healthcare facilities, especially the traditional healers.[9]

In 2017, the WHO categorized snakebite envenoming as the highest priority neglected tropical disease and urged countries to collaborate to improve the availability of reliable epidemiological data on snake bites, the regulatory control of antivenoms, and distribution policies with the goal to reduce mortality and morbidity by 50% by 2030 through four key objectives: empower and engage communities, ensure safe and effective treatment, strengthen health systems, and increase partnerships, coordination, and resources.[1,10]

Snake antivenom immunoglobulins are the only specific treatment of snakebite envenoming. However, sufficient availability of antivenom is challenging because of the high cost and short shelf life of antivenoms and the lack of investment and production in antivenoms from manufacturers due to unlikely profitability.[9]

Southeast Asia is among the tropical regions with a disproportionately high incidence of snakebite compared to the other regions of the world.[11] The ASEAN is an economic union comprising ten member countries in Southeast Asia, including Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, with over 600 million population.[12] In the ASEAN countries except for Brunei Darussalam and Singapore, where snakebites rarely occur and/or exact data is lacking, around 78,000 to 470,000 cases of snakebite envenoming occurred in each year resulting in 700 to 18,000 deaths.[11] Approximately 16.6 million

people in ASEAN countries live in snake-inhabited areas without timely access to healthcare facilities.[13]

The global burden of snakebites was previously estimated as the number of snakebites and deaths.[11] However, the burden of snakebite has yet to be extensively studied in ASEAN countries despite being one of the most prevalent snake-inhabited regions. Furthermore, snakebite victims in the region are mostly treated outside healthcare facilities. Thus, the policymakers may find that the burden of snakebites is low and needs no further strategy to improve the situation of snakebites and antivenom in the country.

The information on the economic burden associated with snakebite and economic evaluation of antivenom availability is required to understand the magnitude of the problem, formulate local clinical practice guidelines, and define national budgets for antivenom allocation and healthcare staff training.[14]

1.2 PURPOSES OF STUDY

The purposes of this study are to estimate the economic burden of snakebite and evaluate the potential cost-effectiveness of improving access to snake antivenom in ASEAN countries

1.3 SCOPE OF THE STUDY

The systemic review was conducted to identify the cost of illness studies and economic evaluations of snakebites previously conducted in any country. While, the burden estimation of snakebite and economic evaluation of improving access to snake antivenom will be performed in seven selected countries in ASEAN, including Malaysia, Thailand, Indonesia, Philippines, Vietnam, Lao People's Democratic Republic (PDR), and Myanmar.

1.4 EXPECTED BENEFITS

1. This dissertation will provide comprehensive data on the economic burden of snakebites and the cost-effectiveness of improving access to antivenom in ASEAN countries.
2. This dissertation will support and empower researchers, clinicians, producers, and policymakers to effectively establish informed strategies to address snakebite problems in ASEAN countries.

CHAPTER 2 - LITERATURE REVIEW

2.1 GLOBAL BURDEN OF SNAKEBITE AND GLOBAL STRATEGIES TO ADDRESS SNAKEBITE PROBLEM

Snakebite is an occupational and environmental disease mostly affecting agricultural workers and children, leading to morbidity, disability, and mortality.[1] More than 6.85 billion people globally live within areas inhabited by 278 venomous snake species of medical importance.[13] Approximately 5.4 million people are bitten by snakes, of which 1.8 to 2.7 million cases are snakebite envenoming, and responsible for 81,000 to 138,000 deaths annually.[1] Highly venomous snakes can be classified into two groups based on the level of medical significance based on the WHO's categorization to guide antivenom production; category 1 - highest medical importance, which are snakes that commonly cause snakebites with high levels of morbidity, disability, and mortality, and category 2 – secondary medical importance which are snakes capable of causing morbidity, disability, or death, but are less common or lack of exact epidemiological and clinical data.[4]

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empower and engage communities, ensure safe and effective treatment, strengthen health systems, and increase partnerships, coordination, and resources.[1,10]

2.2 SNAKEBITE IN ASEAN COUNTRIES

The ASEAN is an economic union comprising ten member countries in Southeast Asia, including Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam, with over 600 million population.[12] In the ASEAN countries except for Brunei Darussalam and Singapore, where snakebites rarely occur and/or exact data is lacking, around 78,000 to 470,000 cases of snakebite envenoming occurred each year, resulting in 700 to 18,000 deaths.[11] Approximately 16.6 million people in ASEAN countries live within snake-inhabited areas and lack timely access to healthcare facilities.[13]

There are five manufacturers of antivenom in ASEAN countries, including Queen Saovabha Memorial Institute (QSMI) Thailand, Burma Pharmaceutical Industries (BPI) Myanmar, Institute of Vaccines and Medical Biologicals (IVAC) Vietnam, Research Institute of Tropical Medicines (RITM) Philippines, and Bio Farma Indonesia. These manufacturers produce a total of 15 antivenoms comprising 12 monovalent antivenoms and 3 polyvalent antivenoms.[4]

Most manufacturers of antivenoms in ASEAN countries are highly subsidized by the government in each country because local manufacturers of antivenoms are needed to produce the geographically appropriate antivenoms for snakes of medical importance in each country. Snakes may have different toxicity profiles, even from the same species from different geographical areas. Therefore, importing antivenoms from a foreign country needs evidence of cross-neutralization to show that imported antivenoms could neutralize the venoms of snakes in the designated country.[15]

2.2.1 Malaysia

Malaysia has a total population of 32 million people.[16] In Malaysia, 35 species of land snakes are potentially dangerous.[17] There were 2,612 to 3,658 cases of snakebites annually occurred, with only 1 to 4 deaths in Malaysia from 2010 to 2014.[18] Malaysia is one of the ASEAN countries with an established system to deal with snakebites, including annual statistics of snakebites collected by the Malaysian Health Informatics Center, Malaysian clinical practice guideline for the management of snakebite[18], list of land snakes of medical significance in Malaysia,[17] and the Remote Envenomation Consultancy Services, a 24-hour on-call consultation service established since 2012 by a group of emergency physicians and clinical toxicologists specialized in treating snakebite patients.[19] These strategies help physicians and healthcare professionals, who might not be an expert in snake identification and management of snakebites, manage snakebite patients properly. Malaysia has imported eight antivenoms from the QSMI and one antivenom from Seqirus, Australia, to treat their

population because these antivenoms have been demonstrated to cross-neutralize most of the medically important snakes in Malaysia. Therefore, it has been shown that less than 1% of snakebite patients result in death.[18]

2.2.2 Thailand

Thailand has a total population of 65 million people.[16] There are at least 85 venomous snakes in Thailand.[20] 6,648 patients were treated with antivenom, with 0 death in 2017 in Thailand. Thailand is also one of the ASEAN countries with a well-established system to manage snakebite and antivenom, including locally produced antivenoms for inhabited snakes in Thailand by the QSMI, poison centers in many university hospitals to provide 24-hour clinical consultation services, and the Thai national antidote program which was established in 2010 with the aim to improve stock management of antidotes and antivenoms. The QSMI has produced antivenoms since 1923.[21]: The QSMI produces nine antivenoms, seven monovalent antivenoms, and two polyvalent antivenoms. Moreover, with establishing the Thai national antidote program, the stock of antidotes and antivenoms is better managed using an online system to ensure antidote availability at the point of service, reduce wastage, and save lives.[22]

2.2.3 Indonesia

Indonesia has a total population of 270 million people.[16] There are approximately 450 snake species in Indonesia. Indonesia has its own locally produced antivenom manufacturer, Bio Farma, which produces one polyvalent antivenom (BIOSAVE) for *Calloselasma rhodostoma*, *Bungarus fasciatus,* and *Naja sputatrix* which are the species of snake of medical importance in Indonesia.[23] However, the exact burden of snakebites in Indonesia is still unknown due to the lack of national statistics, with few published epidemiological and clinical studies of snakebites in Indonesia.[23-26] Therefore, lack of data limits the policymakers to formulating an informed strategy to manage the problem of snakebites, especially access to antivenom.

2.2.4 Philippines

The Philippines has a total of 108 million people.[16] There are 145 snake species in the Philippines, of which less than 15% of them are venomous.[27] The RITM produces Purified Cobra Antivenom (PCAV) for the treatment of envenoming from *Naja philippinensis* which also has been proven to cross-neutralize with *Naja samarensis*.[28] There were a number of epidemiological studies of snakebites in the Philippines. However, they were published in the 1980s and most focused on only *Naja philippinensis*.[29-34] Therefore, information on the current burden of snakebite in the Philippines is still lacking.

2.2.5 Lao PDR

Lao PDR has a total of 7 million people.[16] There are 23 venomous snakes in Lao PDR. It has been estimated from a community survey in Lao PDR that the incidence of snakebite could be as high as 1,105 cases per 100,000 population per year, with less than 5% of snakebite victims who were treated in healthcare facilities. Most victims sought traditional healers due to strong cultural beliefs, financial issues, and lack of antivenom at the healthcare facilities.[35] Antivenoms are available in some selected hospitals in Lao PDR under a research project funded by Germany, which directly purchased antivenoms from QSMI and provided training to healthcare professionals on managing snakebites.[36] Therefore, antivenoms must be officially available throughout the country so snakebite victims can timely access antivenom treatment.

2.2.6 Vietnam

Vietnam has a total of 92 million people.[16] There are 31 species of venomous snake in Vietnam.[37] It has been estimated from a community and hospital survey that the incidence of snakebite in the South Vietnam was 48 cases per 100,000 population per year.[38] There are two monovalent antivenoms, which are locally produced by the IVAC, including SAV-Tri for *Trimeresurus alborabris* and SAVE-Naja for *Naja kaouthia*. However, antivenom production was found to be below the national requirement, resulting in healthcare professionals reserving antivenoms for only severe cases. Moreover, the cost of antivenom was found to be expensive for a rural population, which drove victims to seek traditional healers.[39]

2.2.7 Myanmar

Myanmar has a total of 54 million people.[16] There are at least 44 species of deadly venomous snakes in Myanmar.[40] Myanmar also has its own locally produced antivenoms, including Cobra antivenin for *Naja kaouthia*, and Viper antivenin for *Daboia siamensis* produced by the BPI.[4] Snakebites place a considerable amount of burden on Myanmar, given the annual incidence of more than 15,000 cases reported to the Ministry of Health and Sports Myanmar, of which more than 1,000 were dead.[41] However, this number might be underestimating the real burden of snakebites in Myanmar because many victims still seek care from traditional healers only or are dead before reaching healthcare facilities in spite of the availability of locally produced antivenoms.[42] In 2014, the Myanmar Snakebite Project was established with a joint collaboration between Myanmar and Australia with the aim of improving outcomes for snakebite patients. The project has covered three areas of the problem of snakebites in Myanmar, including antivenom production, health system management of snakebites, and antivenom distribution. Since then, antivenom production has been improved with better snake and horse husbandry, and improved immunization, bleeding, and freeze-dried production techniques resulting in improved production capacity of antivenom. Health system

management of snakebites has also been improved by training healthcare professionals on snake identification and proper management of snakebite patients. The antivenom distribution has been improved so that antivenoms are available at all healthcare facilities. However, it was still challenging due to the country's lack of a pharmaceutical logistic system.[43]

2.3 GAP IN KNOWLEDGE

In spite of the availability of local manufacturers of antivenoms, not all snakebite victims in ASEAN countries could access to antivenoms for several reasons, such as out-of-pocket expenses for long travel distances and inpatient services in healthcare facilities, and shortage of antivenoms in healthcare facilities.[35,36,42] As a result, some victims decided to seek care from traditional healers in the community, which costs much lower. Traditional healing methods include the procedures to remove the venom from the victims' bodies by making incisions with a razor blade, tattooing with ink or herbal medicines, sucking out venom, or rolling a heated glass bottle on the bite site and spiritual rituals using holy water, chants, prayers, and astrology.[42] When snakebite victims are mostly treated outside healthcare facilities, the government and responsible authorities may find that the burden of snakebite is low and needs no further strategy to improve the situation of snakebite and antivenom in the country.

The global burden of snakebites was previously estimated as the number of snakebites and deaths.[11] However, the burden of snakebite has not been extensively studied in ASEAN countries despite being one of the most prevalent snake-inhabited regions.[13] Previous literature on snakebites and antivenom in ASEAN countries is mostly performed on the epidemiological aspects. Therefore, the information on the burden of snakebite, the economic burden associated with snakebite, and the economic evaluation of antivenom availability in ASEAN countries are required to understand the magnitude of the problem, formulate local clinical practice guidelines, define national budgets for antivenom allocation and healthcare staff training.[14]

CHAPTER 3 GLOBAL SYSTEMATIC REVIEW OF COST OF ILLNESS AND ECONOMIC EVALUATION STUDIES ASSOCIATED WITH SNAKEBITE

Patikorn C, Leelavanich D, Ismail AK, Othman I, **Taychakhoonavudh S, Chaiyakunapruk N.** Global systematic review of cost of illness and economic evaluation studies associated with snakebite. Journal of Global Health. 2020;10(2).

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3.1 ABSTRACT

Background: Snakebite envenoming, a high priority Neglected Tropical Disease categorized by the World Health Organization (WHO), has been considered as a poverty-related disease that requires greater global awareness and collaboration to establish strategies that effectively decrease economic burdens. This prompts the need for a comprehensive review of the global literature that summarizes the global economic burden and a description of methodology details and their variation. This study aimed to systematically identify studies on cost of illness and economic evaluation associated with snakebites, summarize study findings, and evaluate their methods to provide recommendations for future studies.

Methods: We searched PubMed, EMBASE, Cochrane library, and Econlit for articles published from inception to 31 July 2019. Original articles reporting costs or full economic evaluation related with snakebites were included. The methods and reporting quality were assessed. Costs were presented in US dollars (US$) in 2018.

Results: Twenty-three cost of illness studies and three economic evaluation studies related to snakebites were included. Majority of studies (18/23, 78.26%) were conducted in Low- and Middle-income countries. Most cost of illness studies (82.61%) were done using hospital-based data of snakebite patients. While, four studies (17.39%) estimated costs of snakebites in communities. Five studies (21.74%) used societal perspective estimating both direct and indirect costs. Only one study (4.35%) undertook incidence-based approach to estimate lifetime costs. Only three studies (13.04%) estimated annual national economic burdens of snakebite which varied drastically from US$126,319 in Burkina Faso to US$13,802,550 in Sri Lanka. Quality of the cost of illness studies were varied and substantially under-reported. All three economic evaluation studies were cost-effectiveness analysis using decision tree model. Two of them assessed cost-effectiveness of having full access to antivenom and reported cost-effective findings.

Conclusions: Economic burdens of snakebite were underestimated and not extensively studied. To accurately capture the economic burdens of snakebites at both the global and local level, hospital data should be collected along with community survey and economic burdens of snakebites should be estimated both in short-term and long-term period to incorporate the lifetime costs and productivity loss due to premature death, disability, and consequences of snakebites.

Funding: This systematic review was done without any financial support.

3.2 INTRODUCTION

Snakebite envenoming is one of the most overlooked public health issues globally. Even though almost 4.5-5.4 million people are bitten by snakes annually, snake antivenoms are still not readily and sufficiently available especially in the developing region of the world like Sub-Saharan Africa, South-East Asia and South Asia.[44] Snakebite envenoming can result in fatalities; permanent physical disabilities, such as amputation, blindness and kidney failure; and psychological symptoms, such as Post-Traumatic Stress Disorder (PTSD). In 2017, World Health Organization (WHO) has recognized the importance of snakebite envenoming and categorized it as a high priority Neglected Tropical Disease with the goal of facilitating a cooperation and collaboration across countries to establish strategies to effectively decrease the burden of snakebite envenoming.[45]

To systematically establish the effective strategies to deal with snakebites as well as prioritize resources for making antivenom available, it is important to know the true burden of the public-health threat posed by snakebites. However, only a few studies have estimated the economic burdens of snakebites and include only some regions of the world.[3,45-47] This study aimed to summarize the global economic burden of snakebites by systematically identify studies on cost of illness and economic evaluation associated with snakebites as well as evaluate the methods used in these

studies. Our findings will generate overall findings and methodological recommendations for future economic studies related to snakebites.

3.3 METHODS

This review followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR)[48] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[49] The PRISMA checklist table of this review is provided in **Table A1** in **Appendix A.** The study protocol was submitted to PROSPERO for registration (Record no.147299).

3.3.1 Data source, search strategy, and eligibility criteria

We searched the following four electronic bibliographic databases; PubMed, Embase, Cochrane Library, and EconLit to identify articles related to cost of illness and economic evaluations associated with snakebites from any country which were published from inception to 31 July 2019. The search term used was *snake* AND (burden OR economic* OR cost* OR "cost of illness" OR resource OR expenditure OR "economic evaluation" OR "cost-effectiveness" OR "cost-utility" OR "cost-benefit")*. There was no language restriction in this review. Additional searches were done on the health economic databases including Health Economic Evaluation Database (HEED), Cost-effectiveness Analysis Registry, and Health Technology Assessment Database. The detailed search strategies are provided in **Table A2** in **Appendix A.** To be included, study must meet the following inclusion criteria; original articles reporting costs associated with snakebites estimated by primary data collection and original articles of the full economic evaluations associated with snakebites.

3.3.2 Study selection and data extraction

Two reviewers (CP and DL) independently performed the screening of titles and abstracts for relevance. The full-text articles of the potentially eligible studies were retrieved and selected based on the eligibility criteria by two independent reviewers (CP and DL). Data extraction was performed by two independent reviewers (CP and DL) using the data extraction form in MS Excel (Microsoft Inc, Seattle WA, USA). Discrepancies were discussed among reviewers and resolved by the third reviewer (ST). Methodological characteristics and study findings from the cost of illness studies and economic evaluations were extracted. We extracted the following data from cost of illness studies; study design, country, setting, study period/duration, sample size, perspective, data source, cost estimation method, cost components, currency year, snake species, antivenoms, and cost estimates. The following data were extracted from economic evaluation studies; target population, study perspective, comparators, time horizon, discount rate, choice of health outcomes, resource and cost estimation method, currency year, choice of model, sensitivity analyses, snake species, antivenoms, study parameters, incremental costs and outcomes.

3.3.3 Quality assessment

Two independent reviewers (CP and DL) assessed the quality of the studies. Cost of illness studies were assessed using the cost-of-illness evaluation checklist by Larg and Moss.[50] Economic evaluations were assessed using the ten-item Drummond checklist[51] and the 24-item Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[52]

3.3.4 Data synthesis

Methodological characteristics, study findings, and quality of the studies were summarized and presented. Countries were classified by income level according to the World Bank.[53] Costs were presented according to the recommendations of Turner et al., 2019.[54] For studies that did not provide the year of cost data, the year of publication was used. Adjustment for inflation was done using the Gross Domestic Product (GDP) deflator of the studied country. Cost estimates were then converted and reported in 2018 US dollars (US$). To further facilitate comparison of costs across countries, the total costs associated with snakebites were estimated as percentage of the country's GDP in 2018. GDP deflator, exchange rate, and GDP were obtained from the World Bank.[55-57]

3.4 RESULTS

3.4.1 Study selection

We identified 3,237 articles through electronic database searches. The searches in health economic databases found no additional articles. The detailed process of electronic database searching is presented in Table A2 in Appendix A. We included 26 studies which met the eligibility criteria as shown in **Figure 2**. The included studies comprised of 23 cost of illness studies and 3 economic evaluations. Cost of illness studies were done in 16 countries, of which mainly comprised 13 low- and middle-income countries. Only five studies (21.74%) were conducted in high-income countries.[58-62] Economic evaluation studies were done in India, Nigeria, and 16 West African countries.[63-65]

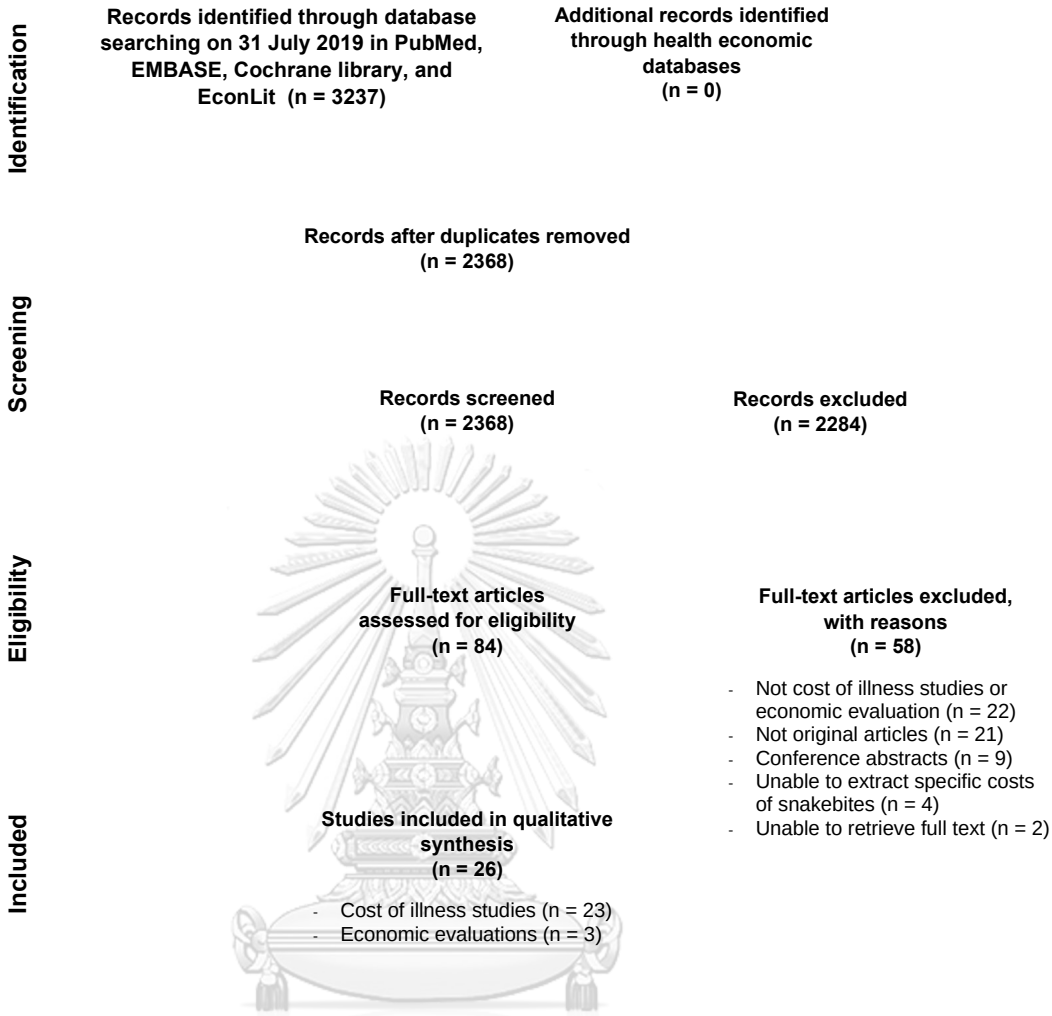

Figure 2 Study selection flow

3.4.2 Study characteristics

The description of the study characteristics of the included studies are presented in detail in **Tables A3** and **A4** in **Appendix A**. Of the 23 cost of illness studies, only 3 studies (13.04%) estimated annual national economic burdens of snakebite (**Table 1**).[3,66,67] Nineteen studies (82.61%) were hospital-based study as they included only snakebite patients presented at hospitals.[58-62,66-79] While the remaining four studies (17.39%) considered snakebite victims in the communities to also include those who did not reach treatment facilities e.g. deaths or those who seek traditional healers.[3,42,80,81] Among these studies, only one study (4.35%) holistically collected both hospital-based and community-based data.[3]

Most studies (95.65%) undertook prevalence-based approach which costs of illness of all prevalent cases in the specific period of the study, usually one episode of snakebite, were estimated.[3,42,58-

[62,66,68-81] Only one study (4.35%) undertook incidence-based approach to estimate lifetime costs of illness including costs of productivity loss due to snakebite, disability, and premature death.[67]

In terms of study perspectives, five studies (21.74%) utilized societal perspective which included both direct and indirect costs.[3,61,67,68,74] Components of indirect costs reported in the included studies were costs of productivity loss due to premature death and disability, income loss, and family income loss. Conversely, direct medical costs especially antivenom costs were estimated in all studies. Direct medical cost components estimated varied across studies. For example, traditional healer costs were reported in three studies (13.04%),[3,42,80] while six studies (26.09%) estimated direct non-medical costs including costs of transportation, communication, food, accommodation, and caregivers.[3,68,71,75,77,80] All of the reported cost components are summarized in **Table A5** in **Appendix A.**

Multiple sources of information were used to quantify, and value healthcare resources utilized by snakebite patients. Sources of healthcare resource utilization data were chart, database, interview, and literature. Chart (n=12, 52.17%)[58,60,67,69,70,72-74,76-79] and interview (n=10, 43.48%)[3,42,67,71,73-75,77,80,81] were the most commonly used sources. Prices of healthcare resources were from interview, listed price, literature, and market price. Listed price was the most common source of price data (n=15, 65.22%).[3,60-62,67-70,72-78]

Only three economic evaluation studies were identified. All of them were cost-effectiveness analysis using decision analytic models.[63-65] Two studies compared no access to antivenom to full access in envenomed snakebite patients presented to hospital.[63,64] While, another study compared antivenom alone with the antivenom adjunct combination strategy to improve the proportion of snake victims reaching healthcare facilities.[65] The health outcomes of snakebite in the models were similar including full recovery, death, and amputation. Lifelong was selected as the time horizon to capture deaths and disabilities. Discount was applied only to outcomes because direct costs of snakebite normally occurred during treatment in healthcare facilities.[63-65]

Table 1 Characteristics of the included cost of illness studies associated with snakebites

Author, year	Income economies	Country	Perspective	Study setting	Sample size	Study design	Direct cost estimation method	Indirect cost estimation method	Source of resource utilization data	Source of price data
East Asia and Pacific										
Schioldann, 2018 [42]	Lower-middle	Myanmar	Patient	Three villages in Mandalay	158 participants	Cross-sectional	Participatory appraisal methods with the communities	Not collected	Interview	Interview
Europe and Central Asia										
Saz-Parkinson, 2012 [62]	High	Spain	Health system	Nationwide	1649 patients	Retrospective	Analysis of Spanish hospital discharge and registry database	Not collected	Database	Listed price
Latin America and Caribbean										
Bachan, 2017 [68]	Upper-middle	Guyana	Societal	Five hinder land regions	57 patients	Retrospective	Analysis of Medical evacuation (medevac) database	Not collected	Database	Listed price, Literature
Sotelo, 2008 [78]	Upper-middle	Mexico	Provider	One children hospital in Northwestern Mexico	79 patients	Retrospective	Review of clinical files	Not collected	Chart	Listed price
Middle East and North Africa										
Nikfar, 2011 [75]	Upper-middle	Iran	Health system	Nationwide	Not reported	Retrospective	Extraction from Iranian drug affair's, drug selection committee, pharmaceuticals statistics. Direct interview with stockholders and key opinion leaders	Not collected	Database, Interview, Literature	Listed price

Author, year	Income economies	Country	Perspective	Study setting	Sample size	Study design	Direct cost estimation method	Indirect cost estimation method	Source of resource utilization data	Source of price data
Mashhadi, 2017 [67]	Upper-middle	Iran	Societal	Three hospitals in Ahvaz	655 patients	Cross-sectional	Review of patients' medical records and self-reports of specialists. Face-to-face or telephone interviews with the patients.	Review of patients' medical records and self-reports of specialists. Face-to-face or telephone interviews with the patients. Productivity loss due to hospitalization and disability were multiplied with average wage. Productivity loss due to premature mortality was calculated using GDP per capita.	Chart, Interview	Interview, Listed price
North America										
Curran-Sills, 2018 [58]	High	Canada	Provider	Nationwide	99 patients	Retrospective	Review of the Health Canada Special Access Program records	Not collected	Chart	Market price
Lopoo, 1998 [60]	High	United States	Provider	One referral children hospital in Oklahoma	37 patients	Retrospective	Review of medical records	Not collected	Chart	Listed price
Narra, 2014 [61]	High	United States	Societal	Thirty-three tertiary children's hospitals	2755 patients	Retrospective	Analysis of Pediatric Health Information System database	Not collected	Database	Listed price
Fowler, 2017 [59]	High	United States	Provider	One regional hospital in Texas	146 patients	Retrospective	Review of medical records	Not collected	Database	Market price
South Asia										
Kasturiratne, 2017 [3]	Upper-middle	Sri Lanka	Societal	All households in nine provinces	695 victims (44,136 households)	Cross-sectional, Modelling	Representative nation-wide community-based household survey for patients' costs. Health system costs were obtained from hospital cost accounting systems and estimates of antivenom usage.	Income lost in victims and their families were derived from the representative nation-wide community-based household survey	Database, Interview	Interview, Listed price
Hasan, 2012 [71]	Lower-middle	Banglad esh	Patient	Four rural tertiary level hospitals	83 patients	Prospective	Interview using structured questionnaires	Loss of wage was derived from interview using structured questionnaires	Interview	Market price, Interview,

Author, year	Income economies	Country	Perspective	Study setting	Sample size	Study design	Direct cost estimation method	Indirect cost estimation method	Source of resource utilization data	Source of price data
Vaiyapuri, 2013 [81]	Lower-middle	India	Patient	Thirty villages in rural Tami Nadu	1115 victims (7578 households)	Cross-sectional	Interview using structured questionnaires	Income loss and economic loss were derived from interview using structured questionnaires	Interview	Interview
Gupt, 2015 [70]	Lower-middle	India	Provider	One hospital in Himachal Pradesh	497 patients	Retrospective	Review of medical records	Not collected	Chart	Listed price
Meena, 2016 [73]	Lower-middle	India	Health system	One tertiary hospital in Southern Rajasthan	200 patients	Prospective	Review of medical records and patients' interview	Not collected	Chart, Interview	Listed price
Ramanath, 2016 [77]	Lower-middle	India	Provider	One rural hospital	190 patients	Prospective, Retrospective	Review of medical records and patients' interview	Not collected	Chart, Interview	Listed price
Qureshi, 2013 [76]	Lower-middle	Pakistan	Health system	Two public-sector hospitals	74 patients	Prospective	Review of medical records	Not collected	Chart	Listed price
Sharma, 2004 [80]	Low	Nepal	Patient	Community-based; Five villages in eastern Terai	143 victims (1817 households)	Cross-sectional	Community-based survey with interview using a standardized questionnaire	Community-based survey with interview using a standardized questionnaire	Interview	Interview
Sub-Saharan Africa										
Darryl, 2016 [69]	Upper-middle	South Africa	Health system	Fifty-six public hospitals in KwaZulu Natal	56 hospitals	Modelling, Retrospective	Analysis of KwaZulu Natal Department of Health central pharmacy antivenom supply data and review of hospital admission records	Not collected	Chart, Database	Listed price, Literature
Michael, 2011 [74]	Lower-middle	Nigeria	Societal	One 22-bed rural hospital in central Nigeria	72 patients	Prospective	Review of medical records and patients' interview	Not collected	Chart, Interview	Listed price
Kasilo, 1993 [72]	Lower-middle	Zimbabwe	Provider	Six urban major referral hospitals	995 patients	Retrospective	Review of hospital records	Not collected	Chart	Listed price

Author, year	Income economies	Country	Perspective	Study setting	Sample size	Study design	Direct cost estimation method	Indirect cost estimation method	Source of resource utilization data	Source of price data
Tagwireyi, 2001 [79]	Lower-middle	Zimbabwe	Provider	One large teaching hospital	78 patients	Retrospective	Review of medical records	Not collected	Chart	Market price
Gampini, 2016 [66]	Low	Burkina Faso	Patient	All public health facilities	114,126 patients	Retrospective	Number of cases were extracted from Statistical Yearbook of the Ministry of Health. Antivenom consumption data were collected from the drug wholesalers established in Burkina Faso.	Not collected	Database	Market price

3.4.3 Quality assessment

Reporting quality of the included studies was assessed and presented in **Tables A6** and **A7** in **Appendix A**. Reporting quality of the included cost of illness studies was substantially varied. Perspective, epidemiologic approach, healthcare resource valuation, and detailed cost components were not clearly specified and reported. None of the included studies performed sensitivity analysis or estimated intangible costs. In contrast, reporting quality of the included economic evaluation studies was high where most aspects were met by all three studies.[63-65]

3.4.4 Annual national cost estimates of snakebite

Among the included cost of illness studies, three studies estimated costs of snakebites as annual national costs in Iran, Sri Lanka, and Burkina Faso.[3,66,67] **Table 2** shows the annual national cost estimates of snakebite in US$ 2018, cost breakdowns, and their contribution to the total costs. The number of snakebite patients ranged from 5,379 patient in Iran[67] to 80,277 patients in Sri Lanka.[3] These numbers were either retrieved from annual report or extrapolated and estimated from studies. The total annual national costs of snakebite drastically varied from US$126,319 in Burkina Faso[66] to US$13,802,550 in Sri Lanka.[3] These three studies estimated the annual national economic burdens of snakebite, of which direct medical costs contributed the most to the total costs (68.01-77.14%) followed by indirect costs (13.16-24.86%), and direct non-medical costs (7.13-9.70%).[3,66,67] Moreover, the total annual national costs from three countries were then calculated as percentage of the country's GDP in 2018 which resulted in less than 0.001% in Iran and Burkina Faso and 0.016% in Sri Lanka. Average cost estimates per patient per episode of snakebite were summarized in US$ 2018 in **Table A8** in **Appendix A**.

Table 2 Annual national cost estimates of snakebite in US$ 2018

Author, year	Country	Perspective	Study approach	Annual number of snakebite patients	Source of annual incident cases	Annual national cost estimates in US$ 2018 with cost contribution to total costs			
						Direct medical costs (%)	Direct non-medical costs (%)	Indirect costs (%)	Total costs
Mashhadi, 2017 [67]	Iran	Societal	Incidence-based	5,379	Annual report	2,658,464 (68.01%)	278,665 (7.13%)	971,612 (24.86%)	3,908,741
Kasturiratne, 2017 [3]	Sri Lanka	Societal	Prevalence-based	80,277	Extrapolated from community survey and previous studies	10,647,355 (77.14%)	1,338,614 (9.70%)	181,6581 (13.16%)	13,802,550
Gampini, 2016 [66]	Burkina Faso	Patients	Prevalence-based	22,337	Estimated from previous studies	126,319 (100.00%)	NR	NR	126,319

N/A – Not Applicable, NR – Not reported

3.4.5 Findings of economic evaluation studies associated with snakebite

Two studies reported outcomes as Disability-adjusted life years (DALYs) and deaths from snakebite,[63,64] while the other study reported only DALYs.[65] All three studies concluded that their interventions were very-cost effective because the Incremental Cost-Effectiveness Ratio (ICER) per DALY averted of these studies ranged from 69.87 to 256.62 US$, which were much below the willingness-to-pay threshold of one GDP per capita of US$351.60 to US$2,504.14 in the study countries.[63-65] While, the ICER per death averted of two studies ranged from US$1,634.40 to US$5666.75.[63,64] Costs of antivenom[63,64] and proportion of patients with severe envenomation[65] were the most sensitive parameters (**Table A9** in **Appendix A**).

3.5 DISCUSSION

Accurate and comprehensive estimations of economic burdens of snakebites are highly needed to demonstrate the real impact of this neglected tropical disease. Revealing the economic burdens of snakebites will make the policymakers understand the magnitude and contribution of each cost component. Moreover, the cost estimates derived can be further utilized in the subsequent economic evaluation studies which accurate cost estimates will result in less uncertain economic models. Thus, strategies and resources could be better developed and allocated to effectively deal with snakebites.

This review is the first systematic review which comprehensively identified economic studies related to snakebites in published literature. The methodological characteristics and study findings were summarized. Our review found that 23 cost of illness studies and 3 economic evaluations had been conducted so far. Majority of these studies were conducted in Low- and Middle-income countries in regions highly inhabited by snakes. However, the overall methods of the included cost of illness studies related to snakebites were not comprehensive as most of them estimated only non-national direct costs in the hospital setting from non-societal perspectives.

Based on our review findings, several methodological issues should be considered for future research on economic burden estimation. Firstly, the economic burden studies of snakebites should be done from the societal perspective in the national level to fully capture both direct and indirect costs and their relevant cost components. Our review found that collecting only direct medical costs could only capture 68.01-77.14% of the national annual total costs of snakebites. Direct non-medical costs and indirect costs contribute 7.13-9.07% and 13.16-24.86%, respectively.[3,66,67]

Secondly, economic burden studies should capture all snakebite victims by using both hospital-based and community-based data to ensure that those not seeking medical care are included. Hospital-based studies mostly captured envenomed or severe snakebite victims who were more

likely to go to hospital. Therefore, incorporating the community-based survey could further improve the completeness of the economic burdens because not all of the victims could reach hospital. They may die beforehand due to long travel distances, be referred to higher level healthcare facilities, or seek traditional healers for help due to cultural belief.[3,42,80,81] For example, it was found that approximately 45.2% of snakebite victims in Sri Lanka consulted traditional healers which could further delay access to effective antivenom and result in worse outcomes.[82] Therefore, victim transportation and treatment seeking behavior should also be incorporated into the analysis depending on each country. If national epidemiological data of snakebites is lacking, data collection could be done in a representative group of snakebite victims then appropriately extrapolate to national cost estimates.

Thirdly, although snakebites are episodic and most costs occur during the first few weeks, economic burdens of snakebites should be estimated both in short-term and long-term period to take into account the lifetime costs and productivity loss due to premature death and disability. Estimating indirect costs only in the short-term period as income loss might underestimate the indirect costs of snakebites. The contribution of indirect cost estimates to the total costs increased from 13.16% to 24.86% when long-term costs of productivity loss due to premature death and disability from snakebite were incorporated.[3,66,67]

Lastly, consequences of snakebites should be broader to include all relevant disabilities and their following costs and productivity loss such as premature death, amputation, blindness, kidney failure, malignant ulcers, pregnancy loss, scarring, and PTSD.[63] These will be varied by species of venomous snakes within each country. Therefore, all important snake species and their geographical distribution should also be considered to capture all relevant costs and consequences of snakebites.

Our systematic review has several limitations that should be discussed. The quality assessment of the included cost of illness studies could only be done in the aspects of reporting quality, since there are no guidelines or checklist to directly evaluate the methodological quality of the cost of illness studies. Nonetheless, articles with good reporting quality could imply their methodological quality to some extent. Moreover, the global economic burdens of snakebites and country comparison could not be estimated due to the underestimated nature of snakebite economic burdens revealed from our review. Further research should be conducted using both hospital-based and community-based data to gather and highlight the overlooked global economic burdens of this neglected tropical disease taking into account our methodological recommendations.

3.6 CONCLUSION

Economic burdens of snakebite were underestimated and not extensively studied. Majority of studies only provided direct costs of snakebite patients presented to the hospitals. There was a lack of study estimating national economic burdens of snakebites. Due to likely underestimated economic burden, hospital data should be used to combine with community survey to ensure the accurate estimation of overall economic burdens of snakebite victims. Having full access to antivenom was found to be very cost-effective. Future studies should focus on how to make antivenoms available and affordable to snakebite victims.

CHAPTER 4 ESTIMATING ECONOMIC AND DISEASE BURDEN OF SNAKEBITE IN ASEAN COUNTRIES USING A DECISION ANALYTIC MODEL

Patikorn, C., Blessmann, J., Nwe, M. T., Tiglao, P. J. G., Vasaruchapong, T., Maharani, T., Doan, U. V., Zainal Abidin, S. A., Ismail, A. K., Othman, I., **Taychakhoonavudh, S.** and **Chaiyakunapruk, N.** Estimating economic and disease burden of snakebite in ASEAN countries using a decision analytic model. PLOS Neglected Tropical Diseases. 2022;16(9):e0010775.

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4.1 ABSTRACT

Background: Understanding the burden of snakebite is crucial for developing evidence-informed strategies to pursue the goal set by the World Health Organization to halve morbidity and mortality of snakebite by 2030. However, there was no such information in the Association of Southeast Asian Nations (ASEAN) countries.

Methodology: A decision analytic model was developed to estimate annual burden of snakebite in seven countries, including Malaysia, Thailand, Indonesia, Philippines, Vietnam, Lao PDR, and Myanmar. Country-specific input parameters were sought from published literature, country's Ministry of Health, unpublished local data, and expert opinion. Economic burden was estimated from the societal perspective. Costs were expressed in 2019 US Dollars (USD). Disease burden was estimated as disability-adjusted life years (DALYs). Probabilistic sensitivity analysis was performed to estimate a 95% credible interval (CrI).

Principal Findings: We estimated that annually there were 242,648 snakebite victims (95%CrI 209,810-291,023) of which 15,909 (95%CrI 7,592-33,949) were dead and 954 (95%CrI 383-1,797) were amputated. We estimated that 80,813 snakebite victims (69% of victims who were indicated for antivenom treatment) were not treated with antivenom. Annual disease burden of snakebite was estimated at 391,979 DALYs (95%CrI 187,261-836,559 DALYs) with total costs of 2.5 billion USD (95%CrI 1.2-5.4 billion USD) that were equivalent to 0.09% (95%CrI 0.04-0.20%) of the region's gross domestic product. >95% of the estimated burdens were attributed to premature deaths.

Conclusion/Significance: The estimated high burden of snakebite in ASEAN was demonstrated despite the availability of domestically produced antivenoms. Most burdens were attributed to premature deaths from snakebite envenoming which suggested that the remarkably high burden of snakebite could be averted. We emphasized the importance of funding research to perform a comprehensive data collection on epidemiological and economic burden of snakebite to eventually reveal the true burden of snakebite in ASEAN and inform development of strategies to tackle the problem of snakebite.

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4.2 INTRODUCTION

Snakebite is a neglected tropical disease that was estimated to affect 5.4 million victims with up to 138,000 deaths around the world.[11] Snakebite envenoming has been recognized by the World Health Organization (WHO) as the highest priority neglected tropical diseases since 2017. The WHO has set its goal to halve the global morbidity and mortality burden of snakebite by 2030.[1,10]

The Association of Southeast Asian Nations (ASEAN) is an economic union comprising of ten member countries including Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam with over 600 million people.[12] ASEAN is one of the tropical regions with disproportionately high incidence of snakebite. Previous estimation of snakebite in 2007 found that approximately 234,000-1,410,000 people were bitten by snake annually resulting in 700-18,000 deaths in eight ASEAN countries, except Brunei Darussalam and Singapore where snakebite rarely occurred and/or exact data were lacking.[11]

Our previous study found that there are five domestic antivenom manufacturers in ASEAN, including Thailand, Indonesia, Philippines, Vietnam, and Myanmar. Up to 290,000 vials of antivenoms were annually produced by these manufacturers which could treat approximately 42,000 victims with snakebite envenoming. However, these produced antivenoms were not enough to treat all victims indicated for antivenom treatment. Besides, the total demand of antivenoms in ASEAN was not estimated.[83] This warranted a comprehensive research on burden of snakebite in the region to quantitatively highlight the neglected problem.

Understanding the current economic and disease burden of snakebite is crucial for developing evidence-informed strategies to reduce morbidity and mortality of snakebite victims to pursue the goal set by the WHO.[10] Studies have been conducted to estimate the annual national economic and disease burden of snakebite in regions where snakebites are prevalent such as Africa.[2,3,9,46,67,84,85] Nevertheless, there was no such information in ASEAN countries. Thus, we aimed to estimate economic and disease burden of snakebite in ASEAN using a decision analytic modelling approach.

4.3 METHODS

A decision analytic model was developed to estimate the annual economic and disease burden of snakebite in seven ASEAN countries including Malaysia, Thailand, Indonesia, Philippines, Vietnam, Lao PDR, and Myanmar. These seven countries were selected based on the evidence of documented snakebite in the country and availability of local key informants to gather more insights on the situation of snakebite which were not publicly available. Brunei Darussalam and Singapore were not included because snakebite rarely occurred and/or exact data were lacking.[11] Cambodia

was not included due to lack of recently published literature on snakebite and key informants that hindered the proper estimation of the burden of snakebite in Cambodia.

Annual number of snakebite victims in the region were estimated using a decision analytic model which incorporated treatment seeking behavior to include victims who were not treated in healthcare facilities. Economic burden was estimated from the societal perspective to estimate lifetime costs of snakebite victims which occurred from snakebite episode to long-term consequences. To enable comparison of economic burden between countries, all costs of snakebite were presented as annual national total costs for each country in 2019 USD and converted to the percentage of country's gross domestic product (GDP) in 2019. Disease burden of snakebite was estimated and quantified as disability-adjusted life years (DALYs) lost due to snakebite in one year in each country.

4.3.1 Decision analytic model

A decision analytic model was developed to simulate the course of snakebite victims in ASEAN which was adapted from previous economic evaluations of antivenoms for snakebite antivenom in West Africa

(**Figure 3**).[63,64] Victims who were bitten by snake sought for treatment either at conventional treatment (hospitals or healthcare facilities) or traditional treatment through traditional healers to reflect the treatment seeking behavior of victims in the region.[83] Victims who firstly sought traditional healers might subsequently switch to conventional treatment or continue their treatments with traditional healers. Snakebite victims might be indicated for antivenom treatment depending on the occurrence of systemic envenoming following snakebite. Victims who were not indicated for antivenom treatment were assumed to result in being alive as the envenoming is not life-threatening.[25,36,38,41,86-88] Victims indicated for antivenom treatment who sought conventional treatment might be given with antivenom depending on the current level of access to antivenom in each country. Level of access to antivenom was determined by the number of antivenoms treatment available divided by number of victims indicated for antivenom treatment. Victims who received antivenom treatment might have adverse drug reaction (ADR) following antivenom administration. Victims indicated for antivenom treatment regardless of their treatment seeking behavior might be alive or dead. Alive victims might have disability. Disabilities included in this model were digit and limb amputation.

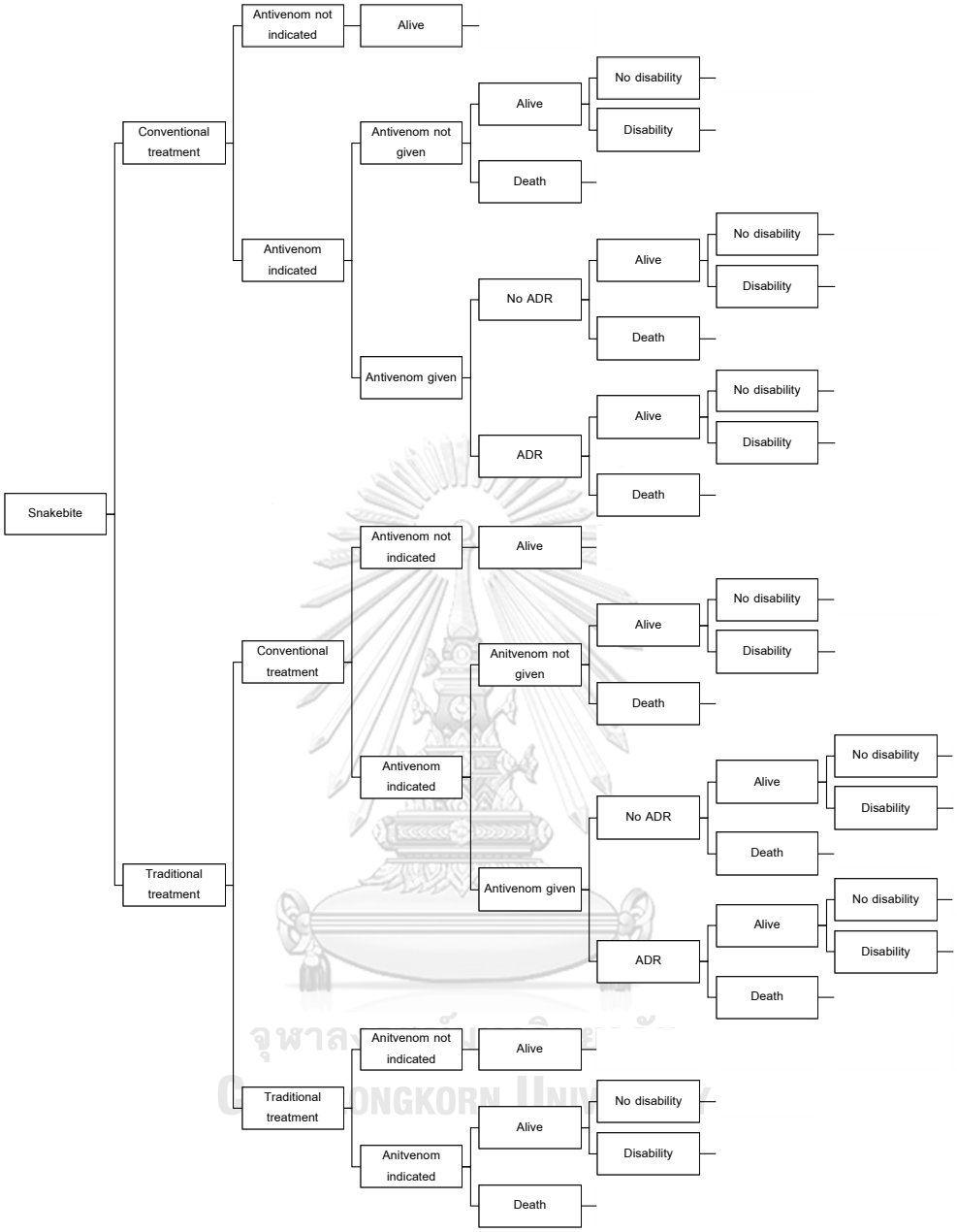

Figure 3 Decision tree to estimate economic and disease burden of snakebite in ASEAN countries

Abbreviation: ADR – adverse drug reaction

4.3.2 Input parameters

Country-specific input parameters were sought from various sources, including published literature, data from the country's Ministry of Health, unpublished local data, and expert opinion (**Table B1** in **Appendix B**).[13,18,25,36-38,41,86-126] An in-depth interview with key informants who were experts in snakebite in ASEAN was also conducted to confirm the retrieved parameters, refer to potential sources of

information that might not be publicly available, and ask for their opinions when data were not available. The input parameters were validated through triangulation of data from literature, unpublished local data, and interview. Justification of input parameters was described in **Methods B1** in **Appendix B**.

Main sources of information were national statistics and published research for the burden estimation of Malaysia, Thailand, and Myanmar. Published research and anecdotal evidence (unpublished local data, and expert opinion) were the main sources of information for the burden estimation of Vietnam, and Lao PDR. Anecdotal evidence was the only source of information for the burden estimation of Indonesia, and Philippines.

4.3.3 Model assumptions

There were three key assumptions of the model. First, one person can be bitten by snake only once in a lifetime. Second, snakebite victims were accompanied by relatives or family members who took care of them during snakebite episode. Third, antivenom was given to reverse snakebite envenoming and save lives. However, there was no data on the efficacy or effectiveness of antivenom in ASEAN countries. Thus, antivenom effectiveness was based on a study in Nigeria which found a 2.33 fold (95% confidence interval [CI]; 1.26-4.06) increase risk of death in antivenom indicated victims who were not treated with antivenom compared to those treated with antivenom.[104] This relative risk was used to calculate the probability of death due to snakebite in those who were not treated with geographically appropriate antivenoms.

4.3.4 Total number of snakebite victims

Estimating the total number of snakebite victims occurring in one year in each country was done by applying the country-specific input parameters into the model. The estimated snakebite victims were categorized by their gender, age groups, treatment seeking behavior, indication for antivenom treatment, and disease consequences, i.e., deaths, alive without disabilities, and alive with disabilities.

4.3.5 Costs of snakebite

Costs of snakebite were estimated from societal perspective, including direct medical costs, direct non-medical costs, and indirect costs (Method B1 and Table B1 in Appendix B). Direct medical costs were estimated using a bottom-up approach which included costs of hospitalization, antivenom treatment, antivenom logistics, ADR management, and amputation. Direct non-medical costs included costs of transportation and additional food for victims and their relatives during snakebite episodes. Indirect costs were estimated using a human capital approach by multiplying the time lost due to illness to the daily income based on the GDP per capita of each country.[125] Indirect costs included productivity losses during snakebite episode of victims and their relatives

and productivity losses due to premature death. Productivity losses during snakebite episodes for victims and their relatives were estimated by multiplying length of stay to the daily income. Productivity losses due to premature death were estimated by multiplying the remaining working years from the age of death up to retirement age at 60 years to the GDP per capita. Productivity losses were not quantified for those who died after the age of 60. Productivity losses due to premature death were discounted at the rate of 3% and adjusted for annual growth of GDP per capita in each country.[122-124,126]

4.3.6 Disease burden of snakebite

Disease burden of snakebite was calculated as DALYs using the template developed by WHO.[127] DALYs were the sum of years of life lost (YLL) and years lived with disability (YLD). YLLs due to snakebite envenoming were calculated from the number of deaths multiplied by a global standard life expectancy at the age of death. YLDs of snakebite victims included YLDs for snakebite episode and YLDs for amputation. YLDs were calculated from the duration of disability multiplied to a disability weight for each condition according to the Global Burden of Disease 2013 study (**Table B1** in **Appendix B**).[110]

4.3.7 Analysis

Economic and disease burden of snakebite in ASEAN was estimated using input parameters as base-case estimates. Sensitivity analyses were performed to assess the model robustness. One-way sensitivity analysis was performed to assess uncertainty of the base-case input parameters over their plausible ranges on the model outputs. Scenario analysis was performed by incorporating post-traumatic stress disorder (PTSD) into the model as a mental disability which estimated that PTSD would occur in 8% (95%CI; 2-18%) of the victims who survived from snakebite envenoming.[128] PTSD could also occur following a snakebite without systemic envenoming. However, the incidence was unknown. Therefore, by applying a lower boundary level of the probability of PTSD following snakebite, it was estimated that 2% of snakebite victims without envenoming would have PTSD following snakebite. Estimation of economic burden of PTSD following snakebite is explained in **Method B2** in **Appendix B**.[6,129,130] Probabilistic sensitivity analysis was performed using Monte Carlo simulations for 1,000 times by randomly sampling on a distribution of all parameters to estimate a 95% credible interval (CrI) of the economic and disease burden of snakebite.

4.3.8 Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

4.3.9 Research ethics approval

This study was approved by the Monash University Research Ethics Committee (Project ID: 23246).

4.3.10 Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

4.4 RESULTS

4.4.1 Snakebite victims in ASEAN

The model estimated that there were 242,648 snakebite victims (95%CrI 209,810-291,023) annually occurring in ASEAN with annual incidence of 38.03 per 100,000 population (95%CrI 32.89-45.62). The estimated incidence of snakebite ranged from the lowest in Malaysia (10.68 per 100,000 population) to the highest in Lao PDR (200.00 per 100,000 population) (**Among 117,575** snakebite victims who were indicated for antivenom treatment (95%CrI 73,790-175,390), there were 954 amputations (95%CrI 383-1,797) and 15,909 deaths (95%CrI 7,592-33,949) following snakebite envenoming. Mortality of snakebite envenoming was estimated at 2.49 per 100,000 population (95%CrI 1.19-5.32), ranging from the lowest in Thailand (0.006 per 100,000 population) to the highest in Lao PDR (14.04 per 100,000 population) (**Figure 4 and Table B2 in Appendix B).**

It was estimated **that 80,813** snakebite **victims in** ASEAN (69% of victims who were indicated for antivenom treatment) were not treated with antivenom, ranging from the lowest in Lao PDR (4.2%) to the highest in Thailand (99.9%) (**Figure 5**).

Table 3 and **Table B2** in **Appendix B**).

Among 117,575 snakebite victims who were indicated for antivenom treatment (95%CrI 73,790-175,390), there were 954 amputations (95%CrI 383-1,797) and 15,909 deaths (95%CrI 7,592-33,949) following snakebite envenoming. Mortality of snakebite envenoming was estimated at 2.49 per 100,000 population (95%CrI 1.19-5.32), ranging from the lowest in Thailand (0.006 per 100,000 population) to the highest in Lao PDR (14.04 per 100,000 population) (**Figure 4** and **Table B2** in **Appendix B**).

It was estimated that 80,813 snakebite victims in ASEAN (69% of victims who were indicated for antivenom treatment) were not treated with antivenom, ranging from the lowest in Lao PDR (4.2%) to the highest in Thailand (99.9%) (**Figure 5**).

Table 3 Estimated annual disease burden of snakebite in ASEAN countries

	Snakebite victims, n	Antivenom indicated victims, n	Deaths, n	Amputations, n	YLLs	YLDs	DALYs	DALYs per 100,000 population
Malaysia*	3,412 (3,303-3,533)	481 (254-767)	2 (0-6)	0	50 (0-151)	1.4 (0.6-2.5)	52 (1-152)	0.2 (0.003-0.5)
Thailand*	8,715 (8,525-8,906)	5,166 (3,766-6,482)	4 (2-7)	2 (0-7)	102 (51-178)	8 (4-14)	110 (57-185)	0.2 (0.1-0.3)
Indonesia*	135,000 (134,297-135,689)	49,632 (34,229-65,496)	10,547 (5,012-22,563)	799 (355-1,426)	262,302 (124,650-561,145)	586 (246-1,120)	262,888 (125,252-562,144)	97 (46-208)
Philippines¶	13,377 (11,452-15,772)	1,755 (1,457-2,127)	550 (274-1,099)	12 (6-16)	13,311 (6,624-26,641)	7 (4-11)	13,320 (6,632-26,649)	12 (6-25)
Vietnam¶	46,745 (17,500-91,013)	41,236 (15,290-80,701)	1,655 (490-4,440)	0	40,136 (11,869-107,679)	114 (38-258)	40,250 (11,931-107,876)	42 (12-112)
Lao PDR*	14,339 (14,111-14,571)	3,029 (2,917-3,138)	1,007 (510-2,009)	141 (22-348)	24,468 (12,420-48,837)	61 (10-189)	24,532 (12,462-48,880)	342 (174-682)
Myanmar*	21,059 (20,623-21,540)	16,275 (15,877-16,679)	2,145 (1,303-3,824)	0	50,786 (30,877-90,632)	44 (27-67)	50,830 (30,926-90,673)	94 (57-168)
Total	242,648 (209,810-291,023)	117,575 (73,790-175,390)	15,909 (7,592-33,949)	954 (383-1,797)	391,154 (186,491-835,263)	825 (329-1,661)	391,979 (187,261-836,559)	61 (29-131)

Note: Estimates are presented as base-case estimates with their 95% credibility interval (in parentheses) based on probabilistic sensitivity analysis. Abbreviations: DALYs – disability-adjusted life years; YLDs – years lived with disabilities; YLLs – years of life lost; * input parameters were based on national statistics and published literature; ¶ Input parameters were based on published literature and anecdotal evidence; + Input parameters were based on anecdotal evidence.

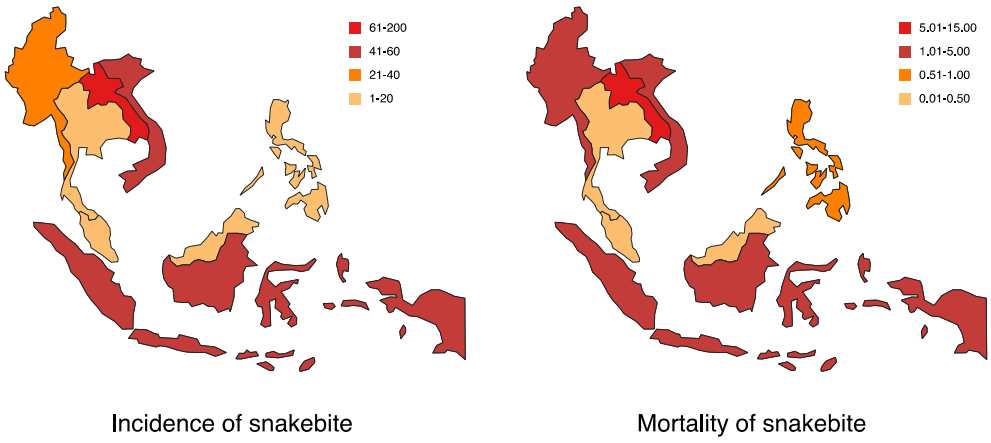

Figure 4 Estimated annual epidemiological burden of snakebite in ASEAN countries

The estimated incidence of snakebite ranged from the lowest in Malaysia (10.68 per 100,000 population) to the highest in Lao PDR (200.00 per 100,000 population). The estimated mortality of snakebite envenoming ranged from the lowest in Thailand (0.006 per 100,000 population) to the highest in Lao PDR (14.04 per 100,000 population). Main sources of information were national statistics and published research for the burden estimation of Malaysia, Thailand, and Myanmar. Published research and anecdotal evidence (unpublished local data, and expert opinion) were the main sources of information for the burden estimation of Vietnam, and Lao PDR. Anecdotal evidence was the only source of information for the burden estimation of Indonesia, and Philippines. Made with Natural Earth. Free vector and raster map data @ naturalearthdata.com.

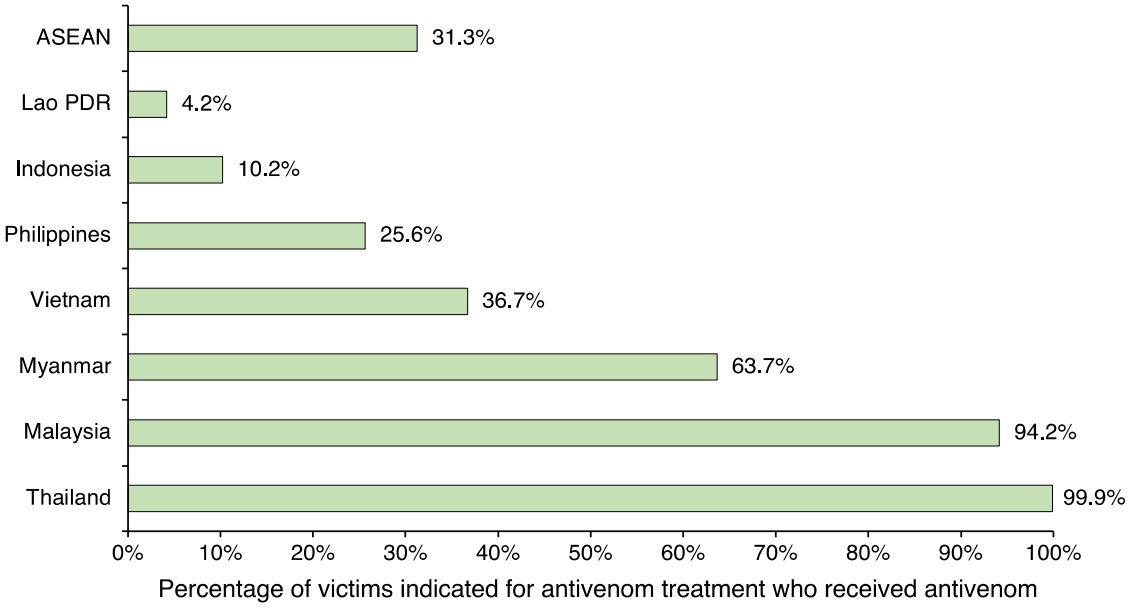

Figure 5 Estimated proportions of snakebite victims treated with antivenom in ASEAN countries

Percentages are estimated from number of snakebite victims treated with antivenom divided by total number of snakebite victims with systemic envenoming who need antivenom; Main sources of information were national statistics and published research for the burden estimation of Malaysia, Thailand, and Myanmar. Published research and anecdotal evidence (unpublished local data, and expert opinion) were the main sources of information for the burden estimation of Vietnam, and Lao PDR. Anecdotal evidence was the only source of information for the burden estimation of Indonesia, and Philippines.

4.4.2 Economic burden of snakebite in ASEAN

Annual economic burden of snakebite in ASEAN was estimated at 2.5 billion USD (95%CrI 1.2-5.4 billion USD) which was equivalent to 0.09% (95%CrI 0.04-0.20%) of the GDP (**Table 4** and **Figure 6**). The total costs of snakebite included direct medical costs of 69.0 million USD (95%CrI 49.0-94.8 million USD), direct non-medical costs of 6.5 million USD (95%CrI 4.2-10.3 million USD), and indirect costs of 2.4 billion USD (95%CrI 1.1-5.3 billion USD). The estimated economic burden of snakebite ranged from the lowest in Malaysia (2 million USD) to the highest in Indonesia (1.9 billion USD).

Table 4 Estimated annual economic burden (x1,000 USD) of snakebite in ASEAN countries

	Direct medical costs, x1,000 USD			Direct non-medical costs, x1,000 USD		Indirect costs, x1,000 USD			
	Healthcare costs	Antivenom-related costs	Amputation costs	Transportation costs	Additional food costs	Productivity losses during Snakebit episode	Productivity losses due to Premature death	Total costs, x1,000 USD	Total costs, % of GDP
Malaysia*	754 (620-932)	475 (249-758)	0	38 (34-42)	29 (23-40)	366 (289-484)	622 (0-1,866)	2,284 (1,380-3,736)	0.001% (0.000-0.001%)
Thailand*	2,027 (1,615-2,531)	1,176 (844-1,506)	0.2 (0-0.6)	58 (54-64)	50 (37-67)	925 (702-1,190)	762 (381-1,333)	4,999 (3,861-6,260)	0.001% (0.001-0.001)
Indonesia+	51,836 (36,900-70,844)	4,129 (3,727-4,520)	100 (44-178)	1,579 (1,431-1,738)	1,442 (1,027-1,970)	8,752 (6,506-11,566)	1,922,241 (914,489-4,110,887)	1,988,891 (975,513-4,202,049)	0.178% (0.087-0.375%)
Philippines¶	444 (338-578)	147 (130-162)	1 (1-2)	63 (52-76)	46 (35-60)	638 (518-793)	81,905 (40,762-163,735)	83,244 (42,165-165,246)	0.022% (0.011-0.044%)
Vietnam¶	3,208 (1,090-7,137)	1,094 (447-1,210)	0	853 (299-1,874)	1,463 (494-3,264)	3,801 (1,320-8,251)	257,594 (76,180-690,928)	268,013 (82,106-710,764)	0.102% (0.031-0.271%)
Lao PDR+	55 (42-71)	27 (23-32)	12 (2-34)	13 (12-15)	16 (13-20)	427 (361-501)	80,031 (40,573-159,767)	80,583 (41,188-160,291)	0.443% (0.227-0.882%)
Myanmar*	1,382 (1,047-1,815)	2,159 (1,910-2,425)	0	474 (417-526)	394 (303-516)	1,208 (952-1,551)	73,569 (44,703-131,172)	79,186 (50,302-136,615)	0.104% (0.066-0.180%)
Total	59,706 (41,652-83,950)	9,208 (7,329-10,613)	114 (46-215)	3,078 (2,299-4,335)	3,441 (1,932-5,938)	16,117 (10,648-24,335)	2,416,724 (1,117,087-5,259,687)	2,507,199 (1,196,516-5,384,962)	0.091% (0.043-0.195%)

Note: Estimates are presented as base-case estimates (x 1000 USD) with their 95% credibility interval (in parentheses) based on probabilistic sensitivity analysis. Costs are presented as 2019 USD where 1 USD = 14,147.67 Indonesian Rupees = 51.80 Philippine Pesos = 23,050.24 Vietnamese Dong = 8,679.41 Lao Kip = 1,518.26 Myanmar Kyat. Abbreviation: GDP – gross domestic product; USD - US Dollar; * input parameters were based on national statistics and published literature; ¶ Input parameters were based on published literature and anecdotal evidence; + Input parameters were based on anecdotal evidence.

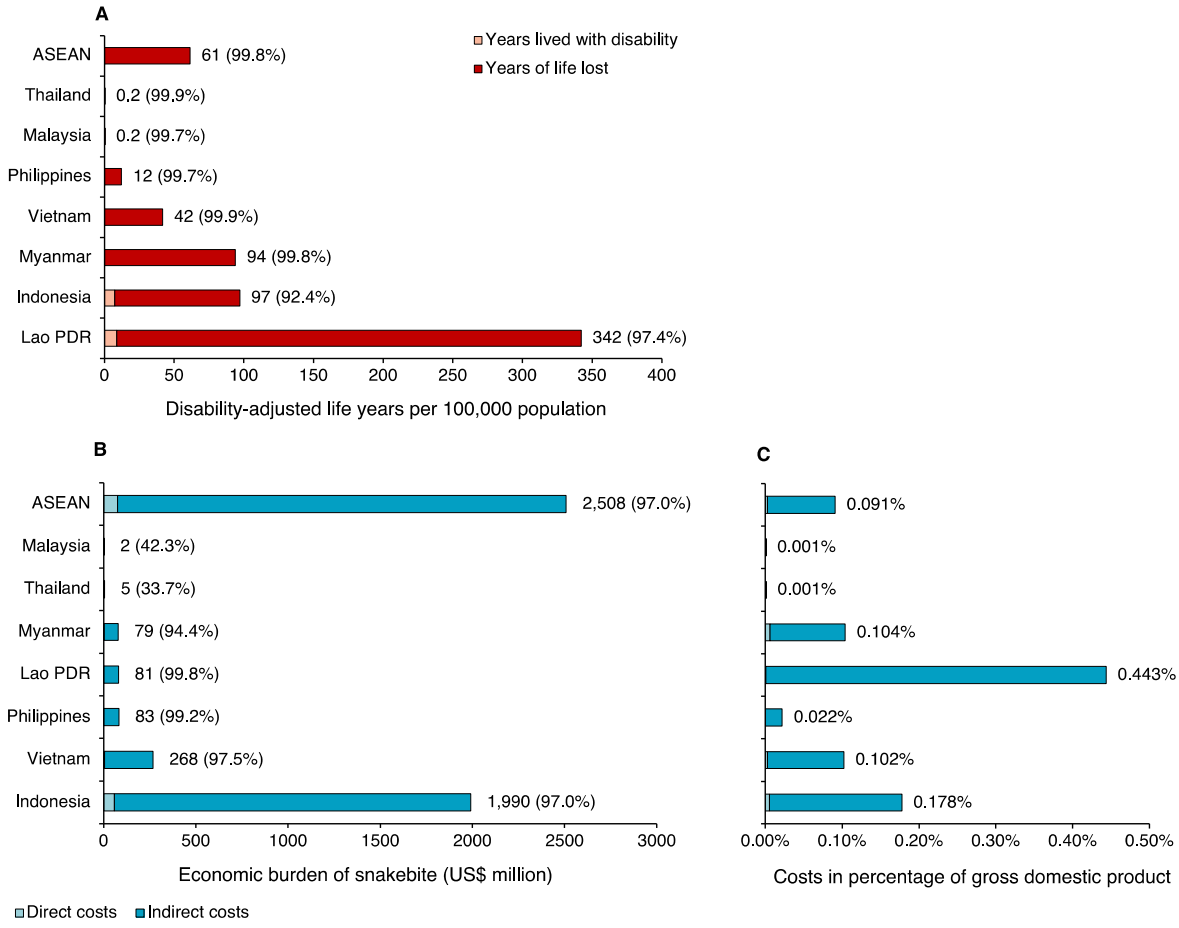

Figure 6 Estimated annual economic and disease burden of snakebite in ASEAN countries

(A) Disease burden of snakebite; data in parentheses are the percentages of disease burden attributable to years of life lost. (B) Costs in million USD; data in parentheses are the percentages of economic burden attributable to indirect costs. (C) Costs in percentage of gross domestic product; Main sources of information were national statistics and published research for the burden estimation of Malaysia, Thailand, and Myanmar. Published research and anecdotal evidence (unpublished local data, and expert opinion) were the main sources of information for the burden estimation of Vietnam, and Lao PDR. Anecdotal evidence was the only source of information for the burden estimation of Indonesia, and Philippines. Costs are presented as 2019 USD where 1 USD = 14,147.67 Indonesian Rupees = 51.80 Philippine Pesos = 23,050.24 Vietnamese Dong = 8,679.41 Lao Kip = 1,518.26 Myanmar Kyat. Abbreviation: GDP – gross domestic product; USD - US Dollar.

The total economic burden of 2.5 billion USD was broken down into hospitalization costs (59.7 million USD; 2.4% of the total economic burden), antivenom-related costs (9.2 million USD; 0.4%), amputation costs (0.1 million USD, 0.005%), transportation costs (3.1 million USD, 0.1%), food costs (3.4 million USD, 0.1%), productivity losses of victims and relatives during snakebite episode (16.1 million USD, 0.6%), and productivity losses due to premature death (2.4 billion USD, 96.4%).

4.4.3 Disease burden of snakebite in ASEAN

We estimated an annual disease burden of snakebite in ASEAN of 391,979 DALYs (95%CrI 187,261-836,559), which was equivalent to 61 DALYs per 100,000 population (95%CrI 29-131) (**Table 4**, **Figure 6**, and **Table B2** in **Appendix B**). The estimated disease burden of snakebite involved 391,154 YLLs due to death from snakebite envenoming (95%CrI 186,491-835,263; 99.8% of the total DALYs), 330 YLDs for snakebite episode (95%CrI 154-613; 0.08%), and 495 YLDs for amputation (95%CrI 175-1,049; 0.13%). DALYs lost due to snakebite ranged from the lowest in Malaysia (52 DALYs) to the highest in Indonesia (262,888 DALYs).

4.4.4 Comparison of economic and disease burden per victim with snakebite envenoming across countries

Economic and disease burden per victim with snakebite envenoming was compared across ASEAN countries (**Table B3** in **Appendix B**). Mortality rate of snakebite envenoming ranged from the lowest in Thailand (0.001) to the highest in Lao PDR (0.332). Amputation rate of snakebite envenoming ranged from the lowest in Malaysia, Vietnam, and Myanmar (0.000) to the highest in Lao PDR (0.047). DALYs lost due to snakebite envenoming per victim ranged from the lowest in Thailand (0.02 DALYs per victim) to the highest in Lao PDR (8.10 DALYs per victim). Total costs of snakebite envenoming per victim ranged from the lowest in Thailand (861 USD per victim) to the highest in Philippines (47,072 USD per victim).

4.4.5 Sensitivity analysis

One-way sensitivity analysis found that influential parameters for economic and disease burden were discount rate, probability of death due to snakebite envenoming, relative risk of death when antivenoms are not available, probability of systemic envenoming indicated for antivenom treatment, incidence of snakebite, and length of stay of victims indicated for antivenom treatment (**Figures B1** and **B2** in **Appendix B**). When PTSD was incorporated in the model in scenario analysis, the model estimated that there would be 10,293 cases of PTSD (95%CrI 4,651-20,954) with disease burden of 17,458 YLDs (95%CrI 5,869-40,035 YLDs) and productivity losses of 12.7 million USD (95%CrI 4.7-27.9 million USD) (**Table B4** in the **Appendix B**). PTSD following snakebite was found to slightly increased the economic (total costs of 2.52 billion USD; 0.5% increase) and disease burden (405,102 DALYs; 4.5% increase).

4.5 DISCUSSION

To achieve the goal set by the WHO to halve burden of snakebite by 2030, countries should know their current economic and disease burden of snakebite to understand their current standpoint. To

our understanding, this is the first study conducted to estimate the economic and disease burden of snakebite in Southeast Asia. The annual economic and disease burden of snakebite in seven ASEAN countries were estimated using a decision analytic model incorporating input parameters from various sources including published literature and local sources to estimate the burden of all snakebite victims regardless of their treatment seeking behavior.

We estimated that annually there were 242,648 snakebite victims (95%CrI 209,810-291,023) of which 15,909 victims (95%CrI 7,592-33,949) were dead and 954 victims (95%CrI 383-1,797) were amputated. The estimated number of snakebite victims and deaths were comparable to the previous estimates in 2007 of approximately 234,000-1,410,000 snakebite victims and 700-18,000 deaths.[11] Annual disease burden of snakebite was estimated at 391,979 DALYs (95%CrI 187,261-836,559). Total costs of snakebite were estimated at 2.5 billion USD (95%CrI 1.2-5.4 billion USD) which were equivalent to 0.09% (95%CrI 0.04-0.20%) of the region's GDP. The share of the estimated economic burden from snakebite of the country's GDP ranged from 0.001% in Malaysia to 0.443% in Lao PDR which were remarkably high compared to less than 0.001%. in Iran and Burkina Faso and 0.016% in Sri Lanka.[2,3,46,67] The estimated disease burden of snakebite of 391,979 DALYs in seven ASEAN countries (61 DALYs per 100,000 population) was low compared to the previous estimates of 319,874 DALYs in 16 Western African countries (approximately 93 DALYs per 100,000 population)[84] and 1,029,209 DALYs in 41 Sub-Saharan African countries (approximately 120 DALYs per 100,000 population).[9] This could be partly explained by the differences in the incidence and mortality of snakebite and access to antivenom treatment. Compared to the disease burden of neglected tropical diseases in seven ASEAN countries that were estimated in the Global Burden of Disease 2019 study, snakebite was the second highest burden ranking below dengue (909,899 DALYs) (**Figure B3** in **Appendix B**). The disease burdens of malaria (72,844 DALYs) and rabies (66,525 DALYs) were much lower than snakebite.[131]

In Malaysia and Thailand, >90% of victims indicated for antivenom could access to it. In contrast, remarkably lower proportions were demonstrated in Lao PDR, Indonesia, Philippines, Vietnam, and Myanmar of which 4-64% antivenom indicated victims were treated with antivenoms. These victims either sought traditional healers or were treated in healthcare facilities but did not receive antivenom due to inadequate supply of antivenom. Consequently, most deaths from snakebite envenoming (99.9%) in ASEAN were from Indonesia, Philippines, Vietnam, Lao PDR, and Myanmar which contributed to high economic and disease burden of premature death from snakebite envenoming. We found that more than 95% of the estimated economic and disease burden was attributed to premature deaths. Treating all snakebite victims who need antivenoms in these countries would save their lives which would result in a tremendous decrease in the burden of snakebite in ASEAN.

However, increasing access to antivenom was not only about producing antivenoms but the whole surrounding supporting and management system especially the information system to inform decision making and logistics to efficiently deliver antivenoms even to the farthest healthcare facilities. We previously assessed the situation of snakebite in ASEAN and provided the potential opportunities to improve situation of snakebite in ASEAN to meet the WHO's target of halving snakebite mortality and morbidity by 2030. These potential opportunities included accurate estimation of antivenom demand, rigorous regulations of antivenom, strengthening the supply chain system, raising public awareness about the importance of treating snakebite envenoming by healthcare professionals, strengthening the health system to ensure appropriate snakebite management and rational use of antivenoms, and expanding collaboration of local and international stakeholders and funders.[83]

There were few important limitations of this study worth mentioning. Firstly, Cambodia was not included in this study because we were not able to identify published literature and key informants that could be utilized to estimate the burden of snakebite in Cambodia. It is important to note that Cambodia is one of the countries that imported antivenoms from Thailand, indicating that there were snakebite victims in this country.[83] Secondly, consequences of snakebite included in the model and its sensitivity analysis were limited to death, amputation, and PTSD. Other disabilities such as blindness, malignant ulcers, and pregnancy loss were not included due to a lack of empirical evidence in ASEAN.[63] This warrants future studies in ASEAN to evaluate all relevant consequences and disabilities and associated costs of snakebite to allow better estimation of burden of snakebite. Lastly, there was no nation-wide community and hospital study to comprehensively collect the number of snakebite victims in some of the included countries. Hence, input parameters must be estimated based on non-national studies, unpublished local data, and expert opinions, resulting in a wide range of the estimated economic and disease burden of snakebite in ASEAN. This is especially relevant in Lao PDR and Indonesia where snakebite incidences were very high and estimated by local experts. Nevertheless, our findings suggested that there was high burden of snakebite despite the availability of domestically produced antivenoms in the region. We emphasized the importance of funding research to perform a comprehensive data collection on epidemiological and economic burden of snakebite to eventually reveal the true burden of snakebite in ASEAN. These data will yield more accurate information on burden of snakebite to guide decision making in not only the ASEAN but also the WHO to develop global strategies to tackle the problem of snakebite.

4.6 CONCLUSION

Annual production of 290,000 vials of antivenom in ASEAN were given to only 31% of victims who were indicated for antivenom treatment. Our estimates highlighted the high economic and disease burden of snakebite in ASEAN despite the availability of domestically produced antivenoms. Almost all of the estimated economic and disease burdens were attributed to premature deaths from snakebite envenoming which suggested that the remarkably high burden of snakebite could be averted, especially in countries where large proportions of victims who needed antivenom were not treated with geographically appropriate antivenoms. Strategies should be developed with the goal to improve health outcomes of snakebite victims. However, strategies used to achieve this goal are likely to be complex and different across countries depending on each country's context and situation such as accurate informatics, rigorous regulations of antivenoms, efficient supply chain, rational use of antivenoms, appropriate treatment seeking behaviors, and good governance to support a strong healthcare system

CHAPTER 5 POTENTIAL ECONOMIC AND CLINICAL IMPLICATIONS OF IMPROVING ACCESS TO SNAKE ANTIVENOM IN FIVE ASEAN COUNTRIES: A COST-EFFECTIVENESS ANALYSIS

Patikorn C, Ismail AK, Zainal Abidin SA, Othman I, **Chaiyakunapruk N, Taychakhoonavudh S**. Potential economic and clinical implications of improving access to snake antivenom in five ASEAN countries: A cost-effectiveness analysis. PLOS Neglected Tropical Diseases. 2022;16(11):e0010915.

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5.1 ABSTRACT

Background: Despite domestic production of antivenoms in the Association of Southeast Asian Nations (ASEAN) countries, not all victims with snakebite envenomings indicated for antivenom received the appropriate or adequate effective dose of antivenom due to insufficient supply and inadequate access to antivenoms. We aimed to conduct a cost-effectiveness analysis to project the potential economic and clinical impact of improving access to antivenoms when all snakebite envenomings in ASEAN countries were hypothetically treated with geographically appropriate antivenoms.

Methodology: Using a decision analytic model with input parameters from published literature, local data, and expert opinion, we projected the impact of "full access" (100%) to antivenom, compared to "current access" in five most impacted ASEAN countries, including Indonesia (10%) , Philippines (26%), Vietnam (37%), Lao PDR (4%), and Myanmar (64%), from a societal perspective with a lifetime time horizon. Sensitivity analyses were performed.

Principal Findings: In base-case analyses, full access compared to current access to snake antivenom in the five countries resulted in a total of 9,362 deaths averted (-59%), 230,075 disability-adjusted life years (DALYs) averted (-59%), and cost savings of 1.3 billion USD (-53%). Incremental cost-effectiveness ratios (ICERs) of improving access to antivenom found higher outcomes but lower costs in all countries. Probabilistic sensitivity analyses of 1,000 iterations found that 98.1-100% of ICERs were cost-saving.

Conclusion/Significance: Improving access to snake antivenom will result in cost-saving for ASEAN countries. Our findings emphasized the importance of further strengthening regional cooperation, investment, and funding to improve the situation of snakebite victims in ASEAN countries.

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5.2 INTRODUCTION

Snakebite is a highly prioritized neglected tropical disease recognized by the World Health Organization (WHO). Due to the high global burden of snakebite, WHO has set its goal to reduce morbidity and mortality of snakebite by 50% by 2030.[1,10,11] WHO has developed four strategic objectives to tackle the problems, including empowering and engaging communities, ensuring safe and effective treatment, strengthening health systems, and increasing partnerships, coordination, and resources.[10]

The Association of Southeast Asian Nations (ASEAN) is an economic union comprising of ten member countries including Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam with over 600 million population.[12] ASEAN is among the tropical regions with a disproportionately high incidence of snakebite. Our previous study estimated that there were approximately 243,000 snakebite victims with 16,000 deaths and 950 amputations from snakebite envenoming in seven ASEAN countries, namely, Malaysia, Thailand, Indonesia, Philippines, Vietnam, Lao PDR, and Myanmar. The annual economic and disease burden of snakebite in these countries was estimated at approximately 2.5 billion US Dollars (USD) and 392,000 disability-adjusted life years (DALYs) lost due to snakebite.[132]

Previous economic evaluations have demonstrated the cost-effectiveness of antivenoms over no treatment for victims who suffered from snakebite envenoming indicating that antivenoms should be included as part of the pharmaceutical benefits schemes.[2,63,64] Antivenoms are already included in the essential medicine lists in many countries in the ASEAN.[83] However, not all victims with snakebite envenoming in ASEAN countries could access to geographically appropriate antivenoms for many reasons including inadequate supplies of antivenom, inefficient supply chain system, and inappropriate treatment seeking behavior.[83] Especially in Indonesia, Philippines, Vietnam, Lao PDR, and Myanmar, where 4-64% of victims with snakebite envenoming were treated with antivenoms.[132] Lack of access to antivenom in ASEAN countries could actually be avoided with evidence-informed strategies to improve access to snake antivenom with the goal that every victim with snakebite envenoming should receive antivenoms. However, strategies used to achieve this are likely to be complex and different across countries depending on each country's context and situation. Moreover, improving access to antivenoms could not be solely done by increasing the production of antivenoms. It requires a multifaceted approach involving strengthening the whole system surrounding the management of snakebite victims, such as accurate informatics, rigorous regulations of antivenoms, efficient supply chain, rational use of antivenoms, appropriate treatment seeking behaviors, and good governance to support a strong healthcare system. To accelerate the development of strategies to improve access to snake antivenoms, it is needed to demonstrate the potential impact of treating all victims with snakebite envenoming with snake antivenoms. Therefore, we aimed to conduct a cost-effectiveness analysis to project the potential economic and clinical impact of improving access to snake antivenoms when all victims with snakebite envenomings in ASEAN countries were hypothetically treated with geographically appropriate antivenoms. Our findings would emphasize the unmet medical needs of snakebite victims in ASEAN countries and the importance of developing strategies to provide access to geographically appropriate antivenoms for all victims with snakebite envenoming to reduce the burden of snakebite in the region.

5.3 METHODS

An economic evaluation was conducted using a decision analytic model to assess the cost-effectiveness of improving access to snake antivenom from the current level to full access in ASEAN countries. We projected the economic and clinical implications of "full access" to antivenom relative to "current access" in a hypothetical cohort of snakebite victims in each country from a societal perspective with a lifetime time horizon to capture lifetime costs and consequences of snakebite victims. We developed our study following the methodological considerations for economic

evaluations of snakebites described in the previous systematic review.[2] We reported our study following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 statement (**Table C1** in **Appendix C**).[133]

5.3.1 Setting

We selected the five most impacted ASEAN countries for this study, including Indonesia, Philippines, Vietnam, Lao PDR, and Myanmar because the previous estimates in these countries found that only 4-64% of victims who were indicated for antivenoms were treated with antivenoms.[132]

Malaysia and Thailand were not selected because more than 90% of victims in these countries who were indicated for antivenoms were treated with antivenoms.[134] Brunei Darussalam and Singapore were not selected because snakebite rarely occurs and/or exact data were lacking.[11] Cambodia was not selected due to a lack of information and key informants, although it is one of the countries with a high incidence of snakebites.[11]

5.3.2 Decision analytic model

A decision analytic model (**Figure 7**) was adapted from the previously developed model to estimate the number of snakebite victims occurring in one year in ASEAN countries and the economic and disease burden of snakebite victims.[132] Briefly, victims who were bitten by snakes sought either conventional treatment or traditional treatment. The victims who were indicated for antivenom treatment might be treated with antivenom depending on the level of access. Snakebite victims might be alive, alive with disabilities, or dead. Disabilities included in this model were digit and limb amputation.

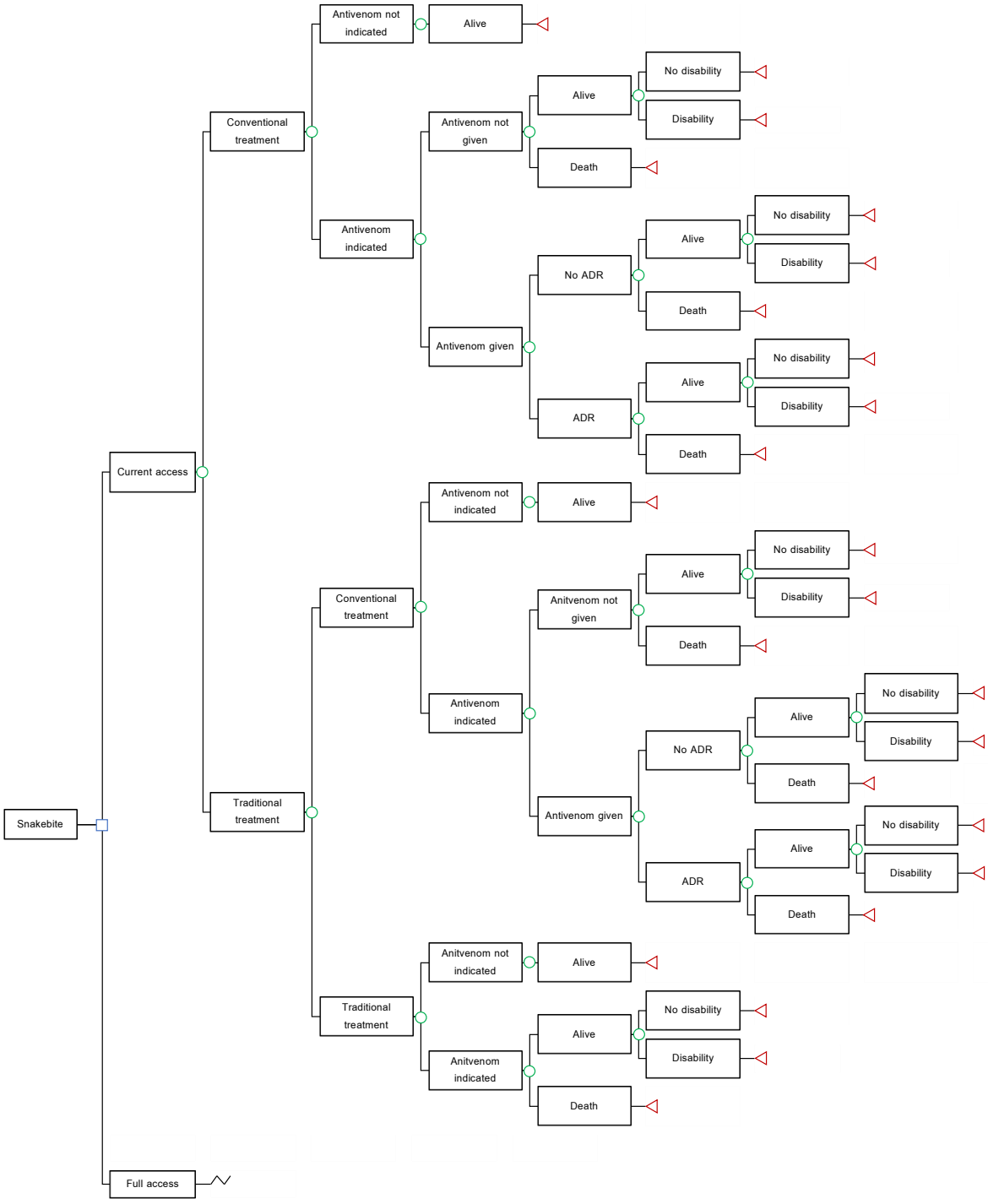

Figure 7 Decision analytic model to estimate economic and disease burden of snakebite in ASEAN countries

Abbreviation: ADR – adverse drug reaction.

There were four key assumptions of the model.[132] First, one person can be bitten by a snake only once in a lifetime. Second, snakebite victims were accompanied by relatives or family members who took care of them during the snakebite episode. Third, due to lack of data, antivenom effectiveness was based on a study in Nigeria which found 2.33 folds (95% confidence interval; 1.26-4.06) increased risk of death in antivenom indicated victims who were not treated with antivenom compared to those treated with antivenom.[104] Fourth, current access to antivenom was determined as the proportion of the number of antivenoms treatment available by a total number of victims indicated for antivenom treatment with the values of 0.04 (Lao PDR), 0.10 (Indonesia), 0.26 (Philippines), 0.37 (Vietnam), and 0.64 (Myanmar) that were previously estimated.[132] Full access was modeled as all snakebite victims who were indicated for antivenom could be treated with geographically appropriate antivenoms. In the full access scenario, all snakebite victims who firstly sought traditional healers when access is now full are assumed to switch to conventional treatment.

5.3.3 Input parameters

Input parameters for each country (**Table C2** in **Appendix C**) were based on the previous study that estimated the economic and disease burden of snakebite in ASEAN countries.[134] These parameters were sought from published literature, data from the Ministry of Health in each country, local data, and expert opinion.[16,25,36-38,41,86,88,104,110,112-117,120,121,123-126] The input parameters were validated by triangulation of data from the literature, local data, and interview with key informants who were experts in snakebite in ASEAN.

Main sources of information were national statistics and published research for the burden estimation of Malaysia, Thailand, and Myanmar. Published research and anecdotal evidence (local data, and expert opinion) were the main sources of information for the burden estimation of Vietnam and Lao PDR. Anecdotal evidence was the main source of information for the burden estimation of Indonesia, and Philippines.

5.3.4 Costs

Costs of snakebite in this model included direct costs and indirect costs (**Table C2** in **Appendix C**).[132] Direct costs included costs of hospitalization, antivenom treatment, antivenom logistics, adverse drug reaction management, amputation, transportation, and additional food for victims and their relatives. Costs of antivenom treatment were estimated based on the average dose of antivenom vials used in the treatment of snakebite envenoming with the consideration of different types of snakes and antivenoms in each country. Indirect costs included productivity losses during snakebite episodes of victims and their relatives and productivity losses due to premature death. Productivity losses due to premature death were discounted at the rate of 3% and adjusted for the annual growth of GDP per capita in each country.[123-126]

5.3.5 Health outcomes

Health outcomes of the model included the number of deaths from snakebite envenoming and disability-adjusted life years (DALYs) lost due to snakebite. DALYs were estimated using the template developed by WHO.[127] DALYs were the sum of years of life lost (YLL) and years lived with disability (YLD). YLLs due to snakebite envenoming were calculated from the number of deaths multiplied by a global standard life expectancy at the age of death. YLDs of snakebite victims included YLDs for snakebite episodes and YLDs for amputations. YLDs were calculated from the duration of disability multiplied by a disability weight for each condition according to the Global Burden of Disease 2013 study (**Table C2** in **Appendix C**).[110]

5.3.6 Discounting

Costs and health outcomes that occurred after one year were discounted at the rate of 3%.[123,124]

5.3.7 Base-case analyses

In the base-case analyses, the expected costs and outcomes for each level of access were calculated. Primary outcomes of the model were deaths averted, DALYs averted, and incremental costs of full access compared to current access. Costs were expressed in 2019 US Dollars (USD) which equaled to 14,147.67 Indonesian Rupees, 51.80 = Philippine Pesos, 23,050.24, Vietnamese Dong, 8,679.41 Lao Kip, and 1,518.26 Myanmar Kyat.[135]

The results were presented as incremental cost-effectiveness ratio (ICER) per death averted and ICER per DALY averted in each country. The willingness-to-pay (WTP) thresholds were based on the local pharmacoeconomic guidelines in Indonesia (4,136 USD)[124], set by the Formulary Executive Council in the Philippines (2,317 USD)[136], and based on the country's GDP per capita in countries without explicit WTP thresholds including Vietnam (2,715 USD), Lao PDR (2,625 USD), and Myanmar (1,421 USD).[125] ICERs per death averted and ICER per DALY averted with values below these WTP thresholds were considered cost-effective.

5.3.8 Sensitivity analyses

A series of sensitivity analyses were performed to evaluate the robustness of the base-case conclusions. One-way sensitivity analyses were performed to assess the impact of varying input parameters from minimum to maximum values on the ICERs.

We performed a series of scenario analyses. In the base-case analyses, antivenom had no effect on amputation. Thus, we performed scenario analyses by assuming that antivenom treatment could reduce the amputation rate of snakebite victims with the same relative risk of 2.33 in antivenom indicated victims who were not treated with antivenom compared to those treated with antivenom.[104] Scenario analyses were performed by incorporating post-traumatic stress disorder (PTSD) in the model as a mental disability occurring in 8% of victims who survived snakebite envenoming.[6,129,130,132]

We performed scenario analyses by excluding indirect costs from the model. Lastly, scenario analyses were performed by increasing the logistic costs from 5% to 10% of antivenom price because these could be higher, especially in archipelagic countries like Indonesia and Philippines. Threshold sensitivity analyses were performed to estimate the lowest level of antivenom effectiveness and the highest level of costs of antivenom treatment that would result in the "not cost-saving" situation where ICER is equal to zero but still considered cost-effective.

Probabilistic sensitivity analyses were performed to assess the model robustness and uncertainty of the base case input parameters over their plausible ranges on the model output. Monte Carlo simulations for 1,000 iterations of ICERs were performed by randomly sampling all input parameters based on the probability distributions. Results of probabilistic sensitivity analyses were presented using the cost-effectiveness plane and the cost-effectiveness acceptability curves (CEACs).

5.4 RESULTS

5.4.1 Base-case analyses

We projected the economic and clinical impact of improving access to snake antivenom in ASEAN countries from the societal perspective (**Table 5**). When compared to current access, full access to antivenom in each country could save 433 lives in Philippines to 5,981 lives in Indonesia and reduce 10,473 DALYs in Philippines to 148,684 DALYs in Indonesia. However, full access to antivenom resulted in a higher number of patients with amputations (4 amputees in Philippines to 122 amputees in Indonesia) since more patients are being treated and as a result, more survivors from snakebite envenoming. Full access to antivenom had higher direct costs (2 million USD in Philippines to 50 million USD in Indonesia) but less indirect costs (-1,091 million USD in Indonesia to -28 million USD in Philippines) when compared to current access which resulted in total cost savings of 27 million USD in Philippines to 1,040 million USD in Indonesia. In total, when compared to current access, full access to snake antivenom in ASEAN countries resulted in 9,362 deaths averted (-59%), 230,075 DALYs averted (-59%), and cost savings of 1.3 billion USD (-53%).

Table 5 Estimated economic and clinical impact of snakebite victims between current access and full access to snake antivenom in ASEAN countries

	Indonesia			Philippines			Vietnam			Lao PDR			Myanmar		
	Current	Full	Difference	Current	Full	Difference	Current	Full	Difference	Current	Full	Difference	Current	Full	Difference
Health outcomes															
Deaths, n	10,547	4,566	-5,981	550	117	-433	1,655	619	-1,037	1,007	141	-866	2,145	1,099	-1,046
Amputations, n	799	921	+122	12	16	+4	0	0	0	141	202	+60	0	0	0
DALYs for snakebite	262,888	114,203	-148,684	13,317	2,844	-10,473	40,250	15,111	-25,139	24,532	3,513	-21,019	50,830	26,070	-24,759
Economic burden, million USD															
Direct costs	59	109	+50	1	2	+2	7	16	+9	0.1	1	+1	4	11	+7
Indirect costs	1,931	840	-1,091	83	54	-28	261	100	-161	80	12	-69	75	39	-36
Total costs	1,990	950	-1,040	83	57	-27	268	116	-152	81	13	-68	79	50	-29

Costs are presented as USD where 1 USD = 14,147.67 Indonesian Rupees = 51.80 Philippine Pesos = 23,050.24 Vietnamese Dong = 8,679.41 Lao Kip = 1,518.26 Myanmar Kyat. DALY - disability-adjusted life year; USD – US Dollar.

Base-case analyses of ICERs per death averted and ICERs per DALY averted of full access compared to current access found higher outcomes (0.02 deaths averted in Vietnam to 0.06 death averted in Lao PDR and 0.5 DALYs averted in Vietnam to 1.2 DALYs averted in Myanmar) but lower costs (-7,698 USD in Indonesia to -1,370 USD in Myanmar) in all five ASEAN countries. Thus, improving access to snake antivenom will result in cost-saving (**Table 6**).

5.4.2 Sensitivity analyses

One-way sensitivity analyses were presented with tornado diagrams to show the percentage change of base-case ICERs corresponding to varying values of the input parameters (**Figures C1** and **C2** in **Appendix C**). The most influential parameters for ICERs per death averted were discount rate and relative risk of death when antivenoms are not available. The most sensitive parameters for ICERs per DALY averted were relative risk of death when antivenoms are not available, discount rate, and probability of death in snakebite victims treated with antivenom. One-way sensitivity analyses found that the base-case conclusions were robust.

Scenario analyses were presented in **Tables C3** and **C4** in **Appendix C**. Incorporating PTSD in the model, assuming that antivenom could reduce the risk of amputation, and increasing the logistic costs of antivenom resulted in similar ICERs per death averted and ICERs per DALY averted in all countries indicating that improving access will result in cost-saving. Excluding indirect costs from the model resulted in ICERs per death averted ranging from 1,488 in Lao PDR to 8,632 USD per death averted in Vietnam. These ICERs per death averted were above the WTP thresholds in all countries except Lao PDR. While ICERs per DALY averted excluding indirect costs from the model ranged from 61 in Lao PDR to 356 in Vietnam. These ICERs per DALY averted were below the WTP thresholds in all countries.

Threshold analyses of antivenom effectiveness and costs of antivenom treatment resulted in an ICER of 0 are shown in **Table C5** in **Appendix C**. The lowest level of antivenom effectiveness, presented as a risk ratio of death in indicated victims who were not treated with antivenom compared to those treated with antivenom, was ranging from 0.35 in Lao PDR to 1.19 in Myanmar. The highest level of costs of antivenom treatment was ranging from 9 to 149 times the base-case value in Myanmar and Lao PDR, respectively.

Table 6 Cost-effectiveness of improving access to snake antivenom in ASEAN countries

	Costs, USD	Deaths, n	DALYs	Incremental costs, USD	Deaths averted, n	DALYs averted	Incremental costs per Death averted, USD	Probability of being cost-saving*	Incremental costs per DALY averted, USD	Probability of being cost-saving*	WTP Threshold, USD per DALY averted
Indonesia											
Current access (reference)	14,733	0.08	1.9								
Full access	7,035	0.03	0.8	-7,698	0.04	1.1	Cost-saving	99.8%	Cost-saving	100%	4,136
Philippines											
Current access (reference)	6,223	0.04	1.0								
Full access	1,536	0.01	0.2	-4,687	0.03	0.8	Cost-saving	99.9%	Cost-saving	99.9%	2,317
Vietnam											
Current access (reference)	5,733	0.04	0.9								
Full access	2,473	0.01	0.3	-3,260	0.02	0.5	Cost-saving	99.9%	Cost-saving	100%	2,715
Lao PDR											
Current access (reference)	5,620	0.07	1.7								
Full access	910	0.01	0.2	-4,710	0.06	1.5	Cost-saving	100%	Cost-saving	100%	2,625
Myanmar											
Current access (reference)	3,760	0.10	2.4								
Full access	2,390	0.05	1.2	-1,370	0.05	1.2	Cost-saving	98.1%	Cost-saving	98.1%	1,421

Note: *Percentage of 1,000 iterations that were cost-saving based on a probabilistic sensitivity analysis. Costs are presented as 2019 USD where 1 USD = 14,147.67 = Indonesian Rupees = 51.80 = Philippine Pesos = 23,050.24 Vietnamese Dong = 8,679.41 Lao Kip = 1,518.26 Myanmar Kyat. DALY – Disability-adjusted life year; USD – US Dollars; WTP – Willingness-to-pay.

Probabilistic sensitivity analyses were performed for 1,000 iterations with the results presented in **Figure 8** and **Figures C2** and **C3** in **Appendix C** We found that 98.1-100% of 1,000 ICERs per death averted and 98.3-100% of 1,000 ICERs per DALYs averted were cost-saving.

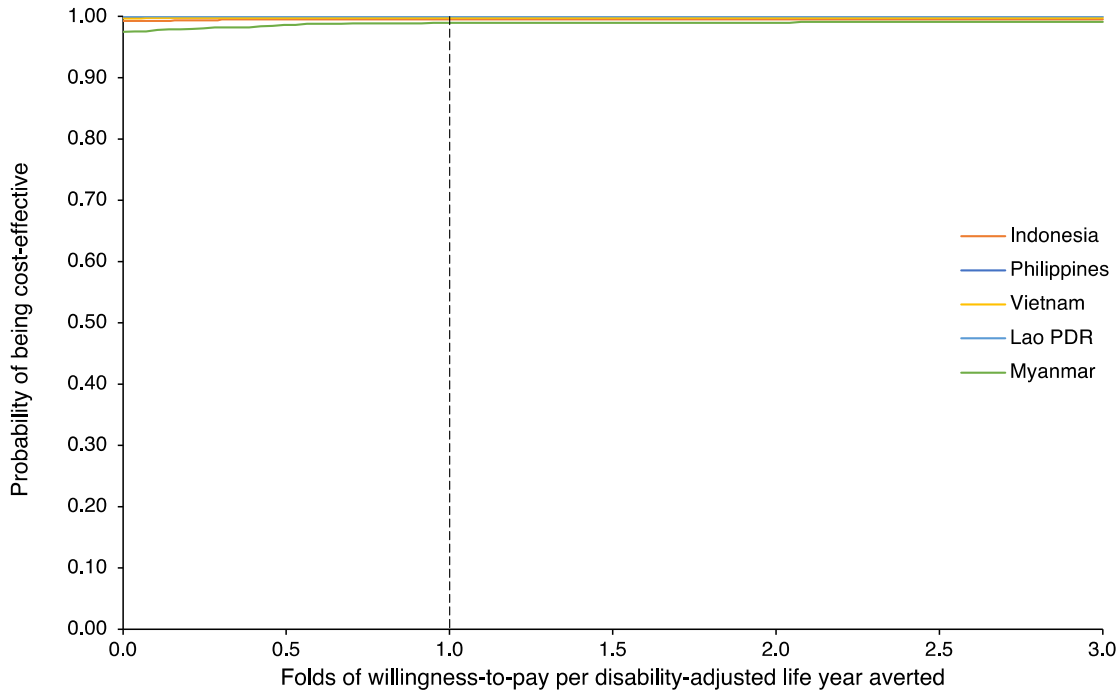

Figure 8 Cost-effectiveness acceptability curves of improving access to snake antivenom in ASEAN countries

Probabilities of full access to snake antivenom being cost-effective compared to current access in each ASEAN country at varying willingness-to-pay thresholds based on 1,000 iterations of a probabilistic sensitivity analysis are presented.

5.5 DISCUSSION

This is the first study to our understanding that projected the cost-effectiveness of improving access to snake antivenom. This cost-effective analysis was not done to evaluate whether antivenom was cost-effective or not because antivenoms were already available in ASEAN but not all victims with snakebite envenoming were treated antivenoms.[83,132] Thus, we tried to evaluate the potential economic and clinical impacts of increasing the access to antivenom in ASEAN countries when all snakebite victims in the full access scenario are treated with geographically appropriate antivenom. We used a decision analytic model with input parameters from various sources including published literature, local sources, and expert opinion. We did not propose specific strategies to improve access to snake antivenoms as each country has different problems which require different strategies and policies to address them.[83] Rather, we demonstrated the potential economic and

clinical impact when all victims with snakebite envenoming in ASEAN countries were treated with geographically appropriate antivenoms.

We found that improving access to snake antivenoms would result in cost-saving with higher outcomes (deaths and DALYs averted) but lower costs. In total, when compared to current access, full access to snake antivenom in five ASEAN countries resulted in 9,362 deaths averted (-59%), 230,075 DALYs averted (-59%), and cost savings of 1.3 billion USD (-53%). Although full access to antivenom compared to current access had higher direct costs because all victims with snakebite envenoming received antivenom treatment, the direct costs were entirely offset by indirect costs because antivenoms could save the victims' lives which would avoid tremendously productivity losses due to premature death.

Mortality and disabilities of snakebite envenoming in each country differ in regards to differences in the toxicity and lethality of the snakes.[83,132] Nevertheless, improving access to antivenom was found to be cost-saving in all five ASEAN countries regardless of differences in snakes causing the snakebite envenoming and baseline level of access to antivenom. We performed a series of sensitivity analyses and found that the conclusion of our study remained robust. Threshold analyses found that the antivenom effectiveness could be as low as 0.35 to 1.19, and the costs of antivenom treatment could increase as high as 9 to 149 times of the base-case value to render improving access to antivenom no longer a cost-saving strategy. This emphasizes the cost-effectiveness of improving access to antivenom.

ASEAN has made significant progress in the management of snakebite and antivenom, but there remain challenges in this region to be addressed especially the lack of snakebite-related informatics system and inadequate access to antivenoms.[83] Our previous estimates highlighted the high burden of snakebite in ASEAN despite the availability of domestically produced antivenoms. It was estimated that there were approximately 243,000 snakebite victims with 16,000 deaths and 950 amputations from snakebite envenoming in these countries with the estimated annual economic and disease burden of snakebite of approximately 2.5 billion USD and 392,000 DALYs lost due to snakebite.[132] Findings of this study indicated that improving access to antivenoms in ASEAN countries would result in tremendous cost savings for the whole society. Thus, further investment and funding is warranted so that we could achieve the WHO's goal to halve the snakebite burden in ASEAN.[10]

This study supports and informs that improving access to snake antivenom where all victims with snakebite envenoming received geographically appropriate antivenoms will result in cost-saving. As a result, policy makers and relevant stakeholders in ASEAN to develop effective strategies to improve access to antivenom and reduce the burden of snakebite victims in the region given that

antivenom is a lifesaving drug that should be universally accessible. However, improving access to antivenom is not only about increasing the production of antivenoms or purchasing more antivenoms, but also strengthening the whole health system to effectively deal with snakebite problems. More importantly, encouraging and engaging communities is needed to change the behavior of snakebite victims to seek care at appropriate healthcare facilities instead of traditional healers or seek no care at all. We previously discussed the potential opportunities to improve access to antivenom in ASEAN that included accurate estimation of antivenom demand, rigorous regulations of antivenom, strengthening the supply chain system, raising public awareness about the importance of treating snakebite envenoming by healthcare professionals, strengthening the health system to ensure appropriate snakebite management and rational use of antivenoms, and expanding collaboration of local and international stakeholders to better improve access to snake antivenom for victims in the region.[83] Nevertheless, there is no single strategy that could improve access to snake antivenom in every country. Strategies should be developed with consideration of the actual challenges and barriers to policy implementation in individual countries such as the infrastructure and capacity of the health system to appropriately tackle the snakebite problem.

5.5.1 Limitations

There were limitations in our approach that needed to be discussed. Firstly, although Cambodia is one of the countries with snakebite victims, Cambodia was not included in this study because of a lack of published literature and key informants. However, given our findings in five ASEAN countries, improving access to antivenom would be highly cost-saving as well. Secondly, all input parameters used in the model were derived from the available published literature, local data, and expert opinion when data were not available. These input parameters carried inherent uncertainty. We assumed antivenom effectiveness based on a study in Nigeria.[104] Most snakebites In Nigeria are inflicted by snakes of the genus *Echis*, for which antivenoms, in general, have high effectiveness.[63] This assumption may have a limitation as snakes in Nigeria are different from ASEAN. Nevertheless, our sensitivity analyses showed robust conclusions of the model. We strongly emphasized the need to conduct comprehensive research to estimate the true burden of snakebite in ASEAN. Thirdly, other disabilities of snakebite envenoming such as blindness, malignant ulcers, and pregnancy loss were not included due to lack of empirical evidence.[63] Chronic kidney disease due to Russell's viper (*Daboia russelii*) bite was not included in our study. It was found that Russell's viper bite caused acute kidney injury. However, information on chronic kidney disease following Russell's viper bite in ASEAN was not documented because patients were lost to follow-up after they were discharged.[137-139] This emphasizes the importance of funding future studies in ASEAN to evaluate all relevant

consequences and disabilities and associated costs of snakebite to allow better estimation of the cost-effectiveness of improving access to antivenom. Fourthly, we assumed that all snakebite victims in full access would eventually seek conventional treatment. However, this might not be possible because not all victims could have timely access to healthcare facilities, especially those who lived in the farthest rural areas. This is especially important as timely access to healthcare facilities is related to the prognosis of the victims, both in terms of mortality and long-term disability.[140,141] Lastly, costs of strategy to improve access of antivenoms from the current level to full e.g., costs of increasing antivenom manufacturing capacity, or costs of improving the supply chain, were not included in the analysis. However, these costs were assumed to be covered by the costs of antivenom treatment.

5.6 CONCLUSION

Our study demonstrated improving access to snake antivenom from the current to the full level of access in five ASEAN countries was cost-saving. Our findings indicated that the WHO's goal to halve the snakebite burden could be achieved by providing full access to snake antivenoms for all victims in ASEAN which emphasized further strengthening regional cooperation, investment, and funding to improve the situation of snakebite victims in ASEAN countries to reach the ultimate goal where all victims with snakebite envenoming needing antivenom adequately received the geographically appropriate antivenoms.

CHAPTER 6 CONCLUSIONS

6.1 CONCLUSIONS

Snakebite envenoming is a neglected tropical disease posing public health challenges globally. The Association of Southeast Asian Nations (ASEAN) countries are among the tropical regions with disproportionately high incidence of snakebite. Understanding the snakebite and antivenom market situation and burden of snakebite is crucial for developing evidence-based strategies to pursue the goal set by the World Health Organization (WHO) to halve morbidity and mortality of snakebite by 2030. However, there was no such information in the ASEAN countries.

Firstly, we identified studies 23 cost of illness studies and 3 economic evaluations. We found that economic burdens of snakebite were underestimated and not extensively studied. Majority of studies only provided direct costs of snakebite patients presented to the hospitals. There was a lack of study estimating national economic burdens of snakebites. Due to likely underestimated economic burden, hospital data should be used to combine with community survey to ensure the accurate estimation of overall economic burdens of snakebite victims. Having full access to antivenom was found to be very cost-effective. Future studies should focus on how to make antivenoms available and affordable to snakebite victims.

Secondly, we estimated that annually there were 242,648 snakebite victims (95% Credibility Interval (CrI) 209,810-291,023) of which 15,909 victims (95%CrI 7,592-33,949) were dead and 954 victims (95%CrI 383-1,797) were amputated. Annual disease burden of snakebite was estimated at 391,979 disability adjusted life years (DALYs) (95%CrI 187,261-836,559 DALYs). Total costs of snakebite were estimated at 2.5 billion USD (95%CrI 1.2-5.4 billion USD) which were equivalent to 0.09% (95%CrI 0.04-0.20%) of the region's gross domestic product. More than 95% of the estimated burden was attributed to premature deaths.

Thirdly, we estimated the potential economic and clinical impact of improving access to snake antivenom in five ASEAN countries including Indonesia, Philippines, Vietnam, Lao PDR, and Myanmar countries. When compared to current access, full access to snake antivenom in resulted in the total of 9,362 deaths averted (-59%), 230,075 disability-adjusted life years (DALYs) averted (-59%), and cost savings of 1.3 billion USD (-53%). Incremental cost-effectiveness ratio (ICERs) of improving access to antivenom found higher outcomes but lower costs in all countries indicating that improving access was a cost-saving strategy. Probabilistic sensitivity analyses of 1,000 iterations found that 98.1-100% of ICERs were cost-saving.

In conclusion, ASEAN have made significant progress in the management of snakebite and antivenom, but there remain challenges in this region to be addressed especially the lack of

snakebite-related informatics system, inadequate antivenoms at the healthcare facilities, and when the majority of snakebite victims seeking traditional healers instead of conventional treatment. Our estimates highlighted the high burden of snakebite in ASEAN despite the availability of domestically produced antivenoms. Almost all of the estimated economic and disease burdens were attributed to premature deaths from snakebite envenoming which suggested that the remarkably high burden of snakebite could be averted by increasing access to antivenom especially in Indonesia, Philippines, Vietnam, Lao PDR, and Myanmar. Our study demonstrated improving access to snake antivenom from current to full level of access in Indonesia, Philippines, Vietnam, Lao PDR, and Myanmar was a cost-saving strategy. Our findings indicated that the WHO's goal to halve snakebite burden could be achieved by providing full access to snake antivenoms for all victims in ASEAN which emphasized the importance of further investment and funding to improve the situation of snakebite victims in ASEAN.

6.2 POLICY IMPLICATIONS

Antivenom is a lifesaving drug which should be universally accessible. Therefore, from the overview of snakebite management system across seven ASEAN countries, we proposed the following potential opportunities to further improve the situation of snakebite and antivenom.

First, the accurate estimation of antivenom demand is fundamentally needed. Comprehensive research on epidemiological and economic burden of snakebite is needed to spotlight the neglected unmet need of snakebite victims. However, the national statistics of snakebite are still lacking in most countries which hinders the accurate prediction of antivenom demand. The available national statistics of snakebite underestimate the real burden of snakebite because snakebites are mostly not a mandatory notifiable disease and not all victims are treated in the healthcare facilities. When an individual country acknowledges the actual burden of snakebite and antivenom demand, they could better decide what types of antivenoms are needed and whether to domestically produce antivenoms or purchase antivenoms from other countries. The estimated demand of antivenoms could also facilitate the procurement of antivenoms so the manufacturers could prepare and produce enough number of antivenoms for both domestic usage and exportation. Periodic updating the information of snakebite and ecological data of snakes is recommended to track the current situation and allocate resources accordingly.

Second, antivenoms should be rigorously regulated by the national regulatory authority to ensure the quality, safety, and efficacy of the antivenoms. Evidence of non-clinical cross-neutralization should be mandatory for countries who import antivenoms from other countries to ensure that the purchased antivenoms could be effectively reverse snakebite envenoming in the destination countries. The

quality of antivenom production should also be further improved such as lyophilization to prolong shelf-life, and purification to reduce immunogenicity.[142] The technology transfer of antivenom production among ASEAN countries may provide the suitable antivenom for neutralizing particular snake venom of each countries to address the venom variability from different geographical areas.

Third, strengthening the supply chain of antivenoms to ensure that antivenoms are readily accessible at the point of service. Centralized pooled procurement is encouraged to increase negotiation power with the manufacturers to ensure constant and reliable antivenom supplies at the affordable prices. Inventory and logistics of antivenom should be managed with support from online system to ensure availability of antivenom at healthcare facilities and provide real-world data of antivenom utilization which allows reallocation of antivenoms and better estimation of antivenom demand and supply within country.

Fourth, raising public awareness about snakebite is important. Healthcare authorities should engage with communities to educate people regarding the danger of snakebite envenoming, how to avoid and prevent snakebite, appropriate first aid measures, and when to seek care at healthcare facilities. In areas where there is a strong cultural belief on traditional healing methods, the collaboration with traditional healers is vital to engage the traditional healers on performing safe treatments and to encourage victims to receive proper treatment at healthcare facilities.

Fifth, health system should be further strengthened to ensure appropriate snakebite management especially efficient use of antivenom with support from the local clinical practice guidelines, training for healthcare professionals, clinical consultation services, and snakebite identification services with the goal of better outcomes of snakebite victims. Healthcare professionals should also be trained periodically to remind the current practices since some might not be familiar with snakebite or snakebite rarely occurs in their hospitals.

Lastly, international collaboration should be expanded to multi-stakeholder alliance from public and private sectors in ASEAN. There is an opportunity for the PAAV consortium to further raise awareness of policymakers on the burden of snakebite and advocate development of informed strategic solutions especially through capacity building to strengthen health management system to address this neglected snakebite issue in ASEAN. There is the need to develop snakebite and antivenom accessibility index to monitor the situation over time. This index can be helpful to evaluate situation and identify areas that could be rectified through collaborative strategic efforts to improve overall population health.

In conclusion, improving the situation of snakebite and antivenom is not only about the availability of antivenom, but the whole landscape of surrounding management and supporting system. The assessment of the situation of snakebite and antivenom is crucial for countries or regions where

snakebites are prevalent to recognize their current standpoint to inform the development of strategies to address snakebite problems in ASEAN countries.

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APPENDICES

APPENDIX A GLOBAL SYSTEMATIC REVIEW OF COST OF ILLNESS AND ECONOMIC EVALUATION STUDIES ASSOCIATED WITH SNAKEBITE

Table A9 PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3.1 Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3.2 Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3.2 Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration	3.3 Methods

Section/topic	#	Checklist item	Reported on page #
		information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3.3.1 Data source, search strategy, and eligibility criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3.3.1 Data source, search strategy, and eligibility criteria
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3.3.1 Data source, search strategy, and eligibility criteria, Table A2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3.3.2 Study selection and data extraction
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for	3.3.2 Study selection

Section/topic	#	Checklist item	Reported on page #
		obtaining and confirming data from investigators.	and data extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3.3.2 Study selection and data extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3.3.3 Quality assessment
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			

Section/topic	#	Checklist item	Reported on page #
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3.4.1 Study selection, Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3.4.2 Study characteristics, Table 1, Tables A3 and A4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	3.4.3 Quality assessment, Tables A6 and A7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table S5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			

Section/topic	#	Checklist item	Reported on page #
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	3.5 Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3.5 Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	3.6 Conclusion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table A10 Full search strategies.

Searches were conducted for articles published up to 31 July 2019.

1. **PubMed**

Search number	Search terms	Results
#1	snake*	25363
#2	burden OR economic* OR cost* OR “cost of illness” OR resource OR expenditure	1481775
#3	"economic evaluation" OR "cost-effectiveness" OR "cost-utility" OR "cost-benefit"	113425
#4	#2 OR #3	1481775
#5	#1 AND #4	1317

2. **EMBASE (via Elsevier)**

Search number	Search terms	Results
#1	snake*	23162
#2	burden OR economic* OR cost* OR “cost of illness” OR resource OR expenditure	1527675
#3	"economic evaluation" OR "cost-effectiveness" OR "cost-utility" OR "cost-benefit"	214963
#4	#2 OR #3	1527675
#5	#1 AND #4	1783

3. Cochrane library

Search number	Search terms	Results
#1	snake*	458
#2	burden OR economic* OR cost* OR “cost of illness” OR resource OR expenditure	108006
#3	"economic evaluation" OR "cost-effectiveness" OR "cost-utility" OR "cost-benefit"	26054
#4	#2 OR #3	108006
#5	#1 AND #4	48

4. EconLit (via EBSCO)

Search number	Search terms	Results
#1	snake*	107
#2	burden OR economic* OR cost* OR “cost of illness” OR resource OR expenditure	1259448
#3	"economic evaluation" OR "cost-effectiveness" OR "cost-utility" OR "cost-benefit"	12663
#4	#2 OR #3	1259448
#5	#1 AND #4	89

Additional searches in health economic databases

1. Health Economic Evaluation Database (HEED)

   HEED ceased to publish and was inaccessible since 2014.

2. Tuft's Cost-effectiveness Analysis (CEA) Registry

   Search found no result.

3. Health Technology Assessment Database

   Search found no result.

Table A3 Methodological characteristics of the included cost of illness studies associated with snakebites.

Region/ Income economies	Country	Author, year	Perspective	Study population	Study setting	Study period	Sample size	Study design	Study approach	Currency (Costing year)	Direct cost estimation method	Indirect cost estimation method	Source of resource utilization	Source of price
East Asia and Pacific														
Lower-middle	Myanmar	Schioldann, 2018 [42]	Patient	Snakebite victims	Three villages in Mandalay	2016	158 participants	CS	PB	MMK, USD (NR)	Bottom-up		Interview	Interview
Europe and Central Asia														
High	Spain	Saz-Parkinson, 2012 [62]	Health system	Envenomed snakebite patients	Nationwide	1997-2009	1649 patients	R	PB	EUR (NR)	Bottom-up		Database	Listed price
Latin America and Caribbean														
Upper-middle	Guyana	Bachan, 2017 [68]	Societal	Snakebite patients required medical evacuation	Five hinder land regions	2011-2015	57 patients	R	PB	USD (NR)	Bottom-up		Database	Listed price, Literature
Upper-middle	Mexico	Sotelo, 2008 [78]	Provider	Snakebite children	One children hospital in Northwestern Mexico	1977-2006	79 patients	R	PB	MXN (NR)	Bottom-up		Chart	Listed price
Middle East and North Africa														
Upper-middle	Iran	Nikfar, 2011 [75]	Health system	Patients required antidotes	Nationwide	2004-2008	N/A (national data)	R	PB	IRR (NR)	Bottom-up		Database, Interview, Literature	Listed price
Upper-middle	Iran	Mashhadi, 2017 [67]	Societal	Snakebite and scorpion sting patients	Three hospitals in Ahvaz	January to December 2015	655 patients	CS	IB	I$ (NR)	Bottom-up	Human-capital	Chart, Interview	Interview, Listed price
North America														
High	Canada	Curran-Sills, 2018 [58]	Provider	Snakebite patients	Nationwide	January 2008 to April 2016	99 patients	R	PB	USD (2017)	Bottom-up		Chart	Market price
High	United States	Lopoo, 1998 [60]	Provider	Snakebite children	One referral children hospital in Oklahoma	1987-1997	37 patients	R	PB	USD (NR)	Bottom-up		Chart	Listed price
High	United States	Narra, 2014 [61]	Societal	Envenomed children	Thirty-three tertiary children's hospitals	2009	2755 patients	R	PB	USD (NR)	Bottom-up		Database	Listed price
High	United	Fowler, 2017	Provider	Crotaline Snakebite	One regional	January 2010	146 patients	R	PB	USD (NR)	Bottom-up		Database	Market price

Region/ Income economies	Country	Author, year	Perspective	Study population	Study setting	Study period	Sample size	Study design	Study approach	Currency (Costing year)	Direct cost estimation method	Indirect cost estimation method	Source of resource utilization	Source of price
	States	[59]		patients	hospital in Texas	to November 2014								
South Asia														
Upper-middle	Sri Lanka	Kasturiratne, 2017 [3]	Societal	Snakebite victims	All households in nine provinces	August 2012 to June 2013	695 victims (44,136 households)	CS, M	PB	LKR, USD (NR)	Bottom-up	Human-capital	Database, Interview	Interview, Listed price
Lower-middle	Bangladesh	Hasan, 2012 [71]	Patient	Snakebite patients	Four rural tertiary level hospitals	June to October 2006	83 patients	P	PB	USD (NR)	Bottom-up	Human-capital	Interview	Market price, Interview,
Lower-middle	India	Vaiyapuri, 2013 [81]	Patient	Snakebite victims	Thirty villages in rural Tami Nadu	November to December 2010	1115 victims (7578 households)	CS	PB	EUR, INR (NR)	Bottom-up	Human-capital	Interview	Interview
Lower-middle	India	Gupt, 2015 [70]	Provider	Snakebite patients	One hospital in Himachal Pradesh	January 2008 to December 2012	497 patients	R	PB	INR, USD (NR)	Bottom-up		Chart	Listed price
Lower-middle	India	Meena, 2016 [73]	Health system	All patients	One tertiary hospital in Southern Rajasthan	2014-2015	200 patients	P	PB	INR (NR)	Bottom-up		Chart, Interview	Listed price
Lower-middle	India	Ramanath, 2016 [77]	Provider	Snakebite patients	One rural hospital	January 2011 to February 2015	190 patients	P, R	PB	INR (NR)	Bottom-up		Chart, Interview	Listed price
Lower-middle	Pakistan	Qureshi, 2013 [76]	Health system	Envenomed snakebite adults	Two public-sector hospitals	June to September 2010	74 patients	P	PB	PKR (NR)	Bottom-up		Chart	Listed price
Low	Nepal	Sharma, 2004 [80]	Patient	Snakebite victims	Community-based; Five villages in eastern Terai	December 2001	143 victims (1817 households)	CS	PB	USD (NR)	Bottom-up	Human-capital	Interview	Interview
Sub-Saharan Africa														
Upper-middle	South Africa	Darryl, 2016 [69]	Health system	Snakebite patients	Fifty-six public hospitals in KwaZulu Natal	2012-2013	56 hospitals	M, R	PB	USD (NR)	Bottom-up		Chart, Database	Listed price, Literature
Lower-middle	Nigeria	Michael, 2011 [74]	Societal	Snakebite patients	One 22-bed rural hospital in central	April to July 2006	72 patients	P	PB	NGN, USD (NR)	Bottom-up		Chart, Interview	Listed price

Region/ Income economies	Country	Author, year	Perspective	Study population	Study setting	Study period	Sample size	Study design	Study approach	Currency (Costing year)	Direct cost estimation method	Indirect cost estimation method	Source of resource utilization	Source of price
					Nigeria									
Lower-middle	Zimbabwe	Kasilo, 1993 [72]	Provider	Snakebite patients	Six urban major referral hospitals	1980-1989	995 patients	R	PB	USD, ZWD (NR)	Bottom-up		Chart	Listed price
Lower-middle	Zimbabwe	Tagwireyi, 2001 [79]	Provider	Uncomplicated envenomed snakebite patients	One large teaching hospital	January 1996 to December 1999	78 patients	R	PB	USD, ZWD (2000)	Bottom-up		Chart	Market price
Low	Burkina Faso	Gampini, 2016 [66]	Patient	Snakebite patients	All public health facilities	2010-2014	N/A (national data)	R	PB	USD (NR)	Bottom-up		Database	Market price

Abbreviations: CS – Cross-sectional, EUR – Euro, I$ - International Dollar, IB – Incidence-based, INR – Indian Rupee, IRR – Iranian Rial, LKR – Sri Lankan Rupee, M – Modelling, MMK – Myanmar Kyat, MXN – Mexican Peso, N/A – Not Applicable, NGN – Nigerian Naira, NR – Not reported, PB – Prevalence-based, PKR – Pakistani Rupee, R – Retrospective, USD – United States Dollar, ZWD – Zimbabwean Dollar

Description of methodological characteristics of included cost of illness studies

Perspective

Eight studies undertook analysis from the healthcare provider's perspective [58-60,70,72,77-79], and five studies utilized health system's perspective. [62,69,73,75,76] All of these studies only focused on direct medical costs such as antivenom costs, and hospitalization costs. Other five studies utilized patient's perspective [42,66,71,80,81] and the remaining five studies utilized societal perspective. [3,61,67,68,74] These studies incorporated broader scope of costs including both direct and indirect costs.

Study population and setting

Most studies included population from all age groups. Only three studies focused on children [60,61,78], and one studies focused on adult.[76] Studies were categorized from study location as hospital-based and community-based study. Nineteen studies were hospital-based study as they focused only snakebite patients presented at hospitals.[58-62,66-79] While the remaining four studies focused on snakebite victims in the communities to also include those who did not reach treatment facilities.[3,42,80,81]

Study design and study approach

Study design was classified as cross-sectional, modelling, prospective, and retrospective. Twelve studies collected data retrospectively using data in medical records or databases. [58-62,66,68,72,75,78,79] Cross-sectional studies were done in four studies.[42,67,80,81] Four studies prospectively collected data from snakebite patients. [71,73,74,76] One study collected data both retrospectively and prospectively.[77] The remaining two studies collected data which were further used in modelling costs of snakebite.[3,69]

Study approach for cost of illness study includes prevalence-based and incidence-based approach. Prevalent-based approach estimates cost of illness of all prevalent cases in the specific period of the study, usually one episode of snakebite. While, incidence-based estimates lifetime costs including costs related to disability or sequelae due to the diseases. Most

studies undertook prevalence-based approach [3,42,58-62,66,68-81], except one study which estimated costs of productivity loss due to disease and to premature death using incidence-based approach.[67]

Costing year and reported currency

Year of cost estimation was reported only in two studies.[58,79] The costing years of the other 21 studies were not reported. Therefore, they were imputed using the publication year. [3,42,59-62,66-78,80,81] Cost estimates were reported in local currencies in nine studies [59-62,73,76-78], international currencies in six studies [58,66-69,71,80], and International Dollars (a hypothetical currency unit that is designed to capture differences in relative prices across different settings) in one study. [67] The other seven studies reported their results in both local and international currencies. [3,42,70,72,74,79,81]

Direct cost estimation method

Direct costs are commonly quantified using top-down or bottom-up approach. The top-down approach estimates direct costs by allocating aggregate costs at the national level according to the resources used by the disease cases. The bottom-up approach quantifies direct costs by calculating the resources used by the disease cases at the patient level. The costs per patient quantified using both approaches can be then extrapolated to national costs using relevant epidemiological data.[50] In this review, all of the included studies utilized bottom-up approach. [3,42,58-62,66-81]

Indirect cost estimation method

Indirect costs are costs of productivity losses due to premature death or consequences of the disease. Indirect costs are normally estimated by either human-capital or friction cost approach. Human-capital approach values the productivity losses as output lost due inability to fully perform productive activities. While, the friction cost approach values the productivity losses as the employment costs to replace the ill workers.[50] Only five of the included cost of illness studies estimated indirect costs due to snakebite, all of which utilized human-capital approach.[3,67,71,80,81] Therefore, only these studies could be considered as economic burden study because they estimated both direct and indirect costs

Sources of healthcare resource utilization

Sources of healthcare resource utilization are defined as Chart, Database, Interview, and Literature. Chart includes patient medical records. Database includes electronic medical records, claim databases, and national registries. Interview is conducted using questionnaire. Literature includes articles in published or

unpublished sources and government documents. Studies might use more than one source of information. Chart was the most used source of healthcare resource utilization (n=12) [58,60,67,69,70,72-74,76-79], followed by interview (n=10) [3,42,67,71,73-75,77,80,81], database (n=7) [59,61,62,66,68,69,75], and literature (n=1).[75]

Sources of price of healthcare resource

Sources of price of healthcare resource are defined as Interview, Listed price, Literature, and Market price. Interview includes prices or costs of illness revealed by interview especially out of pocket costs paid by patients and families. Listed price includes prices set in the hospital and financial or accounting databases. Literature includes standard cost database and published articles. Market price includes retail and wholesale prices. Studies might use more than one source of information. Listed price was assumed to be used when studies utilized hospital records to quantify resource utilization but not clearly stated the price source. Listed price was the most used source of price of healthcare resource (n=15) [3,60-62,67-70,72-78], followed by interview (n=6) [3,42,67,71,80,81], market price (n=5) [58,59,66,71,79], and literature (n=2).[68,69]

Table A4 Methodological characteristics of the included economic evaluation studies associated with snakebites.

Author, year	Country	Study Setting	Target population	Type of snake	Type of antivenom	Intervention	Comparator	Type of EE	Type of model	Study perspective	Health outcomes	Time horizon	Discount rate	Sensitivity analysis
Habib, 2015 [63]	Nigeria	Public healthcare facilities in Nigeria	Envenomed snakebite victims	- Carpet viper - non-carpet viper snakes	- Monovalent - Polyvalent	Availability of geographically appropriate and effective antivenoms	No availability of effective antivenoms	CEA	Decision analytic model	Public healthcare system	- Full recovery - Amputation - Death	Lifelong	3% only outcomes	- One-way - Best-worst - Scenario
Hamza, 2016 [64]	16 West Africa countries	Public healthcare facilities in West Africa	Envenomed snakebite victims	- Vipers - non-viper snakes	- Monovalent - Polyvalent	Availability of effective antivenoms	No availability of effective antivenoms	CEA	Decision analytic model	Public healthcare system	- Full recovery - Amputation - Death	Lifelong	3% only outcomes	- One-way - PSA - Scenario
Herzel, 2018 [65]	India	Prehospital setting and Private health-care providers in South India	Snakebite victims	Any snakes	Not reported	Antivenom/adjunct combination strategy with supportive care	Antivenom and supportive care	CEA	Decision analytic model	Private healthcare provider	- Full recovery - Finger/Toe amputation - Below-knee amputation - Death	Lifelong	3% only outcomes	- One-way - PSA - Scenario

Abbreviations: CEA – Cost-effectiveness analysis, PSA – Probabilistic sensitivity analysis

Description of methodological characteristics of economic evaluation studies

All three included economic evaluation studies are cost-effectiveness analysis utilized decision analytic models.[63-65] Two studies compared no access to antivenom to full access from the public healthcare system's perspective. These studies only focused on envenomed snakebite patients presented to hospital. [63,64] While, another study compared antivenom alone with the antivenom adjunct combination strategy to improve the proportion of victims reaching healthcare facilities from the private healthcare system's perspective. This study focused on snakebite victims outside of the hospital.[65] Antivenoms were part of the analysis in all three studies. The health outcomes of snakebite in the models were similar including full recovery, death, and amputation. Lifelong was selected as the time horizon to capture deaths and disabilities. However, discount was applied only to outcomes because direct costs of snakebite normally occurred during treatment in healthcare facilities. All three studies performed sensitivity analyses.[63-65]

Table A5 Cost components reported in the included cost of illness studies associated with snakebites.

Region/ Income economies	Country	Author, year	Direct medical costs	Direct non-medical costs	Indirect costs

			Antivenom cost	Antibiotic cost	Other medicine cost	Hospitalization cost	Diagnosis cost	Health worker and service cost	Laboratory cost	Medical product cost	Traditional healer cost	Forfeited antivenom cost	Medical evacuation cost	Transportation cost	Communication cost	Food cost	Accommodation cost	Caregiver cost	Cost of productivity loss	Income lost in employed victim	Income loss in self-employed victims	Family income loss
East Asia and Pacific																						
Lower-middle	Myanmar	Schioldann, 2018 [42]	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-
Latin America and the Caribbean																						
High	Spain	Saz-Parkinson, 2012 [62]	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Middle East and North Africa																						
Upper-middle	Guyana	Bachan, 2017 [68]	+	-	+	-	-	-	-	+	-	-	+	+	-	+	+	-	-	-	-	-
Upper-middle	Mexico	Sotelo, 2008 [78]	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Upper-middle	Iran	Nikfar, 2011 [75]	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	-	+	-	-	-
Upper-middle	Iran	Mashhadi, 2017 [67]	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
North America																						
High	Canada	Curran-Sills, 2018 [58]	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-
High	United States	Lopoo, 1998 [60]	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
High	United States	Narra, 2014 [61]	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
High	United States	Fowler, 2017 [59]	+	+	-	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
South Asia																						
Upper-middle	Sri Lanka	Kasturiratne, 2017 [3]	+	-	+	+	-	-	+	+	+	-	-	+	+	+	-	+	-	+	+	+
Lower-middle	Bangladesh	Hasan, 2012 [71]	+	+	+	-	-	+	-	-	-	-	-	-	+	+	+	+	-	+	-	-
Lower-middle	India	Vaiyapuri, 2013 [81]	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
Lower-middle	India	Gupt, 2015 [70]	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lower-middle	India	Meena, 2016 [73]	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lower-middle	India	Ramanath, 2016 [77]	+	+	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
Lower-middle	Pakistan	Qureshi, 2013 [76]	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Low	Nepal	Sharma, 2004 [80]	+	+	+	+	-	+	-	-	+	-	-	+	-	-	-	-	-	+	-	-
Sub-Saharan Africa																						
Upper-middle	South Africa	Darryl, 2016 [69]	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lower-middle	Nigeria	Michael, 2011 [74]	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lower-middle	Zimbabwe	Kasilo, 1993 [72]	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lower-middle	Zimbabwe	Tagwireyi, 2001 [79]	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Low	Burkina Faso	Gampini, 2016 [66]	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
No. of studies reporting cost component			23	8	7	10	2	3	3	3	3	1	1	5	3	4	3	2	1	3	1	2

Region/ Income economies	Country	Author, year	Direct medical costs											Direct non-medical costs					Indirect costs			
			Antivenom cost	Antibiotic cost	Other medicine cost	Hospitalization cost	Diagnosis cost	Health worker and service cost	Laboratory cost	Medical product cost	Traditional healer cost	Forfeited antivenom cost	Medical evacuation cost	Transportation cost	Communication cost	Food cost	Accommodation cost	Caregiver cost	Cost of productivity loss	Income lost in employed victim	Income loss in self-employed victims	Family income loss
Percentage (%)			100	34.78	30.43	43.48	8.70	13.04	13.04	13.04	13.04	4.35	4.35	21.74	13.04	17.39	13.04	8.70	4.35	13.04	4.35	8.70

Description of reported cost components of snakebite

Direct medical costs

Direct medical costs were estimated in all studies. Medicine costs for the treatment of snakebite were commonly reported. Anti-snake venom costs were estimated in all studies, antibiotic costs in eight studies (34.78%) [61,67,71,77-81], and other medicine costs such as analgesics in seven studies (30.43%).[3,67,68,71,77,80,81] Hospitalization costs were also reported in ten studies (43.48%).[3,60-62,67,69,72,74,78,80] The other cost components were varied by studies. For example, traditional healer costs were reported in three studies (13.04%). [3,42,80]

Direct non-medical costs

Six studies estimated direct non-medical costs [3,68,71,75,77,80]. Components of direct non-medical cost reported in the included studies were costs of transportation, communication, food, accommodation, and caregivers. Transportation and food costs were the most commonly reported components among the six studies.

Indirect costs

Five studies estimated indirect costs. [3,67,71,80,81] Components of indirect costs reported in the included studies were costs of productivity loss due to premature death and disability, income loss, and family income loss. Income loss in employed snakebite victims were the most commonly reported components among the five studies.

Table A6 Quality assessment of the included cost of illness studies associated with snakebites.

Author, year	Specified perspective	Specified Epidemiologic approach	Specified study question	Specified Resource quantification method	Specified Healthcare resource valuation	Specified Productivity loss valuation	Estimated Intangible cost	Description of statistical analyses	Performed sensitivity analysis	Reporting of detailed cost components
Kasilo, 1993 [72]	NO	NO	NO	YES	NO	NO	NO	YES	NO	NO
Lopoo, 1998 [60]	NO	NO	NO	YES	NO	NO	NO	YES	NO	NO
Tagwireyi, 2001 [79]	NO	NO	YES	YES	YES	NO	NO	YES	NO	YES
Sharma, 2004 [80]	NO	NO	YES	YES	YES	YES	NO	YES	NO	YES
Sotelo, 2007 [78]	NO	NO	YES	YES	YES	NO	NO	YES	NO	NO
Michael, 2011 [74]	NO	NO	YES	YES	NO	NO	NO	YES	NO	NO
Nikfar, 2011 [75]	NO	NO	NO	YES	YES	NO	NO	YES	NO	YES
Hasan, 2012 [71]	NO	NO	YES	YES	YES	YES	NO	YES	NO	YES
Saz-Parkinson, 2012 [62]	NO	NO	YES	YES	NO	NO	NO	YES	NO	NO
Qureshi, 2012 [76]	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO
Vaiyapuri, 2013 [81]	NO	NO	YES	YES	YES	NO	NO	YES	NO	NO
Narra, 2014 [61]	NO	NO	YES	YES	YES	NO	NO	YES	NO	NO
Gupt, 2015 [70]	NO	NO	NO	YES	NO	NO	NO	YES	NO	NO
Darryl, 2016 [69]	NO	NO	YES	YES	YES	NO	NO	YES	NO	YES
Gampini, 2016 [66]	NO	NO	YES	YES	YES	NO	NO	YES	NO	NO
Meena, 2016 [73]	NO	NO	NO	YES	NO	NO	NO	YES	NO	NO

Author, year	Specified perspective	Specified Epidemiologic approach	Specified study question	Specified Resource quantification method	Specified Healthcare resource valuation	Specified Productivity loss valuation	Estimated Intangible cost	Description of statistical analyses	Performed sensitivity analysis	Reporting of detailed cost components
Ramanath, 2016 [77]	NO	NO	NO	YES	YES	NO	NO	YES	NO	NO
Bachan, 2017 [68]	NO	NO	YES	YES	NO	NO	NO	NO	NO	YES
Fowler, 2017 [59]	NO	NO	YES	YES	YES	NO	NO	YES	NO	NO
Kasturiratne, 2017 [3]	NO	NO	YES	YES	YES	YES	NO	YES	NO	YES
Mashhadi, 2017 [67]	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES
Curran-Sills, 2018 [58]	NO	NO	YES	YES	YES	NO	NO	YES	NO	NO
Schioldann, 2018 [42]	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Kasilo, 1993 [72]	NO	NO	NO	YES	NO	NO	NO	YES	NO	NO
No. of fulfilling studies	1	1	16	22	14	4	0	20	0	8
Percentage	4.35%	4.35%	69.57%	95.65%	60.87%	17.39%	0.00%	86.96%	0.00%	34.78%

Table A7 Quality assessment of included economic evaluation studies associated with snakebites.

Recommended aspects	Author, year			No. of fulfilling studies	Percentage (%)
	Habib, 2015 [63]	Hazam, 2016 [64]	Herzel, 2018 [65]		
Study question	YES	YES	YES	3	100.00
Description of intervention and comparator	YES	YES	NO	2	66.67
Measurement of effectiveness	YES	YES	NO	2	66.67
Assumption of costs and outcomes	YES	YES	YES	3	100.00
Currency and price data	YES	NO	YES	2	66.67
Choice of model	YES	YES	YES	3	100.00
Perspective	YES	YES	YES	3	100.00
Time horizon	YES	YES	YES	3	100.00
Discount rate	YES	YES	YES	3	100.00
Calculated and reported ICER	YES	YES	YES	3	100.00
Sensitivity analysis	YES	YES	YES	3	100.00
Disclosed funding source	YES	YES	YES	3	100.00

Table A8 Cost estimates per episode of snakebite in US$ 2018.

Region/ Income economies	Country	Author, year	Perspective	Average cost per episode of snakebite (US$ 2018)			
				Direct medical costs	Direct non-medical costs	Indirect costs	Total costs
East Asia and Pacific							
Lower-middle	Myanmar	Schioldann, 2018 [42]	Patient	230.80		NR	230.80
Latin America and the Caribbean							
High	Spain	Saz-Parkinson, 2012 [62]	Health system	2339.40	NR	NR	2339.40
Middle East and North Africa							
Upper-middle	Guyana	Bachan, 2017 [68]	Societal	1090.20	1170.91	NR	2261.11
Upper-middle	Mexico	Sotelo, 2008 [78]	Provider	962.34	NR	NR	962.34
Upper-middle	Iran	Nikfar, 2011 [75]	Health system	NR	NR	NR	NR
Upper-middle	Iran	Mashhadi, 2017 [67]	Societal	494.23	546.04	180.63	1220.90
North America							
High	Canada	Curran-Sills, 2018 [58]	Provider	25553.86	NR	NR	25553.86
High	United States	Lopoo, 1998 [60]	Provider	3592.27	NR	NR	3592.27
High	United States	Narra, 2014 [61]	Societal	1296.74	NR	NR	1296.74
High	United States	Fowler, 2017 [59]	Provider	40493.10	NR	NR	40493.10

Region/ Income economies	Country	Author, year	Perspective	Average cost per episode of snakebite (US$ 2018)			
				Direct medical costs	Direct non-medical costs	Indirect costs	Total costs
South Asia							
Upper-middle	Sri Lanka	Kasturiratne, 2017 [3]	Societal	123.60	19.32	26.20	169.12
Lower-middle	Bangladesh	Hasan, 2012 [71]	Societal	106.59	66.89	19.68	193.16
Lower-middle	India	Vaiyapuri, 2013 [81]	Patient	0.00 - 6034.10		34.48 - 1724.03	NR
Lower-middle	India	Gupt, 2015 [70]	Provider	80.91	NR	NR	80.91
Lower-middle	India	Meena, 2016 [73]	Health system	176.37	NR	NR	176.37
Lower-middle	India	Ramanath, 2016 [77]	Provider	522.47	NR	NR	522.47
Lower-middle	Pakistan	Qureshi, 2013 [76]	Health system	78.85	NR	NR	78.85
Low	Nepal	Sharma, 2004 [80]	Patient	68.98	11.76	41.30	122.02
Sub-Saharan Africa							
Upper-middle	South Africa	Darryl, 2016 [69]	Health system	1295.63	NR	NR	1295.63
Lower-middle	Nigeria	Michael, 2011 [74]	Societal	8.44	NR	NR	8.44
Lower-middle	Zimbabwe	Kasilo, 1993 [72]	Provider	4.32	NR	NR	4.32
Lower-middle	Zimbabwe	Tagwireyi, 2001 [79]	Provider	4.33	NR	NR	4.33
Low	Burkina Faso	Gampini, 2016 [66]	Patients	NR	NR	NR	NR

Abbreviation: NR – Not reported

Table A9 Summary of findings of included economic evaluation studies associated with snakebites.

Author, year	Country	Sequalae (rate)	Currency, year	Antivenom price/dose (US$ 2018)	Antivenom price/course (US$ 2018)	Disability weight	Reported outcome	GDP per capita (US$ 2018)	Threshold used	ICER (US$ 2018)	Study conclusion	Most sensitive parameters
Habib, 2015 [63]	Nigeria	- Amputation (3%) - Blindness (0.01%)* - PTSD (20%)*	US$, 2015	US$87.68	US$87.68	- Amputation 0.102 - Blindness 0.552* - PTSD 0.105*	DALYs, Deaths	US$1090.70	1 GDP per capita	- US$1634.40 per Death averted - US$69.87 per DALY averted	Very cost-effective	- Costs of antivenom - Proportion of envenoming due to carpet viper, - Probability of dying following carpet viper envenoming
Hamza, 2016 [64]	16 West Africa countries	- Amputation (3%) - Blindness (0.01%)* - PTSD (20%)*	US$, 2015	US$139.73	US$139.73	- Amputation 0.102 - Blindness 0.552* - PTSD 0.105*	DALYs, Deaths	US$351.60 to US$2504.14	1 GDP per capita	- US$1823.77 to US$5666.75 per Death averted - US$75.80 to US$256.62 per DALY averted	Very cost-effective	- Costs of antivenom - Antivenom effectiveness against non-carpet viper envenoming - Probability of dying following non-carpet viper envenoming
Herzel, 2018 [65]	India	- Amputation (25%)	US$, 2015	US$10.01	US$300.44	- Below-knee amputation 0.164 - Finger/toe amputation 0.02	DALYs	US$1569.72	1 GDP per capita	- US$71.16 per DALYs averted	Very cost-effective	- Proportion of severe envenomation - Cost of severe envenomation - Proportion of patients reaching treatment facilities

Note: * - included in model in sensitivity analysis. Abbreviations: DALYs – Disability-Adjusted Life Years, GDP – Gross Domestic Product, ICER – Incremental Cost-Effectiveness Ratio, PTSD – Post-Traumatic Stress Disorder

APPENDIX B ESTIMATING ECONOMIC AND DISEASE BURDEN OF SNAKEBITE IN ASEAN COUNTRIES USING A DECISION ANALYTIC MODEL

Methods B1 Justification of input parameters.

Country-specific input parameters were sought from various sources, including published literature, data from the country's Ministry of Health, unpublished data, and expert opinion. When parameters were available from multiple sources, the apply value were selected based on the most recent evidence and the representativeness of the data that covered the highest number of subjects in the following order of priority; (1) Published community-based national data, (2) Published hospital-based national data, (3) Unpublished national data (community/hospital based, (4) Published community-based subnational data, (5) Unpublished community based subnational data, (6) Published subnational hospital data, and (7) Expert opinion.[11] When data of the country were not available, the parameters were borrowed from other countries.

An in-depth interview with key informants who were experts in snakebite in ASEAN countries was also conducted to confirm the retrieved parameters, refer to potential sources of information that might not be publicly available, and ask for their opinion when data were not available. The input parameters were validated through triangulation of data from literature and interview. Justification of input parameters for each country was described below.

Malaysia

Incidence of snakebite

- Number of snakebite patients treated in healthcare facilities in 2014[18] = 3,006 cases
- Number of population in 2014[16] = 29,866,559 people
- Number of vulnerable people living within the range of one or more medically important venomous snake species, for which no effective therapy exists, and with a travel time of more than 3 hours from urban centers in 2017[13] = 1,790,903 people
- Number of population in 2017[16] = 31,105,028 people
- Proportion of people who could not access to healthcare facilities and would seek traditional healers in 2017 = $\frac{1,790,903}{31,105,028}$ = 0.0576
- Number of people who could not access to healthcare facilities and would seek traditional healers in 2014 = 0.0576 x 29,866,559 = 1,719,597 people
- Number of people who could access to healthcare facilities = 31,105,028 – 1,719,597 = 28,146,962 people
- Incidence of snakebite patients treated in healthcare facilities in 2014 = $\frac{3,006}{28,146,962}$ = 10.68 cases per 100,000 population per year
- Number of snakebite victims who could not access to healthcare facilities and sought traditional healers in 2014 = 0.0001068 x 1,719,597 = 184 cases
- Total number of snakebite victims in 2014 = 3,006 + 184 = 3,190 cases

Treatment seeking behavior

- Total number of snakebite victims in 2014 = 3,190 cases
- Number of snakebite patients treated in healthcare facilities in 2014[18] = 3,006 cases

- Number of snakebite victims who could not access to healthcare facilities and sought traditional healer in 2014 = 184 cases

- Proportion of snakebite victims in healthcare facilities who sought traditional healer first then switched to conventional treatment (unpublished data) = $\frac{1}{268}$ = 0.0037 (95%CI 0.0001 to 0.0206)

- Number of snakebite victims who sought traditional healer first then switched to conventional treatment in 2014 = 0.0037 x 3,006 = 11 cases

- Number of snakebite victims who sought conventional treatment only = 3,006 – 11 = 2,995

- Proportion of snakebite victims who sought conventional treatment only = $\frac{2,995}{3,190}$ = 0.939

- Proportion of snakebite victims who sought traditional healer first = 1 – 0.939 = 0.061

- Proportion of snakebite victims who sought traditional healer first then switched to conventional treatment = $\frac{11}{195}$ = 0.058

- Proportion of snakebite victims who sought only traditional healer = 1 – 0.058 = 0.942

Mortality of snakebite

- Probability of systemic envenoming needed antivenom treatment in 2017[86] = $\frac{13}{92}$ = 0.1413 (95%CI; 0.077 to 0.230)

- Number of patients with systemic envenomings treated in healthcare facilities in 2014 = 3,006 x 0.1413 = 421 cases

- Number of deaths from systemic envenoming treated in healthcare facilities in 2014[18] = 1 death

- Probability of death of systemic envenoming treated in healthcare facilities in 2014 = $\frac{1}{421}$ = 0.002 (95%CI 0.001 to 0.013)

- Relative risk of death in snakebite envenoming without antivenom treatment compared to with antivenom treatment[104]= 2.33

- Probability of death of systemic envenoming treated without antivenom treatment in healthcare facilities in 2014 = 0.002 x 2.33 = 0.005

- Probability of death of systemic envenoming not treated in healthcare facilities in 2014 = 0.013 x 2.33 = 0.030

Hospitalization costs for snakebite victims with systemic envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, tetanus toxoid, and wound dressing.

Item	Quantity	Price (MYR)	Cost (MYR)
Hospitalization costs, total			**3,111.03**
Inpatient department services	**6.1**[86]	**109.96**[111]	**666.55**
Laboratory for systemic envenoming, average			**1,907.74**
Proportion of hematotoxic to neurotoxic snakes	6:4*		
Laboratory for systemic envenoming, hematotoxic snakes			2,622.46
• Coagulation profile	12*	126.45[111]	1,517.40
• Complete blood count	12*	43.98[111]	527.79
• Urine analysis	2*	32.99[111]	65.97
• Electrolyte	3*	11.00[111]	32.99
• Blood urea nitrogen	4*	11.00[111]	43.98
• Creatinine	1*	38.48[111]	38.48
• Electrocardiogram	1*	87.97[111]	87.97
• Creatine kinase	12*	21.99[111]	263.90
• Bacterial culture	1*	43.98[111]	43.98
Laboratory for systemic envenoming, neurotoxic snakes			835.67
• Coagulation profile	1*	126.45[111]	126.45
• Complete blood count	3*	43.98[111]	131.95
• Urine analysis	2*	32.99[111]	65.97
• Electrolyte	3*	11.00[111]	32.99
• Blood urea nitrogen	4*	11.00[111]	43.98
• Creatinine	1*	38.48[111]	38.48
• Electrocardiogram	1*	87.97[111]	87.97
• Creatine kinase	12*	21.99[111]	263.90
• Bacterial culture	1*	43.98[111]	43.98
Tetanus toxoid			**3.50**
• Tetanus toxoid	1*	3.15[143]	3.15
• Needle	1*	0.04[144]	0.04
• Syringe	1*	0.31[144]	0.31
Wound dressing	**6.1**[86]	**87.97**[145]	**533.24**

Note: * – expert opinion; MYR – Malaysian Ringgit where 4.14 MYR = 1 United States Dollar.

Hospitalization costs for victims without snakebite envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, tetanus toxoid, and wound dressing.

Item	Quantity	Price (MYR)	Cost (MYR)
Hospitalization costs, total			619.25
Inpatient department services	1*	109.96[111]	109.96
Laboratory for snakebite without systemic envenoming			417.83
• Coagulation profile	1*	126.45[111]	126.45
• Complete blood count	1*	43.98[111]	43.98
• Urine analysis	1*	32.99[111]	32.99
• Electrolyte	1*	11.00[111]	11.00
• Blood urea nitrogen	1*	11.00[111]	11.00
• Creatinine	1*	38.48[111]	38.48
• Electrocardiogram	1*	87.97[111]	87.97
• Creatine kinase	11*	21.99[111]	21.99
• Bacterial culture	1*	43.98[111]	43.98
Tetanus toxoid			3.50
• Tetanus toxoid	1*	3.15[143]	3.15
• Needle	1*	0.04[144]	0.04
• Syringe	1*	0.31[144]	0.31
Wound dressing	1*	87.97[145]	87.97

Note: * – expert opinion; MYR – Malaysian Ringgit where 4.14 MYR = 1 United States Dollar.

Antivenom treatment costs

- Antivenom treatment costs comprise of antivenom, and antivenom administration.

Item	Quantity	Price (MYR)	Cost (MYR)
Antivenom treatment costs, total			4,131.41
Antivenom, average			4,109.06
Proportion of hematotoxic to neurotoxic snakes	6:4*		
Antivenom, hematotoxic snakes	4*	790.20[118]	3,160.81
Antivenom, neurotoxic snakes	7*	790.20[118]	5,531.43
Antivenom administration			22.35
• Needle	1*	0.04[144]	0.04
• Syringe	1*	0.31[144]	0.31
• 0.9% NaCl 100 mL	1*	2.31[118]	2.31
• IV set	1*	19.69[144]	19.69

Note: * – expert opinion; MYR – Malaysian Ringgit where 4.14 MYR = 1 United States Dollar.

Adverse reaction management costs

Item	Quantity	Price (MYR)	Cost (MYR)
Adverse reaction management costs, total			16.29
• Chlorpheniramine	1*	2.71[118]	2.71
• Adrenaline	1*	3.64[118]	3.64
• Hydrocortisone	1*	8.89[118]	8.89
• Needle	3*	0.04[144]	0.13
• Syringe	3*	0.31[144]	0.92

Note: * – expert opinion; MYR – Malaysian Ringgit where 4.14 MYR = 1 United States Dollar.

Thailand

Incidence of snakebite

- Number of snakebite patients treated with antivenom in 2019[89] = 5,160 cases

- Number of population in 2019[16] = 64,929,153 people

- Number of vulnerable people living within the range of one or more medically important venomous snake species, for which no effective therapy exists, and with a travel time of more than 3 hours from urban centers in 2017[13] = 77,295 people

- Number of population in 2017[16] = 69,209,858 people

- Proportion of people who could not access to healthcare facilities and would seek traditional healers in 2017 = $\frac{77,295}{69,209,858}$ = 0.00119 (95%CI 0.00118 to 0.00120)

- Number of people who could not access to healthcare facilities and would seek traditional healers in 2019 = 0.00119 x 69,209,858 = 82,886 people

- Number of people who could access to healthcare facilities = 69,209,858 – 82,886 = 69,542,696 people

- Probability of systemic envenoming required antivenom derived from meta-analysis[87,90,92-103] = 0.59 (95%CI 0.42 to 0.74)

```
            Study       |     ES    [95% Conf. Interval]
--------------------+-------------------------------------------
----
Mitrakul (1984)         |    0.9362      0.8246       0.9866
Malasit (1986)          |    0.8250      0.7238       0.9009
Hutton (1990)           |    0.7083      0.4891       0.8738
Mitrakul (1991)         |    0.6250      0.2449       0.9148
Viravan  (1992)         |    0.1923      0.1682       0.2183
Buranasin (1993)        |    0.3832      0.2908       0.4822
Rojnuckarin (1996)      |    0.7122      0.6551       0.7647
Rojnuckarin (1998)      |    0.7085      0.6505       0.7619
Rojnuckarin (1999)      |    0.1304      0.0494       0.2626
Wongtongkam  (2005)     |    0.8880      0.8192       0.9374
Thiansookon  (2008)     |    0.6649      0.6151       0.7121
Chotenimitkhun  (2008)  |    0.3292      0.2705       0.3922
Laohawiriyakamol (2011)|    0.3793      0.2551       0.5163
Pingpit (2012)          |    0.1237      0.0656       0.2061
Tongpoo (2018)          |    0.8205      0.7172       0.8983
Thumtecho (2020)        |    0.6389      0.5805       0.6944
--------------------+-------------------------------------------
----
Random pooled  ES       |    0.5928      0.4231       0.7429
--------------------+-------------------------------------------
----
LR test: RE vs FE Model chi^2 =   765.8970 (d.f. =  14) p =
0.0000
  Estimate of between-study variance Tau^2 =     1.5260
  Test of ES=0 : z=     1.0732 p =     0.2832
```

- Number of snakebite patients treated in healthcare facilities = = $\frac{5,160}{0.5928}$ = 8,704 cases

- Incidence of snakebite patients treated in healthcare facilities in 2019 = $\frac{8,704}{64,929,153}$ = 12.52 cases per 100,000 population per year

- Number of snakebite victims who could not access to healthcare facilities and sought traditional healers in 2019 = 0.0001252 x 82,886 = 11 cases

- Total number of snakebite victims in 2019 = 8,704 + 11 = 8,715 cases

Treatment seeking behavior

- Proportion of snakebite victims in healthcare facilities who sought traditional healer first then switched to conventional treatment derived from meta-analysis[90-92] = 0.0339 (95%CI 0.0105 to 0.1039)

```
            Study     |     ES    [95% Conf. Interval]
----------------------+-----------------------------------------------
----
Mitrakul (1984)       |    0.0000      0.0000       0.0755
Wongtongkam (2005)    |    0.0235      0.0029       0.0824
Wongtongkam (2005)    |    0.0578      0.0311       0.0968
----------------------+-----------------------------------------------
----
Random pooled  ES     |    0.0339      0.0105       0.1039
----------------------+-----------------------------------------------
----
LR test: RE vs FE Model chi^2 =     0.2354 (d.f. =  1) p =     0.3138
  Estimate of between-study variance Tau^2 =     0.1679
  Test of ES=0 : z=    -5.4922 p =     0.0000
```

- Number of snakebite victims who sought traditional healer first then switched to conventional treatment in 2019 = 0.0339 x 8,704 = 295 cases

- Number of snakebite victims who sought conventional treatment only = 8,704 – 295 = 8,409

- Proportion of snakebite victims who sought conventional treatment only = $\frac{8,409}{8,715}$ = 0.965

- Proportion of snakebite victims who sought traditional healer first = 1 – 0.965 = 0.035

- Proportion of snakebite victims who sought traditional healer first then switched to conventional treatment = $\frac{295}{305}$ = 0.034

- Proportion of snakebite victims who sought only traditional healer = 1 – 0.034 = 0.966

Mortality of snakebite

- Probability of death of systemic envenoming treated with antivenom in healthcare facilities in 2014 to 2018[105] = $\frac{20}{25,747}$ = 0.0008 (95%CI 0.0005 to 0.0012)

- Relative risk of death in snakebite envenoming without antivenom treatment compared to with antivenom treatment[104] = 2.33

- Probability of death of systemic envenoming treated without antivenom treatment in healthcare facilities = 0.0008 x 2.33 = 0.0018

- Probability of death of systemic envenoming not treated in healthcare facilities = 0.0012 x 2.33 = 0.0028

Amputation following snakebite envenoming

- Probability of bitten by *Naja kaouthia* in 2019[89] = $\frac{578}{5,160}$ = 0.112

- Probability of digit amputation following *Naja kaouthia* bite derived from meta-analysis[87,90,91,95,99,102,106-109] = 0.003 (95%CI 0.001 to 0.012)

```
               Study     |     ES    [95% Conf. Interval]
-------------------------+-------------------------------------------
------
Trishnananda (1979)      |    0.0000      0.0000       0.1684
Mitrakul (1984)          |    0.0000      0.0000       0.2180
Malasit (1986)           |    0.0000      0.0000       0.0451
Looareesuwan (1988)      |    0.0000      0.0000       0.0771
Viravan (1992)           |    0.0000      0.0000       0.0435
Buranasin (1993)         |    0.0000      0.0000       0.0974
Pochanugool (1998)       |    0.0000      0.0000       0.6024
Dumavibhat (1997)        |    0.0000      0.0000       0.0672
Pochanugool (1997)       |    0.0000      0.0000       0.0528
Pochanugool (1997)       |    0.0000      0.0000       0.0430
Wongtongkam (2005)       |    0.0118      0.0003       0.0638
Thiansookon (2008)       |    0.0000      0.0000       0.1089
Laohawiriyakamol (2011)  |    0.0172      0.0004       0.0924
-------------------------+-------------------------------------------
------
Random pooled  ES        |    0.0030      0.0008       0.0120
-------------------------+-------------------------------------------
------
LR test: RE vs FE Model chi^2 =     0.0000 (d.f. =  11) p =
.
  Estimate of between-study variance Tau^2 =     0.0000
  Test of ES=0 : z=    -8.1931 p =     0.0000
```

- Probability of digit amputation following snakebite = 0.112 x 0.003 = 0.0003 (95%CI 0.0001 to 0.0013)

- Probability of limb amputation following snakebite = 0.00

Hospitalization costs for snakebite victims with systemic envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, tetanus toxoid, and wound dressing.

Item	Quantity	Price (THB)	Cost (THB)
Hospitalization costs, total			9,992.25
Inpatient department services	3.5	1,948.57[117]	6,816.09
Laboratory for systemic envenoming, average			2,385.66
• Venous clotting time	7*	59.64[117]	417.49
• Prothrombin time	12*	90.05[117]	1,080.56
• Complete blood count	7*	59.64[117]	417.49
• Urine analysis	1*	74.84[117]	74.84
• Electrolyte	1*	120.45[117]	120.45
• Blood urea nitrogen	1*	74.84[117]	43.98
• Creatinine	1*	74.84[117]	74.84
Tetanus toxoid			54.11
• Tetanus toxoid	1*	23.71[117]	23.54
• Intramuscular drug administration	1*	30.41[117]	30.41
Wound dressing	3.5	210.52[117]	736.39

Note: * – expert opinion; THB – Thai Baht where 31.05 THB = 1 United States Dollar.

- Length of stay of victims hospitalized for systemic envenoming derived from meta-analysis[91,92,94,100,101,106,108] = 3.5 days (95%CI 2.6 to 4.4)

```
Meta-analysis summary                       Number of studies =     14
Random-effects model                        Heterogeneity:
Method: REML                                            tau2 =  1.7677
                                                      I2 (%) =   94.09
                                                          H2 =   16.92
```

Study	Effect Size	[95% Conf.	Interval]	% Weight
Mitrakul (1991)	1.500	1.108	1.892	11.11
Buranasin (1993)	2.300	1.849	2.751	11.03
Buranasin (1993)	2.000	-2.371	6.371	2.98
Pochanugool (1997)	10.090	1.976	18.204	1.06
Wongtongkam (2005)	5.500	-0.713	11.713	1.70
Wongtongkam (2005)	5.650	3.925	7.375	7.90
Wongtongkam (2005)	2.870	1.870	3.870	9.91
Wongtongkam (2005)	5.340	3.596	7.084	7.85
Wongtongkam (2005)	3.020	-0.371	6.411	4.22
Wongtongkam (2005)	4.350	3.076	5.624	9.17
Wongtongkam (2005)	2.150	1.895	2.405	11.26
Wongtongkam (2005)	4.330	2.154	6.506	6.70
Tongpoo (2018)	7.000	3.394	10.606	3.90
Thumtecho (2020)	3.000	2.706	3.294	11.22
theta	3.498	2.620	4.377	

```
Sorted by: _meta_id
Test of theta = 0: z = 7.81                     Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(13) = 88.18         Prob > Q = 0.0000
```

Hospitalization costs for victims without snakebite envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, tetanus toxoid, and wound dressing.

Item	Quantity	Price (THB)	Cost (THB)
Hospitalization costs, total			3,209.23
Inpatient department services	1	2,578.90[117]	2,578.90
Laboratory for snakebite without systemic envenoming			630.33
• Venous clotting time	1*	59.64[117]	59.64
• Prothrombin time	1*	90.05[117]	90.05
• Complete blood count	1*	59.64[117]	59.64
• Urine analysis	1*	74.84[117]	74.84
• Electrolyte	1*	120.45[117]	120.45
• Blood urea nitrogen	1*	74.84[117]	43.98
• Creatinine	1*	74.84[117]	74.84
Tetanus toxoid			54.11
• Tetanus toxoid	1*	23.71[117]	23.54
• Intramuscular drug administration	1*	30.41[117]	30.41
Wound dressing	1*	210.52[117]	210.52

Note: * – expert opinion; THB – Thai Baht where 31.05 THB = 1 United States Dollar.

Antivenom treatment costs

- Antivenom treatment costs comprise of antivenom, and antivenom administration.

Item	Quantity	Price (THB)	Cost (THB)
Antivenom treatment costs, total			**6,996.59**
Antivenom, average			**6,748.57**
Proportion of snakes[89]			
Antivenom, hematotoxic snakes	6*	1,000 to 1,200*	6,000 to 7,200
Antivenom, neurotoxic snakes	5 to 10*	1,000 to 1,200*	5,000 to 12,000
Antivenom administration			**248.03**
• IV set	1*	150.86[117]	150.86
• IV drug administration	2*	30.41[117]	60.81
• 0.9% NaCl 100 mL	2*	18.18[117]	36.36

Note: * – expert opinion; THB – Thai Baht where 31.05 THB = 1 United States Dollar.

Adverse reaction management costs

Item	Quantity	Price (THB)	Cost (THB)
Adverse reaction management costs, total			105.46
• Chlorpheniramine	1*	2.27[117]	2.27
• Adrenaline	1*	5.72[117]	5.72
• Dexamethasone	1*	6.25[117]	6.25
• IV drug administration	3*	30.41[117]	91.22

Note: * – expert opinion; THB – Thai Baht where 31.05 THB = 1 United States Dollar.

Indonesia

Incidence of snakebite

- Total number of snakebite victims in 2019 (expert opinion) = 135,000 cases

- Number of population in 2019[16] = 270,625,568 people

- Incidence of snakebite in 2019 = $\frac{135,000}{270,625,568}$ = 49.88 per 100,000 population per year

Treatment seeking behavior

- Proportion of snakebite victims treated in healthcare facilities (expert opinion) = 0.75

- Proportion of snakebite victims who sought only traditional treatment (expert opinion) = 1-0.75 = 0.25

- Proportion of snakebite victims in healthcare facilities who sought traditional healer first then switched to conventional treatment (expert opinion) = 0.00

Mortality of snakebite

- Proportion of snakebite envenoming treated with antivenom from 2004 to 2009[25] = $\frac{17}{42}$ = 0.40 (95%CI 0.26 to 0.57)

- Probability of death of systemic envenoming treated with antivenom treatment in healthcare facilities in 2019 (unpublished data) = $\frac{54}{587}$ = 0.09 (95%CI 0.07 to 0.12)

- Relative risk of death in snakebite envenoming without antivenom treatment compared to with antivenom treatment[104]= 2.33

- Probability of death of systemic envenoming treated without antivenom treatment in healthcare facilities = 0.09 x 2.33 = 0.21

- Probability of death of systemic envenoming not treated in healthcare facilities = 0.12 x 2.33 = 0.28

Amputation due to snakebite envenoming

- Probability of amputation due to snakebite envenoming in 2019 (unpublished data) = $\frac{12}{587}$ = 0.02 (95%CI 0.01 to 0.04)

- Proportion of digit amputation to limb amputation (expert opinion) = 0.50

- Probability of limb amputation due to snakebite envenoming in 2019 (unpublished data) = 0.02 x 0.50 = 0.01 (95%CI 0.005 to 0.018)

Hospitalization costs for snakebite victims with systemic envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, and tetanus toxoid.

Item	Quantity	Price (IDR)	Cost (IDR)
Hospitalization costs, total			14,253,228
Inpatient department services including laboratory based on diagnosis group of non-infectious bacteria for region 1 / class 3 / secondary hospital	6.1[86]	2,326,565*	14,103,637
Tetanus toxoid			149,591
• Tetanus toxoid	1*	146,800[112]	146,800
• Needle	1*	734[144]	734
• Syringe	1*	2,056[144]	2,056

Note: * – expert opinion; IDR – Indonesian Rupee where 14,147.67 IDR = 1 United States Dollar.

Hospitalization costs for victims without snakebite envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, and tetanus toxoid.

Item	Quantity	Price (IDR)	Cost (IDR)
Hospitalization costs, total			2,476,156
Inpatient department services including laboratory based on diagnosis group of non-infectious bacteria for region 1 / class 3 / secondary hospital	1	2,326,565*	2,326,565
Tetanus toxoid			149,591
• Tetanus toxoid	1*	146,800[112]	146,800
• Needle	1*	734[144]	734
• Syringe	1*	2,056[144]	2,056

Note: * – expert opinion; IDR – Indonesian Rupees where 14,147.67 IDR = 1 United States Dollar.

Antivenom treatment costs

- Antivenom treatment costs comprise of antivenom, and antivenom administration.

Item	Quantity	Price (IDR)	Cost (IDR)
Antivenom treatment costs, total			**10,931,952**
Antivenom[112]			**10,892,732**
Antivenom administration			**39,220**
• Needle	1*	734[144]	734
• Syringe	1*	2,056[144]	2,056
• 0.9% NaCl 100 mL	1*	7,197[144]	7,197
• IV set	1*	36,429[144]	36,429

Note: * – expert opinion; IDR – Indonesian Rupee where 14,147.67 IDR = 1 United States Dollar.

Adverse reaction management costs

Item	Quantity	Price (IDR)	Cost (IDR)
Adverse reaction management costs, total			**54,373**
• Chlorpheniramine	1*	14,000[112]	14,000
• Adrenaline	1*	18,000[112]	18,000
• Dexamethasone	1*	14,000[112]	14,000
• Needle	3*	734[144]	2,203
• Syringe	3*	2,056[144]	6,169

Note: * – expert opinion; IDR – Indonesian Rupee where 14,147.67 IDR = 1 United States Dollar.

Philippines

Treatment seeking behavior

- Proportion of snakebite victims seeking only conventional treatment (expert opinion) = 0.00

- Proportion of snakebite victims treated in healthcare facilities in 1987[88] = $\frac{2}{24}$ =0.083 (95%CI 0.10 to 0.27) then applied higher estimate 0.27 for base-case analysis

- Proportion of snakebite victims in healthcare facilities who sought traditional healer first then switched to conventional treatment[88] = 0.27

- Proportion of snakebite victims who sought only traditional treatment = 1-0.27 = 0.73

Incidence of snakebite

- Number of snakebite patients treated in healthcare facility in 2019 (unpublished data) = 157 per 4,700,000 population

- Incidence of snakebite patients treated in healthcare facilities in 2019 = $\frac{157}{4,700,000}$ = 3.34 per 100,000 population per year

- Number of population in 2019[16] = 108,116,615 people

- Number of snakebite patients treated in healthcare facilities in 2019 = $\frac{3.34}{100,000}$ x 108,116,615 = 3,612 cases

- Total number of snakebite victims = $\frac{3,612}{0.27}$ x 108,116,615 = 13,377 cases

- Incidence of snakebite in 2019 = $\frac{13,377}{108,111,615}$ = 12.37 per 100,000 population per year

Mortality of snakebite

- Proportion of snakebite envenoming treated with antivenom from 2018 to 2019 (unpublished data) = $\frac{45}{279}$ = 0.1613

- Probability of death of systemic envenoming treated with antivenom treatment in healthcare facilities from 2018 to 2019 (unpublished data) = $\frac{3}{45}$ = 0.067 (95%CI 0.014 to 0.183)

- Relative risk of death in snakebite envenoming without antivenom treatment compared to with antivenom treatment[104]= 2.33

- Probability of death of systemic envenoming treated without antivenom treatment in healthcare facilities = 0.067 x 2.33 = 0155

- Probability of death of systemic envenoming not treated in healthcare facilities = 0.12 x 2.33 = 0.426

Amputation due to snakebite envenoming

- Probability of amputation due to snakebite envenoming (expert opinion) = 0.01

- Proportion of digit amputation to limb amputation (expert opinion) = 0.70:0.30

- Probability of digit amputation due to snakebite envenoming = 0.01 x 0.70 = 0.007

- Probability of limb amputation due to snakebite envenoming = 0.01 x 0.30 = 0.003

Hospitalization costs for snakebite victims with systemic envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, and tetanus toxoid.

Item	Quantity	Price (PHP)	Cost (PHP)
Hospitalization costs, total			21,135
Inpatient department services including laboratory	6.1[86]	3,479[113]	21,088
Tetanus toxoid			47
• Tetanus toxoid	1*	36[114]	36
• Needle	1*	1[114]	1
• Syringe	1*	10[114]	10

Note: * – expert opinion; PHP – Philippines Peso where 51.80 PHP = 1 United States Dollar.

Hospitalization costs for victims without snakebite envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, and tetanus toxoid.

Item	Quantity	Price (PHP)	Cost (PHP)
Hospitalization costs, total			3,526
Inpatient department services including laboratory	1	3,479[113]	3,479
Tetanus toxoid			47
• Tetanus toxoid	1*	36[114]	36
• Needle	1*	1[114]	1
• Syringe	1*	10[114]	10

Note: * – expert opinion; PHP – Philippines Peso where 51.80 PHP = 1 United States Dollar.

Antivenom treatment costs

- Antivenom treatment costs comprise of antivenom, and antivenom administration.

Item	Quantity	Price (PHP)	Cost (PHP)
Antivenom treatment costs, total			16,161
Antivenom	10*	1,600*	16,000
Antivenom administration			161
• Needle	1*	1[114]	1
• Syringe	1*	10[114]	10
• 0.9% NaCl 100 mL	2*	60[114]	120
•	2*	60[114]	120
• IV set	1*	30[114]	30

Note: * – expert opinion; PHP – Philippines Peso where 51.80 PHP = 1 United States Dollar.

Adverse reaction management costs

Item	Quantity	Price (PHP)	Cost (PHP)
Adverse reaction management costs, total			230
• Diphenhydramine	1*	23[114]	23
• Adrenaline	1*	24[114]	24
• Hydrocortisone	1*	150[114]	150
• Needle	3*	1[114]	4
• Syringe	3*	10[114]	29

Note: * – expert opinion; PHP – Philippines Peso where 51.80 PHP = 1 United States Dollar.

Vietnam

Incidence of snakebite

- Incidence of snakebite patients treated in healthcare facilities in 2017[38] = 20.98 cases per 100,000 population

- Total incidence of snakebite victims in 2017[38] = 48.46 cases per 100,000 population

- Proportion of snakebite victims treated in healthcare facilities in 2017[38]= $\frac{20.98}{48.46}$ =0.43 (95%CI 0.29 to 0.59)

Treatment seeking behavior

- Proportion of snakebite victims seeking only conventional treatment (expert opinion) = 0.00

- Proportion of snakebite victims in healthcare facilities who sought traditional healer first then switched to conventional treatment[38] = 0.43

- Proportion of snakebite victims who sought only traditional treatment = 1-0.43 = 0.57

Mortality of snakebite

- Probability of death of systemic envenoming treated with antivenom in healthcare facilities (unpublished data) = $\frac{15}{1,000}$ = 0.015 (95%CI 0.008 to 0.025)

- Relative risk of death in snakebite envenoming without antivenom treatment compared to with antivenom treatment[104]= 2.33

- Probability of death of systemic envenoming treated without antivenom treatment in healthcare facilities = 0.015 x 2.33 = 0.035

- Probability of death of systemic envenoming not treated in healthcare facilities = 0.025 x 2.33 = 0.057

Hospitalization costs for snakebite victims with systemic envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, and tetanus toxoid.

Item	Quantity	Price (VND)	Cost (VND)
Hospitalization costs, total			3,922,215
Inpatient department services including laboratory	6.1[86]	647,017[116]	3,981,731
Tetanus toxoid			59,515
• Tetanus toxoid	1*	42,049*	42,049
• Needle	1*	2,417*	2,417
• Syringe	1*	15,049*	15,049

Note: * – expert opinion; VND – Vietnamese Dong where 23,050.24 VND = 1 United States Dollar.

Hospitalization costs for victims without snakebite envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, and tetanus toxoid.

Item	Quantity	Price (VND)	Cost (VND)
Hospitalization costs, total			706,532
Inpatient department services including laboratory	1*	647,017[116]	647,017
Tetanus toxoid			59,515
• Tetanus toxoid	1*	42,049*	42,049
• Needle	1*	2,417*	2,417
• Syringe	1*	15,049*	15,049

Note: * – expert opinion; VND – Vietnamese Dong where 23,050.24 VND = 1 United States Dollar.

Antivenom treatment costs

- Antivenom treatment costs comprise of antivenom, and antivenom administration.

Item	Quantity	Price (VND)	Cost (VND)
Antivenom treatment costs, total			1,565,316
Antivenom, average*			1,491,486
Antivenom administration			73,830
• Needle	1*	2,417*	2,417
• Syringe	1*	15,049*	15,049
• 0.9% NaCl 100 mL	2*	23,370*	46,741
• IV set	1*	27,089*	27,089

Note: * – expert opinion; VND – Vietnamese Dong where 23,050.24 VND = 1 United States Dollar.

Adverse reaction management costs

Item	Quantity	Price (VND)	Cost (VND)
Adverse reaction management costs, total			118,703
• Chlorpheniramine	1*	24,878*	24,878
• Adrenaline	1*	23,813*	23,813
• Dexamethasone	1*	17,705*	17,705
• Needle	3*	2,417*	7250
• Syringe	3*	15,049*	45,148

Note: * – expert opinion; VND – Vietnamese Dong where 23,050.24 VND = 1 United States Dollar.

Lao PDR

Incidence of snakebite

- Total incidence of snakebite in 2019 (expert opinion) = 200.00 per 100,000 population per year

- Number of population in 2019[16] = 7,169,455 people

- Total number of snakebite victims = $\frac{200.00}{100,000}$ x 7,169,455 = 14,339 cases

Treatment seeking behavior

- Proportion of snakebite victims seeking only conventional treatment (expert opinion) = 0.00

- Proportion of snakebite victims treated in healthcare facilities (expert opinion) = 0.10

- Proportion of snakebite victims in healthcare facilities who sought traditional healer first then switched to conventional treatment = 0.10

- Proportion of snakebite victims who sought only traditional treatment = 1-0.10 = 0.90

Mortality of snakebite

- Probability of systemic envenoming needed antivenom treatment in 2014[36] = $\frac{43}{158}$ = 0.27 (95%CI 0.20 to 0.35)

- Probability of death of systemic envenoming treated in healthcare facilities in 2014[36] = $\frac{2}{43}$ = 0.05 (95%CI 0.01 to 0.16)

- Relative risk of death in snakebite envenoming without antivenom treatment compared to with antivenom treatment[104]= 2.33

- Probability of death of systemic envenoming treated without antivenom treatment in healthcare facilities = 0.05 x 2.33 = 0.11

- Probability of death of systemic envenoming not treated in healthcare facilities = 0.16 x 2.33 = 0.37

Amputation due to snakebite envenoming

- Probability of digit amputation due to snakebite envenoming in 2014[36] = $\frac{2}{43}$ = 0.05 (95%CI 0.01 to 0.16)

- Probability of limb amputation due to snakebite envenoming in 2014[36] = $\frac{1}{43}$ = 0.02 (95%CI 0.001 to 0.12)

Hospitalization costs for snakebite victims with systemic envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, tetanus toxoid, and wound dressing.

Item	Quantity	Price (LAK)	Cost (LAK)
Hospitalization costs, total			**3,233,043**
Inpatient department services	**6.1**[86]	**90,000**[*]	**545,580**
Laboratory for systemic envenoming, average			**2,301,333**
• Coagulation profile	7[*]	52,667[*]	368,667
• Complete blood count	4[*]	43,667[*]	174,667
• Urine analysis	6[*]	61,000[*]	366,000
• Electrolyte	6[*]	96,000[*]	576,000
• Blood urea nitrogen	6[*]	48,000[*]	288,000
• Creatinine	6[*]	44,000[*]	264,000
• Creatine kinase	6[*]	44,000[*]	264,000
Tetanus toxoid			**22,410**
• Tetanus toxoid	1[*]	15,833[*]	15,833
• Needle	1[*]	910[*]	910
• Syringe	1[*]	5,667[*]	5,667
Wound dressing	**6.1**[86]	**60,000**[*]	**363,720**

Note: * – expert opinion; LAK – Lao Kip where 8,679.41 LAK = 1 United States Dollar.

Hospitalization costs for victims without snakebite envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, tetanus toxoid, and wound dressing.

Item	Quantity	Price (LAK)	Cost (LAK)
Hospitalization costs, total			**598,077**
Inpatient department services	1*	**90,000***	**90,000**
Laboratory for snakebite without systemic envenoming			**485,667**
• Coagulation profile	2*	52,667*	105,333
• Complete blood count	2*	43,667*	87,333
• Urine analysis	1*	61,000*	61,000
• Electrolyte	1*	96,000*	96,000
• Blood urea nitrogen	1*	48,000*	48,000
• Creatinine	1*	44,000*	44,000
• Creatine kinase	1*	44,000*	44,000
Tetanus toxoid			**22,410**
• Tetanus toxoid	1*	15,833*	15,833
• Needle	1*	910*	910
• Syringe	1*	5,667*	5,667
Wound dressing	1*	**60,000***	**60,000**

Note: * – expert opinion; LAK – Lao Kip where 8,679.41 LAK = 1 United States Dollar.

Antivenom treatment costs

- Antivenom treatment costs comprise of antivenom, and antivenom administration.

Item	Quantity	Price (LAK)	Cost (LAK)
Antivenom treatment costs, total			**1,715,377**
Antivenom, average	3*	**560,334***	**1,681,000**
Antivenom administration			**34,376**
• Needle	1*	910*	910
• Syringe	1*	5,667*	5,667
• 0.9% NaCl 100 mL	2*	8,800*	17,600
• IV set	1*	10,200*	10,200

Note: * – expert opinion; LAK – Lao Kip where 8,679.41 LAK = 1 United States Dollar.

Adverse reaction management costs

Item	Quantity	Price (LAK)	Cost (LAK)
Adverse reaction management costs, total			44,697
• Diphenhydramine	1*	9,333*	9,333
• Adrenaline	1*	8,967*	8,967
• Dexamethasone	1*	6,667*	6,667
• Needle	3*	910*	2,730
• Syringe	3*	5,667*	17,000

Note: * – expert opinion; LAK – Lao Kip where 8,679.41 LAK = 1 United States Dollar.

Myanmar

Treatment seeking behavior

- Incidence of snakebite victims reported in communities in 2015[41] = 116 cases per 100,000 population (95%CI 74 to 182)

- Incidence of snakebite patients treated in healthcare facilities in 2015[41] = 44 cases per 100,000 population

- Proportion of snakebite patients treated in healthcare facilities in 2015[41] = $\frac{44}{116}$ = 0.38

- Proportion of snakebite victims treated in healthcare facilities who have sought traditional treatment before in 2015[41] = $\frac{111}{965}$ = 0.12 (95%CI 0.10 to 0.14)

- Number of snakebite patients seeking traditional treatment only in 2015[41] = $\frac{965}{0.38}$ = 2,544 cases

- Proportion of snakebite victims seeking only conventional treatment in 2015[41] = $\frac{854}{2,544}$ = 0.34

- Proportion of snakebite victims in healthcare facilities who sought traditional healer first then switched to conventional treatment in 2015[41] = $\frac{111}{1,690}$ = 0.07

- Proportion of snakebite victims who sought only traditional treatment in 2015[41] = 1-0.07 = 0.93

Incidence of snakebite

- Number of snakebite patients treated in healthcare facilities in 2019 (unpublished data from the Ministry of Health and Sports Myanmar) = 7,988 cases

- Total number of snakebite victims = $\frac{7,988}{0.38}$ = 21,059 cases

- Number of population in 2019[16] = 54,045,420 people

- Incidence of snakebite in 2019 = $\frac{21,059}{54,045,420}$ = 38.97 per 100,000 population per year

Mortality of snakebite

- Proportion of snakebite envenoming treated with antivenom in healthcare facilities 2015[41] = $\frac{762}{965}$ = 0.79 (95%CI 0.76 to 0.81)

- Number of snakebite envenoming treated with antivenom in healthcare facilities 2015[41] = 7,988 x 0.79 = 6,308 cases

- Number of deaths from snakebite envenoming treated in healthcare facilities in 2019 (unpublished data from the Ministry of Health and Sports Myanmar) = 426 deaths

- Probability of death of systemic envenoming treated with antivenom in healthcare facilities in 2019 = $\frac{426}{6,308}$ = 0.068 (95%CI 0.061 to 0.074)

- Relative risk of death in snakebite envenoming without antivenom treatment compared to with antivenom treatment[104]= 2.33

- Probability of death of systemic envenoming treated without antivenom treatment in healthcare facilities = 0.068 x 2.33 = 0.157

- Probability of death of systemic envenoming not treated in healthcare facilities = 0.074 x 2.33 = 0.172

Hospitalization costs for snakebite victims with systemic envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, and tetanus toxoid.

Item	Quantity	Price (MMK)	Cost (MMK)
Hospitalization costs, total			318,232
Inpatient department services including laboratory	6.1[86]	52,163[115]	316,212
Tetanus toxoid			2,020
• Tetanus toxoid	1*	1,900*	1,900
• Needle	1*	20*	20
• Syringe	1*	200*	200

Note: * – expert opinion; MMK – Myanmar Kyat where 1,518.26 MMK = 1 United States Dollar.

Hospitalization costs for victims without snakebite envenoming

- Hospitalization costs comprise of inpatient department services, laboratory, and tetanus toxoid.

Item	Quantity	Price (MMK)	Cost (MMK)
Hospitalization costs, total			54,183
Inpatient department services including laboratory	1*	52,163[115]	52,163
Tetanus toxoid			2,020
• Tetanus toxoid	1*	1,900*	1,900
• Needle	1*	20*	20
• Syringe	1*	100*	100

Note: * – expert opinion; MMK – Myanmar Kyat where 1,518.26 MMK = 1 United States Dollar.

Antivenom treatment costs

- Antivenom treatment costs comprise of antivenom, and antivenom administration.

Item	Quantity	Price (MMK)	Cost (MMK)
Antivenom treatment costs, total			494,883
Antivenom, average*			494,463
Antivenom administration			420
• Needle	1*	20*	20
• Syringe	1*	100*	100
• IV set	1*	300*	300

Note: * – expert opinion; MMK – Myanmar Kyat where 1,518.26 MMK = 1 United States Dollar.

Adverse reaction management costs

Item	Quantity	Price (MMK)	Cost (MMK)
Adverse reaction management costs, total			1,160
• Chlorpheniramine	1*	200*	200
• Adrenaline	1*	350*	350
• Dexamethasone	1*	250*	250
• Needle	3*	20*	60
• Syringe	3*	100*	300

Note: * – expert opinion; MMK – Myanmar Kyat where 1,518.26 MMK = 1 United States Dollar.

Methods B2 Estimation of economic and disease burden of post-traumatic stress disorder following snakebite.

Economic burden of post-traumatic stress disorder (PTSD) following snakebite was estimated as the productivity losses due to PTSD following snakebite. Productivity losses due to PTSD following snakebite were estimated by the number of absent days from work multiplied by daily income. PTSD following snakebite was assumed to last for 41.3 months which was an average duration of chronic PTSD.[129] Lost working days due to PTSD following snakebite was modelled at 36.35 days per year.[130] Thus, lost working days due to PTSD following snakebite were calculated at 125.10 days per case. Productivity losses due to PTSD was valued using a human capital approach by multiplying the time loss due to illness to daily income which was estimated based on the Gross Domestic Product (GDP) per capita of each country.[125]

Disease burden of PTSD following snakebite was estimated as years lived with disability (YLD). YLDs due to PTSD following snakebite envenoming were calculated using the template developed by WHO.[127] YLDs due to PTSD were calculated from the duration of PTSD of 41.3 months multiplied by disability weight of 0.523 for severe anxiety.[110,129]

Table B1 Input parameters for estimating economic and disease burden of snakebite in ASEAN countries.

Parameters (Distribution)	Malaysia	Thailand	Indonesia	Philippines	Vietnam	Lao PDR	Myanmar
Epidemiological parameters							
Total population, million people[16]	32	70	271	108	96	7	54
Incidence of snakebite per 100,000 population (Beta)[18,38,41,88,89]	10.7 (10.3 to 11.1)	12.52 (12.25 to 12.78)	49.9 (49.6 to 50.2)	12.4 (10.5 to 14.5)	48.5 (19.5 to 99.8)	200.0 (196.7 to 203.3)	39.0 (38.4 to 39.5)
Probability of snakebite victims seeking conventional treatment only (Beta)[13,41]	0.94 (0.93 to 0.95)	0.965 (0.961 to 0.969)	0.75	0.00	0.00	0.00	0.34 (0.32 to 0.35)
Probability of snakebite victims firstly seeking traditional treatment then switching to conventional treatment (Beta)[38,41,90-92]	0.06 (0.03 to 0.10)	0.03 (0.02 to 0.06)	0.00	0.27	0.43 (0.29 to 0.59)	0.10	0.07 (0.05 to 0.08)
Probability of systemic envenoming indicated for antivenom treatment for victims seeking conventional treatment (Beta)[25,36,38,41,86,87,90,92-103]	0.14 (0.08 to 0.23)	0.59 (0.42 to 0.74)	0.40 (0.26 to 0.57)	0.16 (0.12 to 0.21)	0.90 (0.87 to 0.93)	0.27 (0.20 to 0.35)	0.79 (0.76 to 0.81)
Probability of systemic envenoming for victims seeking traditional treatment	0.08	0.42	0.26	0.12	0.87	0.20	0.76
Probability of antivenom given to victims with systemic envenoming seeking care at the healthcare facilities*	1.00	1.00	0.12	0.77	0.83	0.33	1.00
Probability of adverse reaction following antivenom treatment (Beta)[36,37,41,87]	0.10	0.04 (0.02 to 0.07)	0.40	0.05	0.22 (0.03 to 0.60)	0.53 (0.38 to 0.69)	0.08 (0.06 to 0.10)
Probability of death in snakebite victims without systemic envenoming[25,36,38,41,86-88]	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Probability of death in systemic envenoming treated with antivenom (Beta)[18,25,36,41,104,105]	0.002 (0.001 to 0.013)	0.0008 (0.0005 to 0.0012)	0.09 (0.07 to 0.12)	0.07 (0.01 to 0.18)	0.015 (0.008 to 0.025)	0.05 (0.01 to 0.16)	0.068 (0.061 to 0.074)
Relative risk of death when antivenoms are not available (Log-normal)[104]	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)
Probability of death in systemic envenoming treated in hospital without antivenom (Beta)	0.005	0.0018	0.21	0.16	0.035	0.11	0.16
Probability of death in systemic envenoming not treated in hospital (Beta)	0.030	0.0028	0.28	0.43	0.057	0.37	0.17
Probability of digit amputation due to snakebite envenoming (Beta)[36,38,41,87,89-91,95,99,102,106-109]	0.00	0.003 (0.001 to 0.012)	0.01 (0.005 to 0.02)	0.007	0.00	0.05 (0.01 to 0.16)	0.00
Probability of limb amputation due to snakebite envenoming (Beta)[36,38,41,87,89-91,95,99,102,106-109]	0.00	0.00	0.01 (0.005 to 0.02)	0.003	0.00	0.02 (0.001 to 0.12)	0.00
Disability weight							
Disability weight for victims not indicated for antivenom treatment (Beta)[110]	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)

Parameters (Distribution)	Malaysia	Thailand	Indonesia	Philippines	Vietnam	Lao PDR	Myanmar
Disability weight for victims indicated for antivenom treatment (Beta)[110]	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)
Disability weight for digit amputation (Beta)[110]	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)
Disability weight for limb amputation (Beta)[110]	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)
Duration of disease							
Length of stay for victims not indicated for antivenom treatment, day	1	1	1	1	1	1	1
Length of stay for victims indicated for antivenom treatment (Gamma)[86,91,92,94,100,101,106,108]	6.1 (4.1 to 8.0)	3.5 (2.6 to 4.4)	6.1 (4.1 to 8.0)	6.1 (4.1 to 8.0)	6.1 (4.1 to 8.0)	6.1 (4.1 to 8.0)	6.1 (4.1 to 8.0)
Unit costs, USD							
Unit cost of hospitalization for victims not indicated for antivenom treatment (Gamma)[111-116]	150 (135 to 164)	103 (93 to 114)	175 (158 to 193)	68 (61 to 75)	31 (28 to 34)	69 (62 to 76)	36 (32 to 39)
Unit cost of hospitalization for victims not indicated for antivenom treatment (Gamma)[111-116]	751 (676 to 826)	332 (290 to 354)	1,007 (907 to 1,108)	408 (367 to 449)	173 (155 to 190)	372 (335 to 410)	210 (189 to 231)
Unit cost of antivenom treatment (Gamma)[111,112,114,117]	992 (893 to 1,091)	217 (196 to 239)	773 (695 to 850)	312 (281 to 343)	68 (61 to 75)	202 (181 to 222)	326 (293 to 359)
Unit cost of antivenom logistics costs, percentage of antivenom price[117]	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Unit cost of adverse reaction management (Gamma)[111,112,114,118]	3.9 (3.5 to 4.3)	3.4 (3.1 to 3.7)	3.8 (3.5 to 4.2)	4.4 (4.0 to 4.9)	5.1 (4.6 to 5.7)	5.1 (4.6 to 5.7)	0.76 (0.69 to 0.84)
Unit cost of digit amputation (Gamma)[117]	96 (86 to 106)	96 (86 to 106)	96 (86 to 106)	96 (86 to 106)	96 (86 to 106)	52 (47 to 57)	96 (86 to 106)
Unit cost of limb amputation (Gamma)[117]	154 (138 to 169)	154 (138 to 169)	154 (138 to 169)	154 (138 to 169)	154 (138 to 169)	158 (143 to 174)	154 (138 to 169)
Unit cost of traditional healer	0	0	0	0	0	0	0
Unit cost of transportation (Gamma)[111,119,120]	5.9 (5.3 to 6.5)	3.4 (3.1 to 3.6)	7.8 (7.0 to 8.6)	5.8 (5.2 to 6.4)	21 (19 to 23)	4.7 (4.2 to 5.1)	20 (18 to 22)
Unit cost of additional food (Gamma)[111,119,121]	2.7 (2.4 to 2.9)	1.2 (1.0 to 1.3)	2.3 (2.1 to 2.6)	2.3 (2.1 to 2.6)	6.5 (5.9 to 7.2)	2.4 (2.3 to 2.5)	3.3 (3.0 to 3.6)
Others							
Discount rate[122-124]	0.03 (0.00 to 0.05)	0.03 (0.00 to 0.06)	0.03 (0.00 to 0.06)	0.03 (0.00 to 0.06)	0.03 (0.00 to 0.06)	0.03 (0.00 to 0.06)	0.03 (0.00 to 0.06)
GDP per capita, USD[125]	11,415	7,808	4,136	3,485	2,715	2,625	1,421
GDP per capita annual growth, %[126]	0.03	0.02	0.04	0.05	0.06	0.03	0.02
Number of relatives or family members who companied snakebite victims	1	1	1	2	1	1	2

Parameters are presented as base-case value (range). Costs are presented as USD where 1 USD equals to 4.14 Malaysian Ringgits, 31.05 Thai Bahts, 14,147.67 Indonesian Rupees, 51.80 Philippine Pesos, 23,050.24 Vietnamese Dongs, 8,679.41 Lao Kips, and 1,518.26 Myanmar Kyats. *– Probability of antivenom given to victims with systemic envenoming seeking care at the healthcare facilities was determined by the number of antivenom treatments available divided by the number of snakebite victims needed antivenom treatment who sought care at the healthcare facilities.

Table B2 Estimated annual epidemiological and disease burden of snakebite in ASEAN countries.

	Incidence per 100,000	Mortality per 100,000	YLLs	YLDs for snakebite episode	YLDs for amputation
Malaysia	10.68 (10.34-11.06)	0.006 (0.001-0.019)	50 (0-151)	1 (1-3)	0
Thailand	12.52 (12.24-12.79)	0.006 (0.003-0.009)	102 (51-178)	8 (4-13)	0.21 (0.01-0.91)
Indonesia	49.88 (49.62-50.14)	3.90 (1.85-8.34)	262,302 (124,650-561,145)	149 (77-252)	437 (170-868)
Philippines	12.37 (10.59-14.59)	0.51 (0.25-1.02)	13,311 (6,624-26,641)	5 (3-8)	2 (1-3)
Vietnam	48.46 (18.14-94.35)	1.72 (0.51-4.60)	40,136 (11,869-107,679)	114 (38-258)	0
Lao PDR	200.00 (196.82-203.23)	14.04 (7.12-28.03)	24,468 (12,420-48,837)	8 (5-13)	56 (5-176)
Myanmar	38.97 (38.16-39.86)	3.97 (2.41-7.08)	50,786 (30,877-90,632)	44 (27-67)	0
Total	38.03 (32.89-45.62)	2.49 (1.19-5.32)	391,154 (186,491-835,263)	330 (154-613)	495 (175-1,049)

Estimates are presented as base-case estimates with their 95% credibility interval (in parentheses) based on probabilistic sensitivity analysis.

Abbreviations: DALYs – disability-adjusted life years; YLDs – years lived with disabilities; YLLs – years of life lost.

Table B3 Estimated annual epidemiological and disease burden of snakebite envenoming per case in ASEAN countries.

	Mortality rate	Amputation rate	DALYs per case	Direct costs per case, USD	Indirect costs per case, USD	Total costs per case, USD
Malaysia	0.004 (0.001-0.013)	-	0.11 (0.00-0.32)	1,736 (1,609-1,874)	1,649 (377-4,360)	3,386 (2,110-6,120)
Thailand	0.001 (0.000-0.001)	0.0003 (0.000-0.001)	0.02 (0.01-0.03)	564 (492-641)	297 (223-377)	861 (739-998)
Indonesia	0.213 (0.107-0.420)	0.016 (0.008-0.028)	5.30 (2.68-10.45)	929 (708-1,157)	38,867 (19,690-76,612)	39,796 (20,616-77,511)
Philippines	0.313 (0.158-0.642)	0.007 (0.004-0.008)	7.59 (3.83-15.52	240 (193-292)	46,833 (23,709-95,880)	47,072 (23,924-96,113)
Vietnam	0.040 (0.021-0.077)	-	0.98 (0.51-1.86)	156 (103-216)	6,337 (3,337-12,025)	6,493 (3,534-12,166)
Lao PDR	0.332 (0.167-0.668)	0.047 (0.007-0.115)	8.10 (4.10-16.23)	32 (25-40)	26,508 (13,351-53,172)	26,540 (13,390-53,199)
Myanmar	0.132 (0.080-0.235)	-	3.12 (1.90-5.56)	260 (231-300)	4,591 (2,819-8,125)	4,851 (3,072-8,378)
ASEAN	0.135 (0.089-0.234)	0.008 (0.004-0.014)	3.33 (2.19-5.78)	519 (381-697)	20,667 (12,391-38,973)	21,186 (12,905-39,710)

Estimates are presented as base-case estimates with their 95% credibility interval (in parentheses) based on probabilistic sensitivity analysis.

Costs are presented as 2019 USD where 1 USD = 14,147.67 Indonesian Rupees = 51.80 Philippine Pesos = 23,050.24 Vietnamese Dong = 8,679.41 Lao Kip = 1,518.26 Myanmar Kyat. Abbreviations: DALYs – disability-adjusted life years; USD – US Dollar.

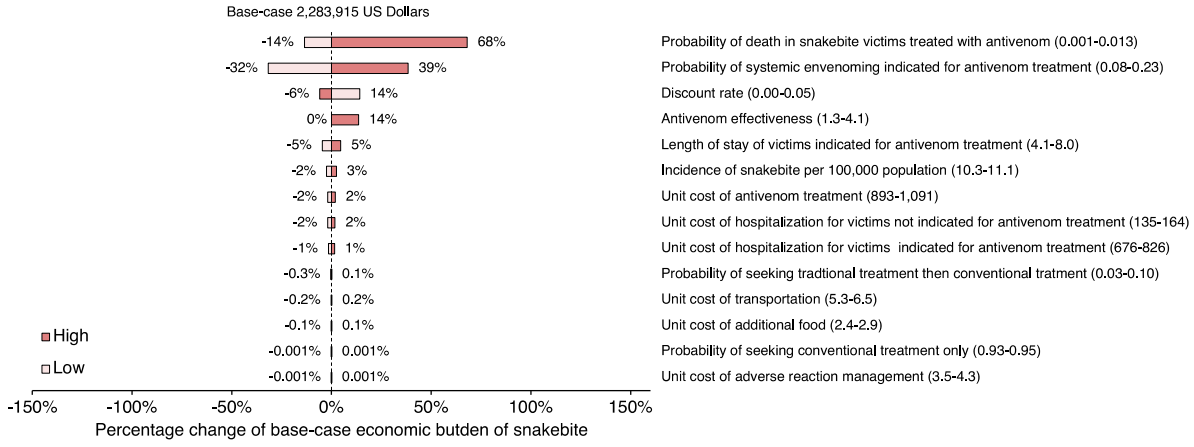
Table B4. Estimated annual economic and disease burden of post-traumatic stress disorder following snakebite.

	PTSD, n	YLDs	Productivity losses, x1000 USD
Malaysia	98 (69-155)	168 (81-324)	382 (206-678)
Thailand	464 (161-977)	794 (239-1,797)	1,228 (371-2,796)
Indonesia	4,738 (2,480-8,514)	8,103 (3,144-16,702)	6,783 (2,866-13,287)
Philippines	334 (250-481)	426 (238-662)	407 (229-667)
Vietnam	3,103 (554-8,792)	5,306 (867-16,305)	2,994 (499-8,962)
Lao PDR	390 (257-587)	666 (304-1,174)	351 (181-618)
Myanmar	1,167 (880-1,448)	1,995 (997-3,070)	563 (319-856)
Total	10,293 (4,651-20,954)	17,458 (5,869-40,035)	12,708 (4,670-27,864)

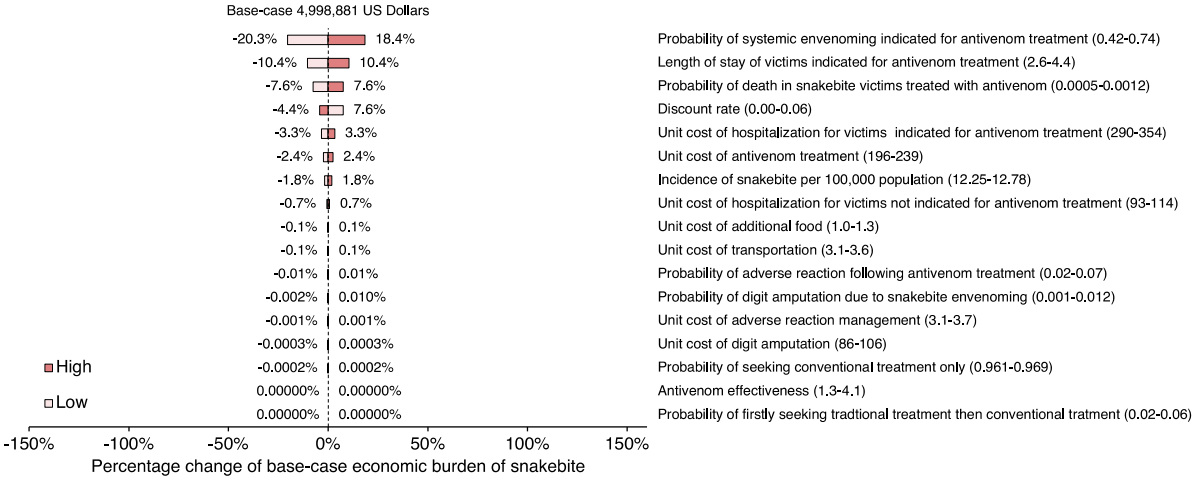
Estimates are presented as base-case estimates as x1000 USD with their 95% credibility interval (in parentheses) based on probabilistic sensitivity analysis. Costs are presented as 2019 USD where 1 USD = 14,147.67 Indonesian Rupees = 51.80 Philippine Pesos = 23,050.24 Vietnamese Dong = 8,679.41 Lao Kip = 1,518.26 Myanmar Kyat. Abbreviations: PTSD – post-traumatic stress disorder; USD – US Dollar, YLDs – years lived with disabilities.

Figure B1 One-way sensitivity analysis of economic burden.

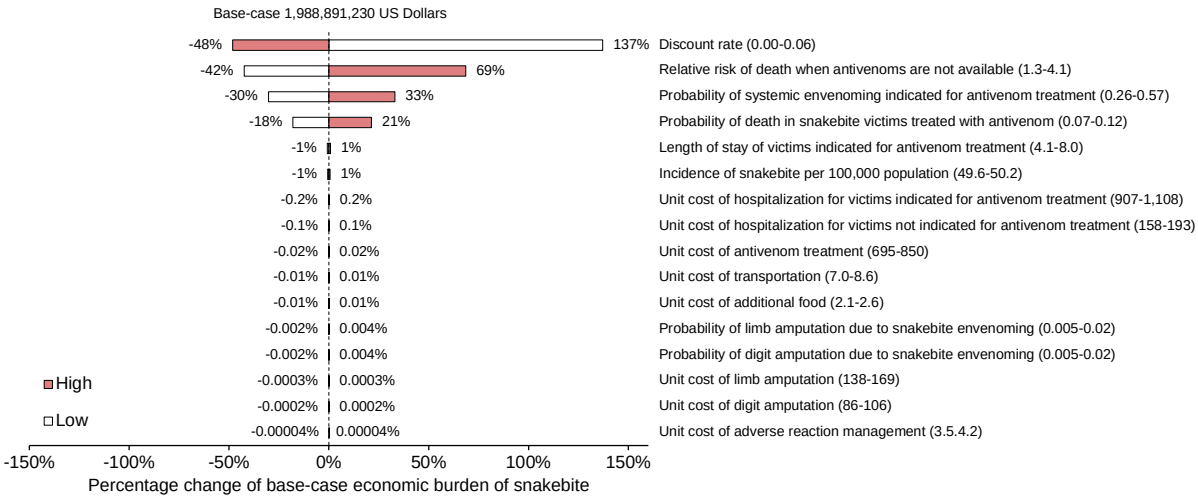
Malaysia



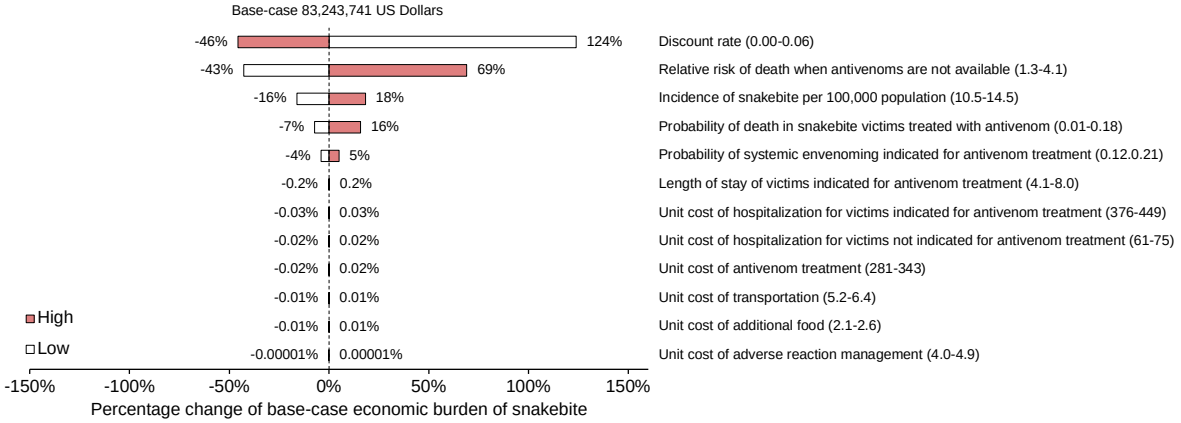
Thailand



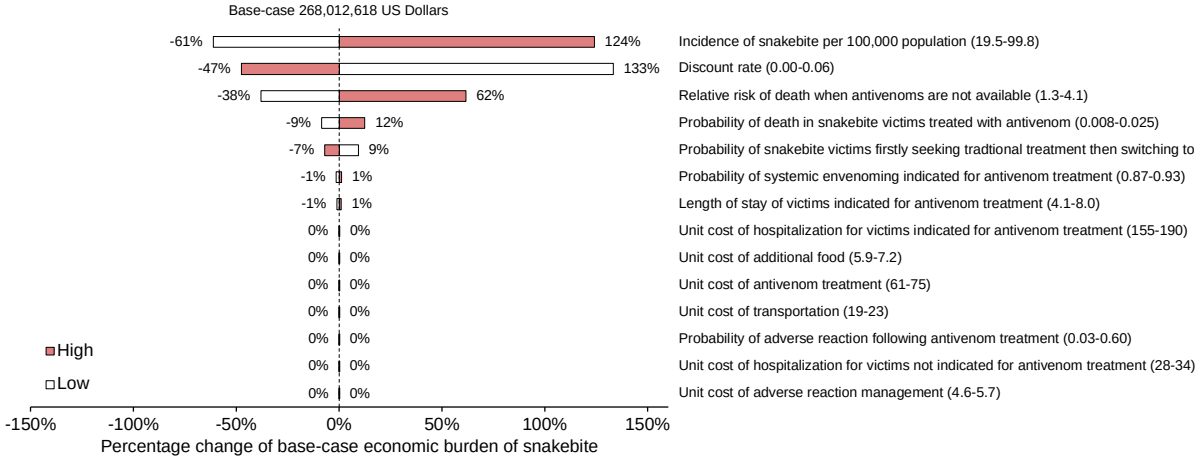
Indonesia



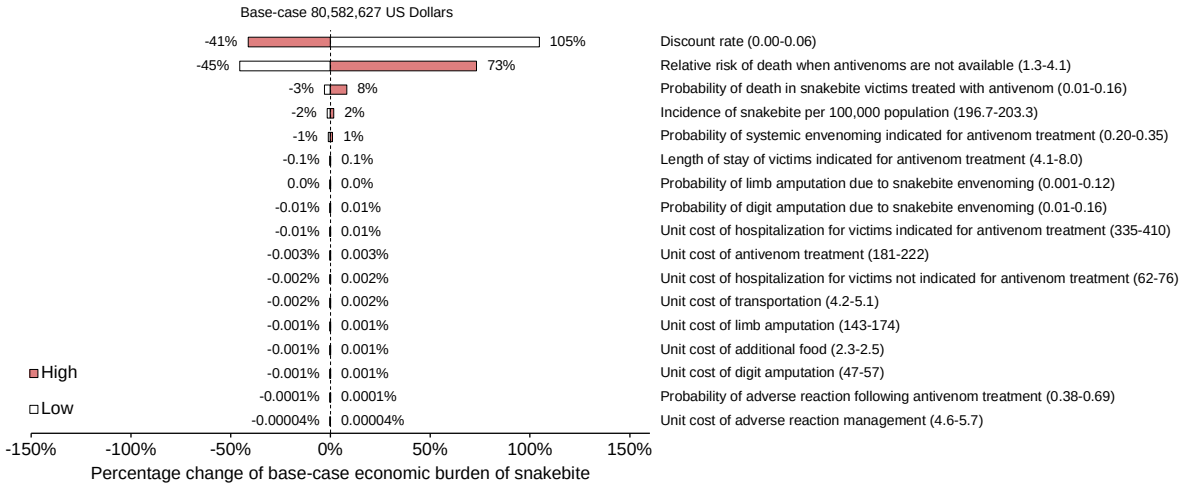
Philippines



Vietnam



Lao PDR



Myanmar

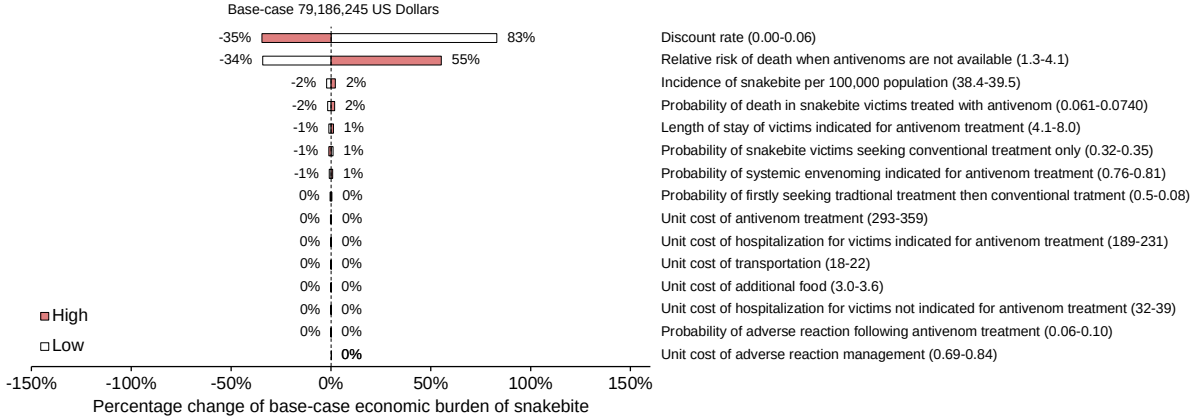
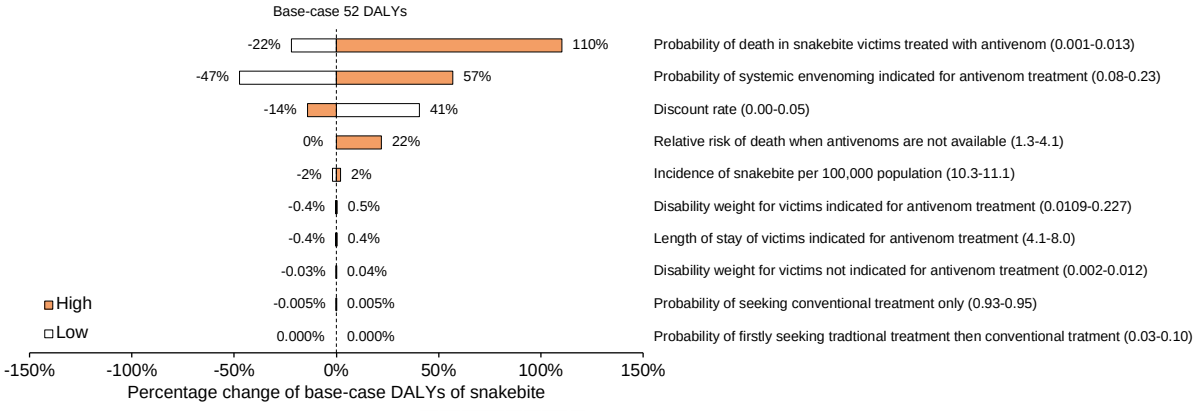
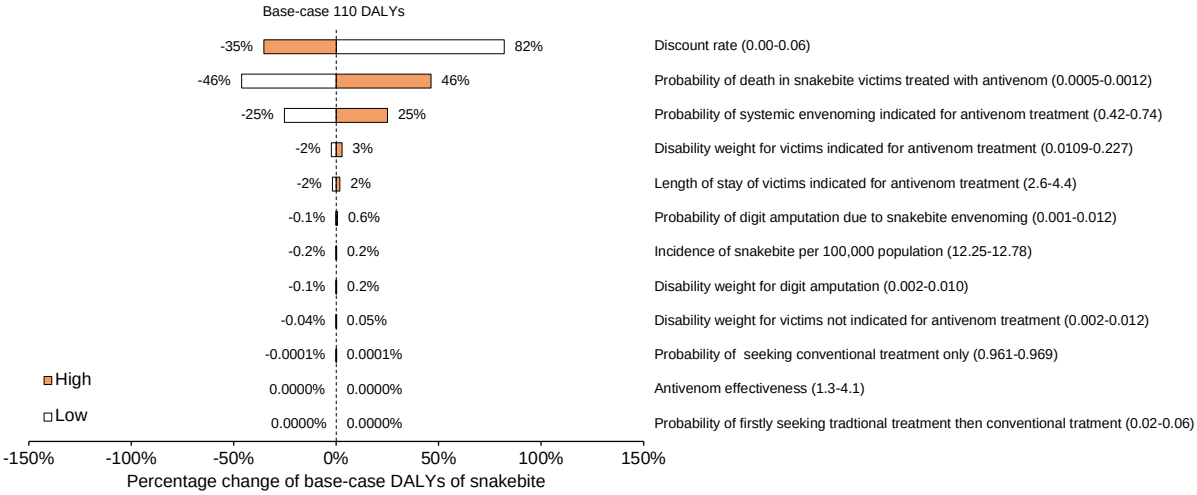


Figure B2 One-way sensitivity analysis of disability-adjusted life years (DALYs) of snakebite.

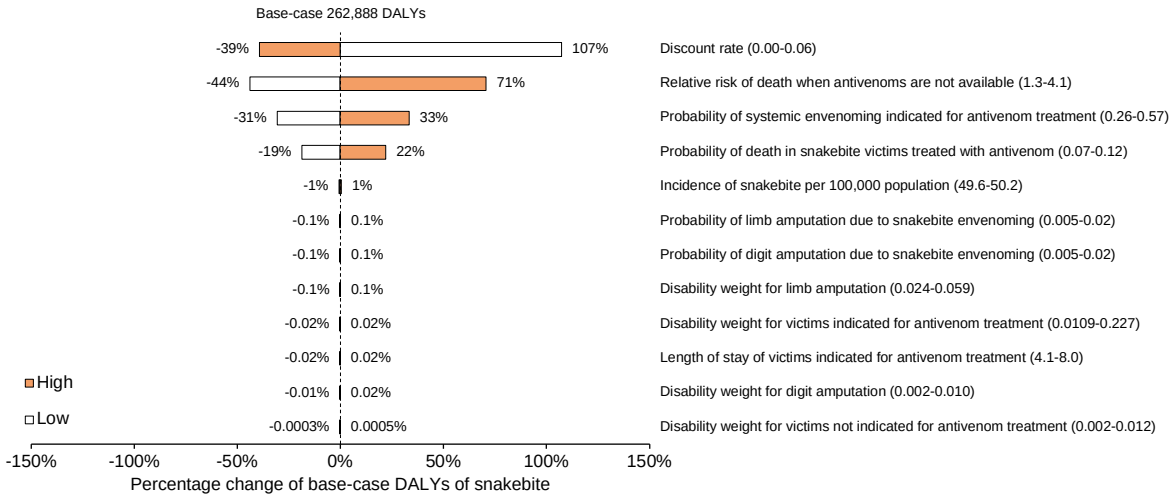
Malaysia



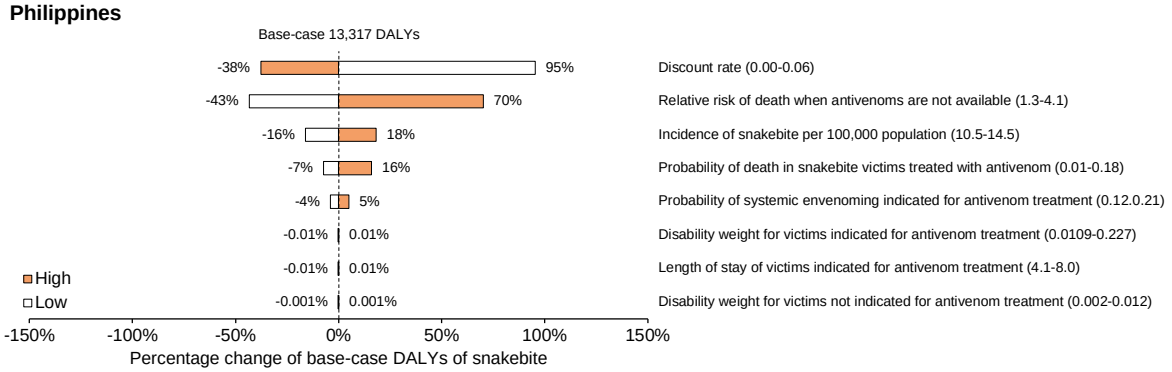
Thailand



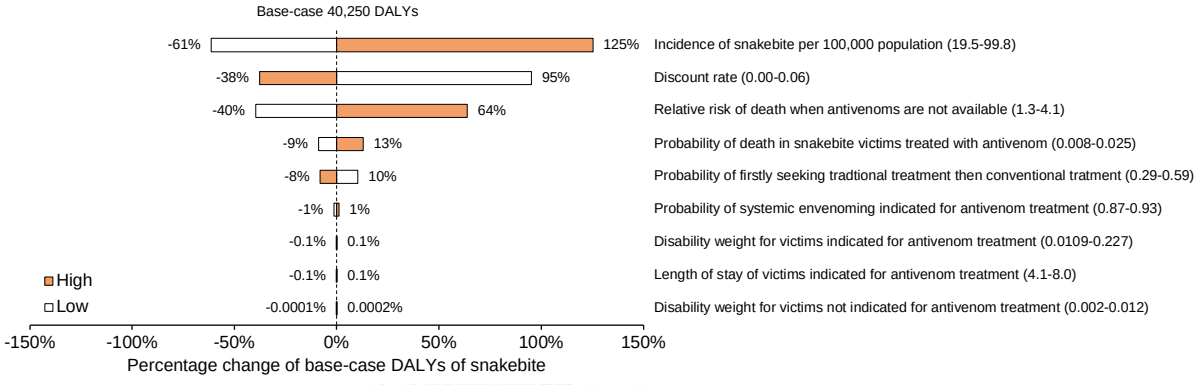
Indonesia



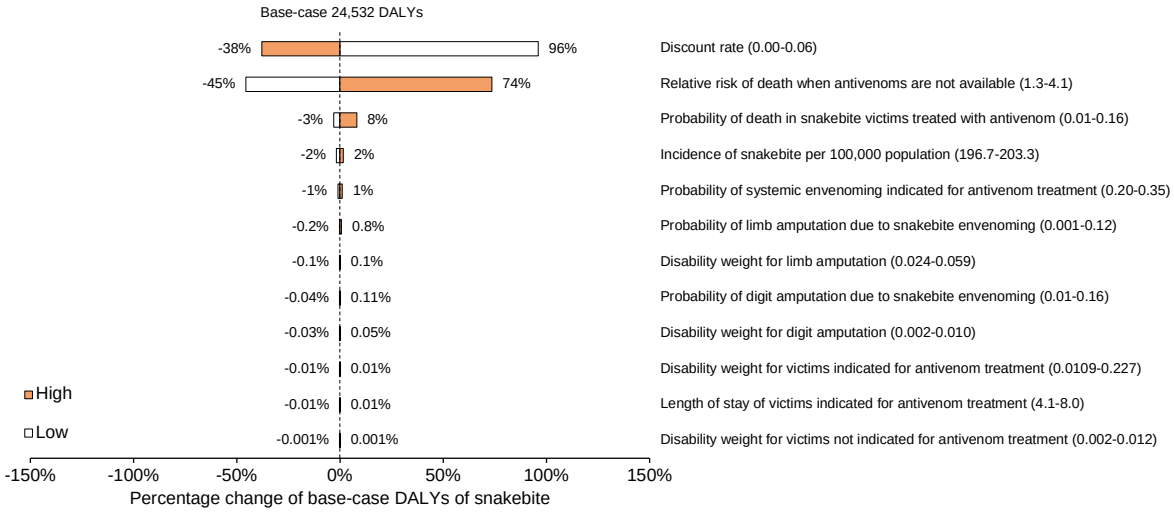
Philippines



Vietnam



Lao PDR



Myanmar

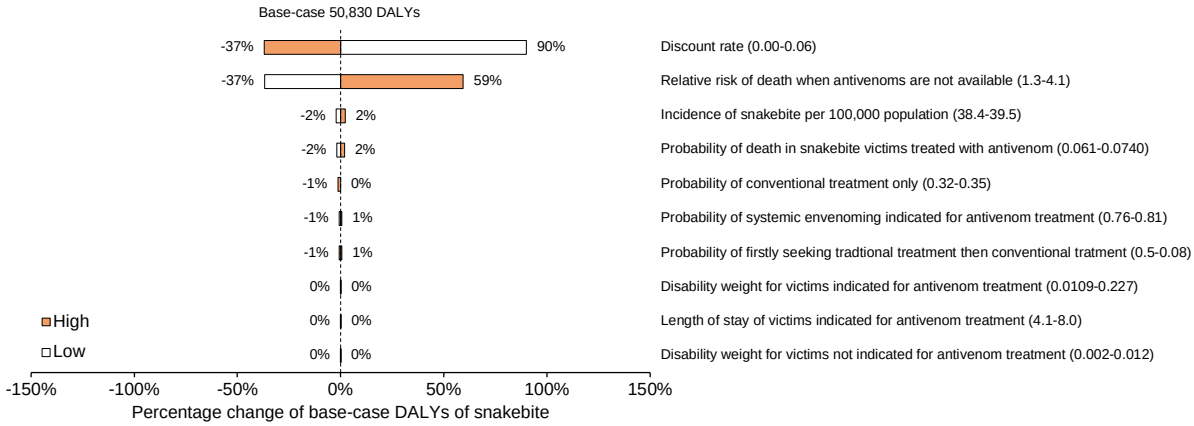
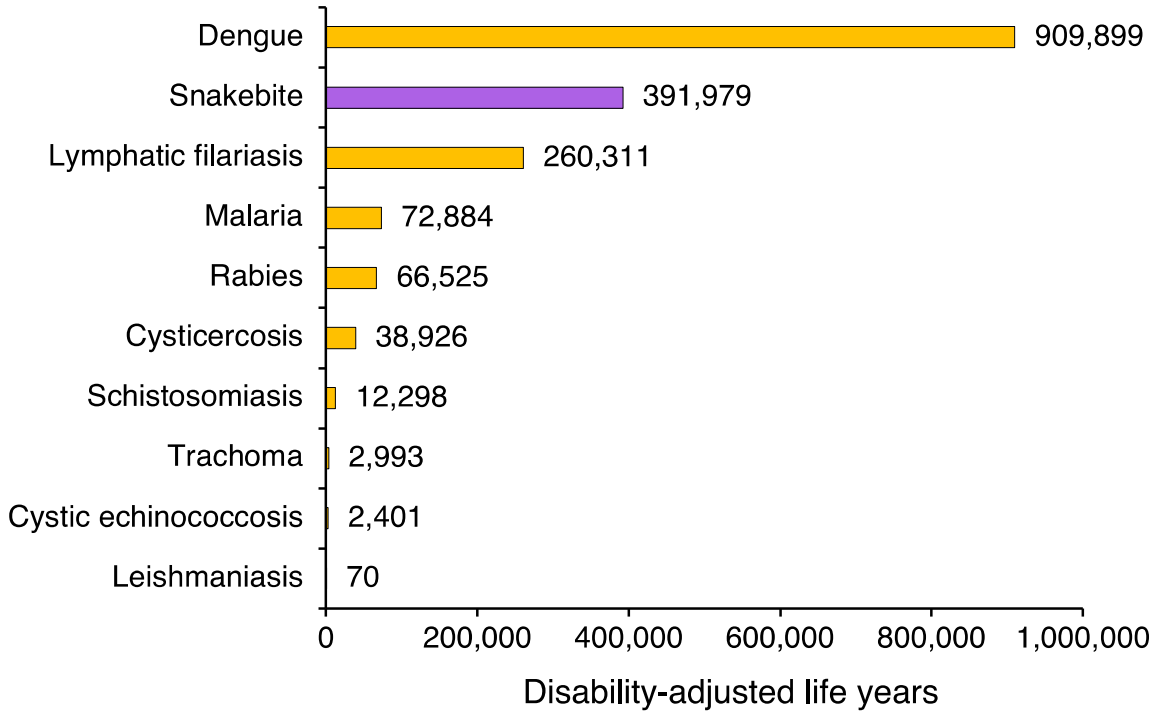


Figure B3 Comparison of annual disease burden of neglected tropical diseases in ASEAN.



Estimated disease burden of snakebite from this study (shown in purple) was compared to the disease burden of neglected tropical diseases in seven ASEAN countries that were estimated in the Global Burden of Disease 2019 study.[131]

APPENDIX C POTENTIAL ECONOMIC AND CLINICAL IMPLICATIONS OF IMPROVING ACCESS TO SNAKE ANTIVENOM IN FIVE ASEAN COUNTRIES: A COST-EFFECTIVENESS ANALYSIS

Table C1 CHEERS 2022 Checklist.

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction, paragraph 3-4
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Not reported
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Methods, paragraph 1-2
Setting and location	6	Provide relevant contextual information that may influence findings.	Methods, paragraph 1
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods, paragraph 2
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods, paragraph 2
Time horizon	9	State the time horizon for the study and why appropriate.	Methods, paragraph 2
Discount rate	10	Report the discount rate(s) and reason chosen.	Methods, Discounting
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods, Decision analytic model
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods, Health outcomes
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods, Health outcomes

Topic	No.	Item	Location where item is reported
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Methods, Costs
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods, Base-case analyses
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Methods, Decision analytic model, Figure 1
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods, Decision analytic model
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Not Applicable
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Not Applicable
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Methods, Sensitivity analyses
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Methods, Input parameters; Methods, Patient and public involvement
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	S1 Table in the supplementary material
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results, Base-case analyses, Table 2, Table 3

Topic	No.	Item	Location where item is reported
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results, Sensitivity analysis, Figure 2, S1 Table, S2 Table, S3 Table, S4 Table, S5 Table, S1 Figure, S2 Figure, S3 Figure, S4 Figure
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Not reported
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Acknowledgement
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Acknowledgement

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008

Table C2 Input parameters for economic evaluation of improving access to snake antivenom in ASEAN countries.

Parameters (Distribution)	Indonesia	Philippines	Vietnam	Lao PDR	Myanmar
Epidemiological parameters					
Total population, million people[16]	271	108	96	7	54
Incidence of snakebite per 100,000 population (Beta)[38,41,88]	49.9 (49.6 to 50.2)	12.4 (10.5 to 14.5)	48.5 (19.5 to 99.8)	200.0 (196.7 to 203.3)	39.0 (38.4 to 39.5)
Probability of snakebite victims seeking conventional treatment only in current access (Beta)[41]	0.75	0.00	0.00	0.00	0.34 (0.32 to 0.35)
Probability of snakebite victims firstly seeking traditional treatment then switching to conventional treatment in current access (Beta)[38,41]	0.00	0.27	0.43 (0.29 to 0.59)	0.10	0.07 (0.05 to 0.08)
Probability of snakebite victims firstly seeking traditional treatment then switching to conventional treatment in full access	1.00	1.00	1.00	1.00	1.00
Probability of systemic envenoming indicated for antivenom treatment for victims seeking conventional treatment (Beta)[25,36,38,41]	0.40 (0.26 to 0.57)	0.16 (0.12 to 0.21)	0.90 (0.87 to 0.93)	0.27 (0.20 to 0.35)	0.79 (0.76 to 0.81)
Probability of systemic envenoming for victims seeking traditional treatment	0.26	0.12	0.87	0.20	0.76
Probability of victims indicated for antivenom treatment regardless of treatment seeking behavior who received antivenom treatment at current level of access*	0.10	0.26	0.37	0.04	0.64
Probability of antivenom given to victims with systemic envenoming seeking care at the healthcare facilities at current level of access*	0.12	0.77	0.83	0.33	1.00
Probability of antivenom given to victims with systemic envenoming seeking care at the healthcare facilities at full level of access	1.00	1.00	1.00	1.00	1.00
Probability of adverse reaction following antivenom treatment (Beta)[36,37,41]	0.40	0.05	0.22 (0.03 to 0.60)	0.53 (0.38 to 0.69)	0.08 (0.06 to 0.10)
Probability of death in snakebite victims without systemic envenoming[25,36,41,88]	0.00	0.00	0.00	0.00	0.00
Probability of death in systemic envenoming treated with antivenom (Beta)[25,36,41,104]	0.09 (0.07 to 0.12)	0.07 (0.01 to 0.18)	0.015 (0.008 to 0.025)	0.05 (0.01 to 0.16)	0.068 (0.061 to 0.074)
Relative risk of death when antivenoms are not available (Log-normal)[104]	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)	2.33 (1.26 to 4.06)
Probability of death in systemic envenoming treated in hospital without antivenom (Beta)	0.21	0.16	0.035	0.11	0.16
Probability of death in systemic envenoming not treated in hospital (Beta)	0.28	0.43	0.057	0.37	0.17
Probability of digit amputation due to snakebite envenoming (Beta)[36,38,41]	0.01 (0.005 to 0.02)	0.007	0.00	0.05 (0.01 to 0.16)	0.00
Probability of limb amputation due to snakebite envenoming (Beta)[41]	0.01 (0.005 to 0.02)	0.003	0.00	0.02 (0.001 to 0.12)	0.00
Disability weight					

Disability weight for victims not indicated for antivenom treatment (Beta)[110]	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)	0.006 (0.002 to 0.012)
Disability weight for victims indicated for antivenom treatment (Beta)[110]	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)	0.163 (0.109 to 0.227)
Disability weight for digit amputation (Beta)[110]	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)	0.005 (0.002 to 0.010)
Disability weight for limb amputation (Beta)[110]	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)	0.039 (0.024 to 0.059)
Duration of disease					
Length of stay for victims not indicated for antivenom treatment, day	1	1	1	1	1
Length of stay for victims indicated for antivenom treatment (Gamma)[86]	6.1 (4.1 to 8.0)	6.1 (4.1 to 8.0)	6.1 (4.1 to 8.0)	6.1 (4.1 to 8.0)	6.1 (4.1 to 8.0)
Unit costs, USD					
Unit cost of hospitalization for victims not indicated for antivenom treatment (Gamma)[112-116]	175 (158 to 193)	68 (61 to 75)	31 (28 to 34)	69 (62 to 76)	36 (32 to 39)
Unit cost of hospitalization for victims not indicated for antivenom treatment (Gamma)[112-116]	1,007 (907 to 1,108)	408 (367 to 449)	173 (155 to 190)	372 (335 to 410)	210 (189 to 231)
Unit cost of antivenom treatment (Gamma)[112,114]	773 (695 to 850)	312 (281 to 343)	68 (61 to 75)	202 (181 to 222)	326 (293 to 359)
Unit cost of antivenom logistics costs, percentage of antivenom price[117]	0.05	0.05	0.05	0.05	0.05
Unit cost of adverse reaction management (Gamma)[112,114]	3.8 (3.5 to 4.2)	4.4 (4.0 to 4.9)	5.1 (4.6 to 5.7)	5.1 (4.6 to 5.7)	0.76 (0.69 to 0.84)
Unit cost of digit amputation (Gamma)[117]	96 (86 to 106)	96 (86 to 106)	96 (86 to 106)	52 (47 to 57)	96 (86 to 106)
Unit cost of limb amputation (Gamma)[117]	154 (138 to 169)	154 (138 to 169)	154 (138 to 169)	158 (143 to 174)	154 (138 to 169)
Unit cost of traditional healer	0	0	0	0	0
Unit cost of transportation (Gamma)[120]	7.8 (7.0 to 8.6)	5.8 (5.2 to 6.4)	21 (19 to 23)	4.7 (4.2 to 5.1)	20 (18 to 22)
Unit cost of additional food (Gamma)[121]	2.3 (2.1 to 2.6)	2.3 (2.1 to 2.6)	6.5 (5.9 to 7.2)	2.4 (2.3 to 2.5)	3.3 (3.0 to 3.6)
Others					
Discount rate[123,124]	0.03 (0.00 to 0.06)	0.03 (0.00 to 0.06)	0.03 (0.00 to 0.06)	0.03 (0.00 to 0.06)	0.03 (0.00 to 0.06)
GDP per capita, USD[125]	4,136	3,485	2,715	2,625	1,421
GDP per capita annual growth, %[126]	0.04	0.05	0.06	0.03	0.02
Number of relatives or family members who companied snakebite victims	1	2	1	1	2

Note: Parameters are presented as base-case value (range). Costs are presented as USD where 1 USD equals to 14,147.67 Indonesian Rupees, 51.80 Philippine Pesos, 23,050.24 Vietnamese Dongs, 8,679.41 Lao Kips, and 1,518.26 Myanmar Kyats. *– Probability of antivenom given to victims with systemic envenoming seeking care at the healthcare facilities was determined by the number of antivenom treatments available divided by the number of snakebite victims needed antivenom treatment who sought care at the healthcare facilities.

Table C3 Sensitivity analysis of cost-effectiveness analysis of improving access to snake antivenom in ASEAN countries in different scenarios.

	Incremental costs per death averted, USD				
Scenario	Indonesia	Philippines	Vietnam	Lao PDR	Myanmar
Base-case	-173,745	-144,872	-146,977	-78,021	-27,595
Antivenom was effective on reducing risk of amputation following snakebite envenoming	-173,755	-144,874	N/A	-78,032	N/A
Incorporating post-traumatic stress disorder as disability following snakebite envenoming	-173,637	-144,781	-146,905	-77,953	-27,558
Excluding indirect costs	8,396	4,092	8,632	1,488	6,708
Logistic costs as 10% of antivenom price	-173,458	-144,826	-146,896	-77,988	-27,439

Note: Willingness-to-pay thresholds of each ASEAN country were 4,136 USD for Indonesia, 2,317 USD for Philippines, 2,715 USD for Vietnam, 2,625 USD for Lao PDR, and 1,421 USD for Myanmar. Costs are presented as 2019 USD where 1 USD = 14,147.67 = Indonesian Rupees = 51.80 = Philippine Pesos = 23,050.24 Vietnamese Dong = 8,679.41 Lao Kip = 1,518.26 Myanmar Kyat. USD – US Dollars; N/A – not applicable.

Table C4 Sensitivity analysis of cost-utility analysis of improving access to snake antivenom in ASEAN countries in different scenarios.

	Incremental costs per disability-adjusted life year averted, USD				
Scenario	Indonesia	Philippines	Vietnam	Lao PDR	Myanmar
Base-case	-6,991	-5,987	-6,062	-3,213	-1,165
Antivenom was effective on reducing risk of amputation following snakebite envenoming	-6,978	-5,985	N/A	-3,207	N/A
Incorporating post-traumatic stress disorder as disability following snakebite envenoming	-7,023	-6,015	-6,091	-3,228	-1,170
Excluding indirect costs	338	169	356	61	283
Logistic costs as 10% of antivenom price	-6,978	-5,983	-6,059	-3,212	-1,159

Note: Willingness-to-pay thresholds of each ASEAN country were 4,136 USD for Indonesia, 2,317 USD for Philippines, 2,715 USD for Vietnam, 2,625 USD for Lao PDR, and 1,421 USD for Myanmar. Costs are presented as 2019 USD where 1 USD = 14,147.67 = Indonesian Rupees = 51.80 = Philippine Pesos = 23,050.24 Vietnamese Dong = 8,679.41 Lao Kip = 1,518.26 Myanmar Kyat. USD – US Dollars; N/A – not applicable.

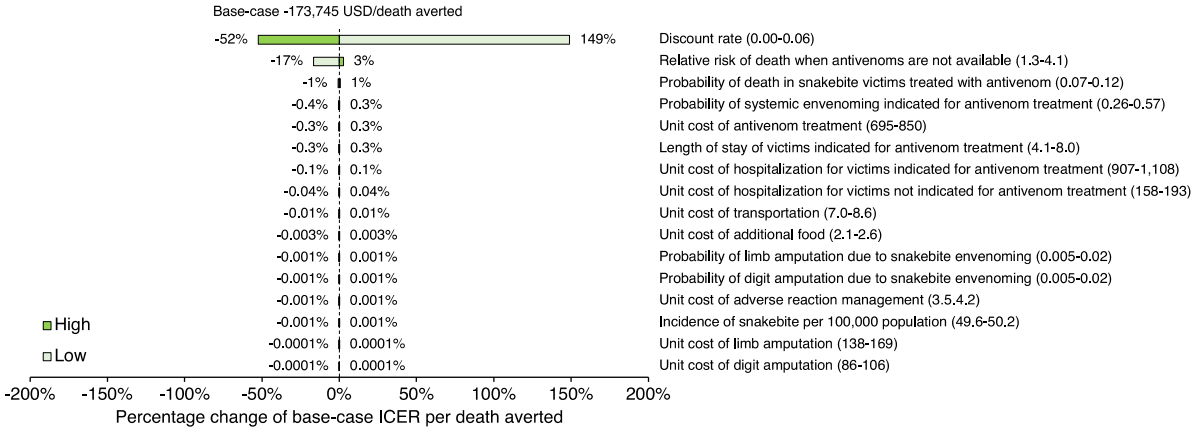
Table C5 Threshold analyses of antivenom effectiveness and costs of antivenom treatment resulted in an incremental cost-effectiveness ratio of 0.

Parameter	Indonesia	Philippines	Vietnam	Lao PDR	Myanmar
Antivenom effectiveness, Relative risk of death					
Base-case value	2.33	2.33	2.33	2.33	2.33
Threshold value resulting in ICER of 0	1.01	0.44	0.73	0.35	1.19
Costs of antivenom treatment, USD					
Base-case value	773	312	68	202	326
Threshold value resulting in ICER of 0	22,985	46,054	5,624	22,365	3,083
Ratio of threshold value to base-case value	30	149	87	113	9

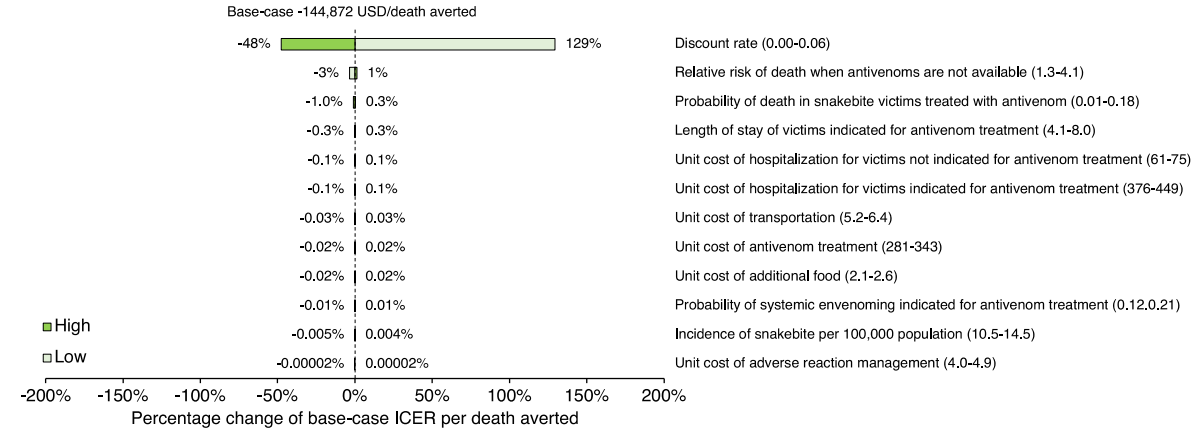
Note: Costs are presented as 2019 USD where 1 USD = 14,147.67 = Indonesian Rupees = 51.80 = Philippine Pesos = 23,050.24 Vietnamese Dong = 8,679.41 Lao Kip = 1,518.26 Myanmar Kyat. DALY – disability

Figure C1 One-way sensitivity analysis of incremental costs per death averted of improving access to snake antivenom in ASEAN countries.

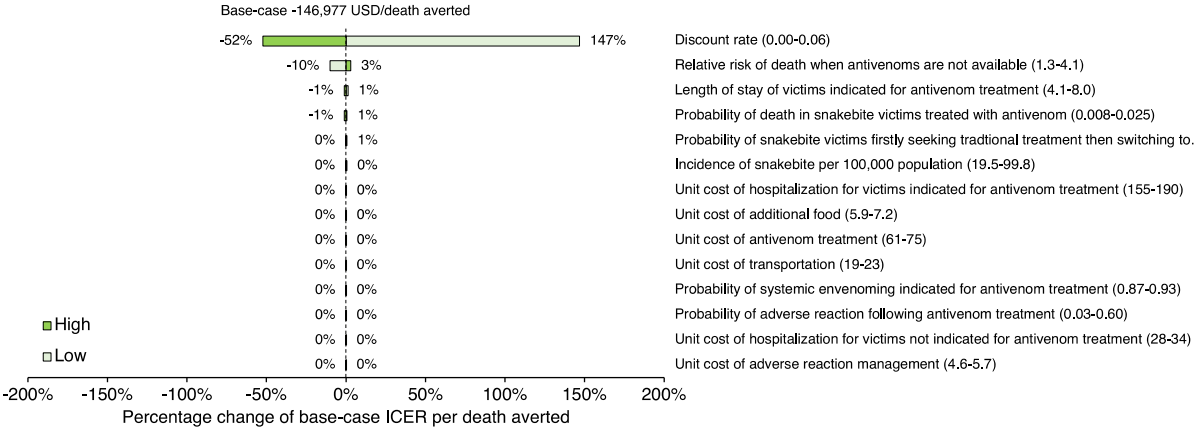
Indonesia



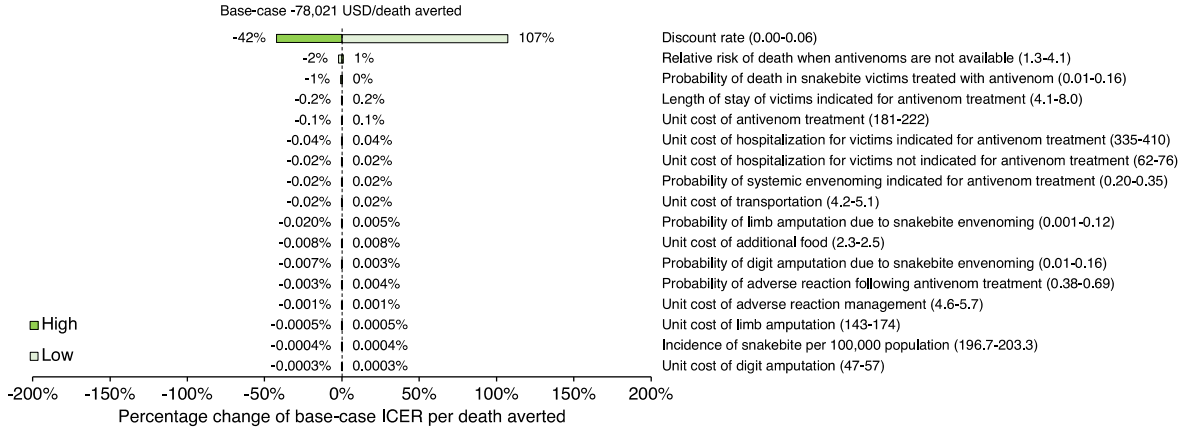
Philippines



Vietnam



Lao PDR



Myanmar

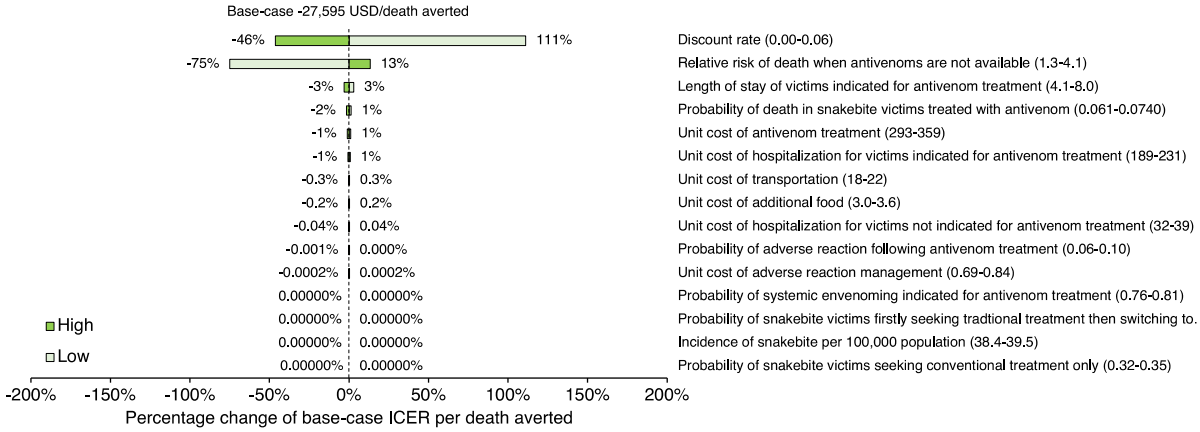
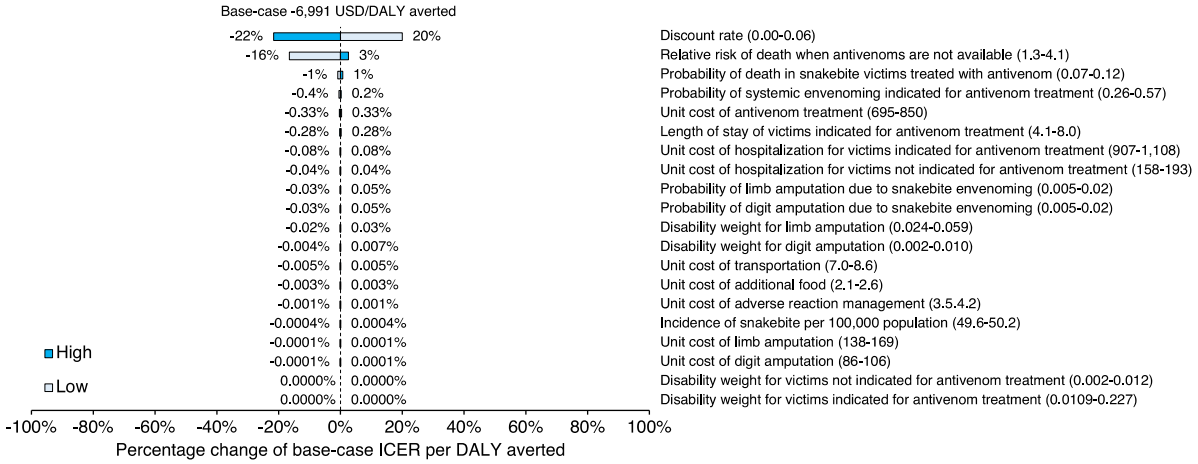
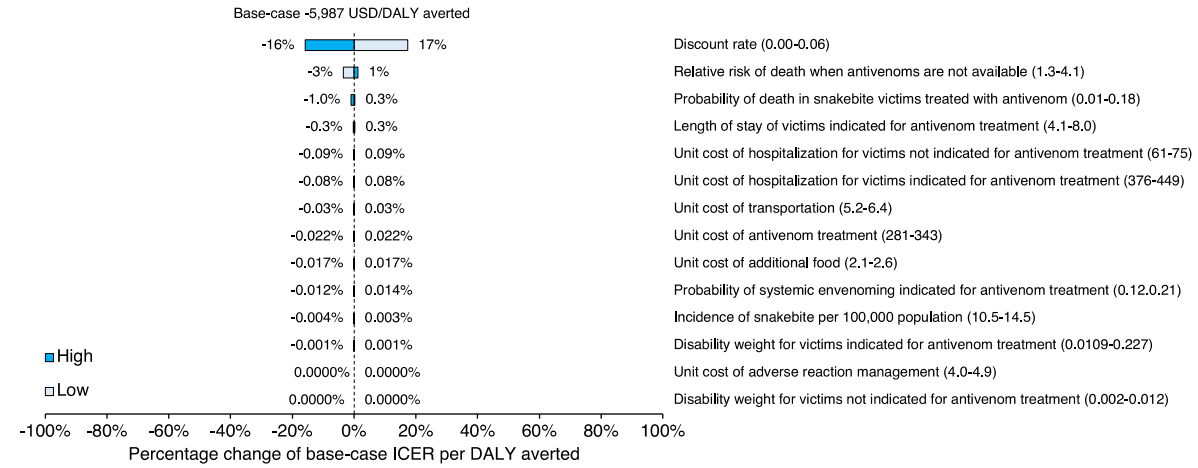


Figure C2 One-way sensitivity analysis of incremental costs per disability-adjusted life year (DALY) averted of improving access to snake antivenom in ASEAN countries.

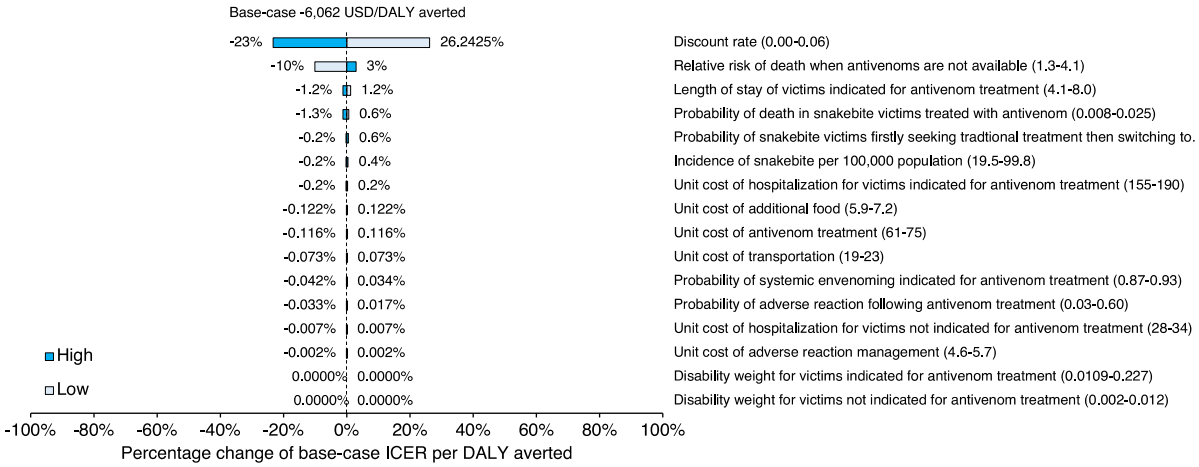
Indonesia



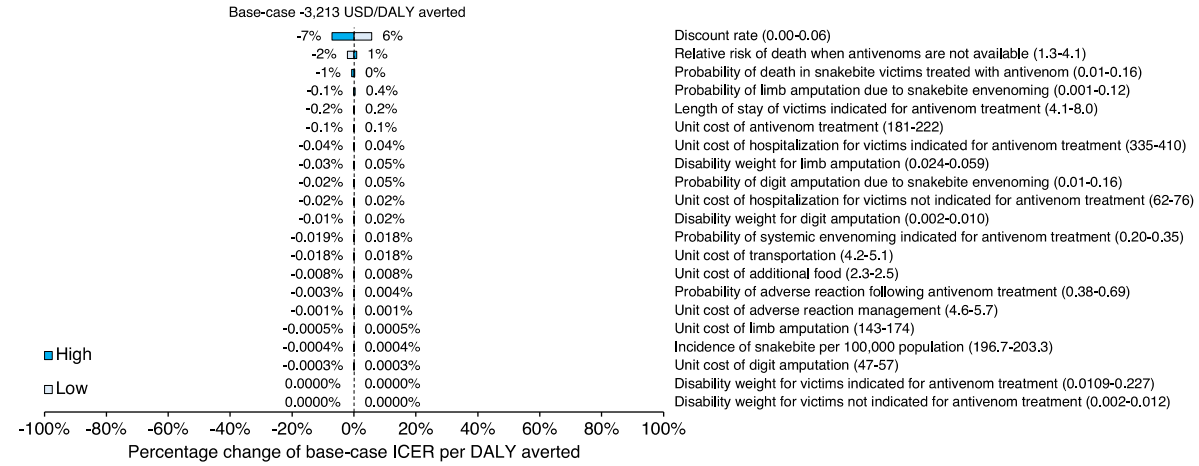
Philippines



Vietnam



Lao PDR



Myanmar

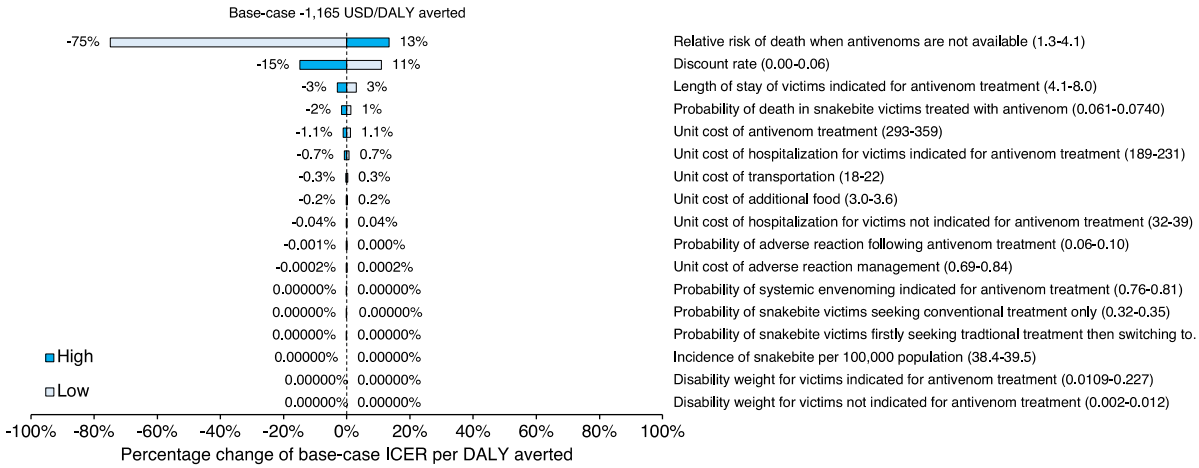


Figure C3 Cost-effectiveness plane of incremental costs per death averted of improving access to snake antivenom in ASEAN countries.

Incremental costs and deaths averted of full access to snake antivenom in each ASEAN country based on a probabilistic sensitivity analysis of 1,000 iterations are presented in dots. Willingness-to-pay thresholds of each country are presented as dash lines with corresponding color.

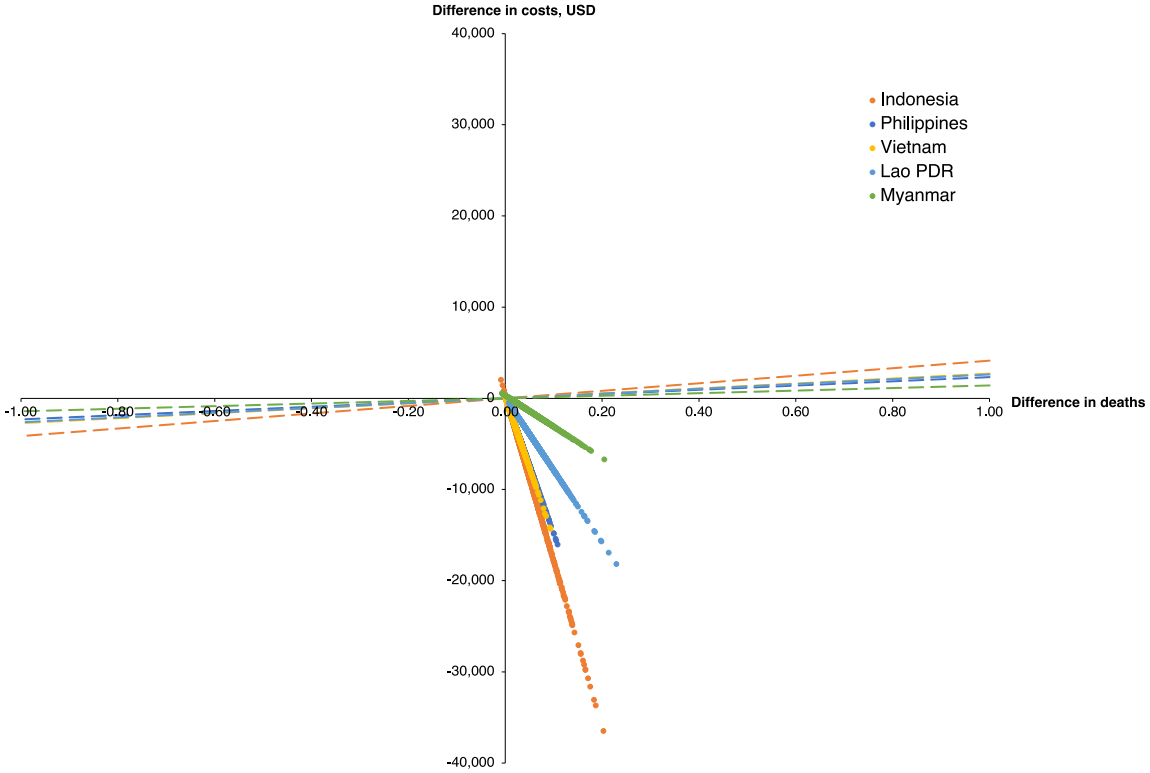
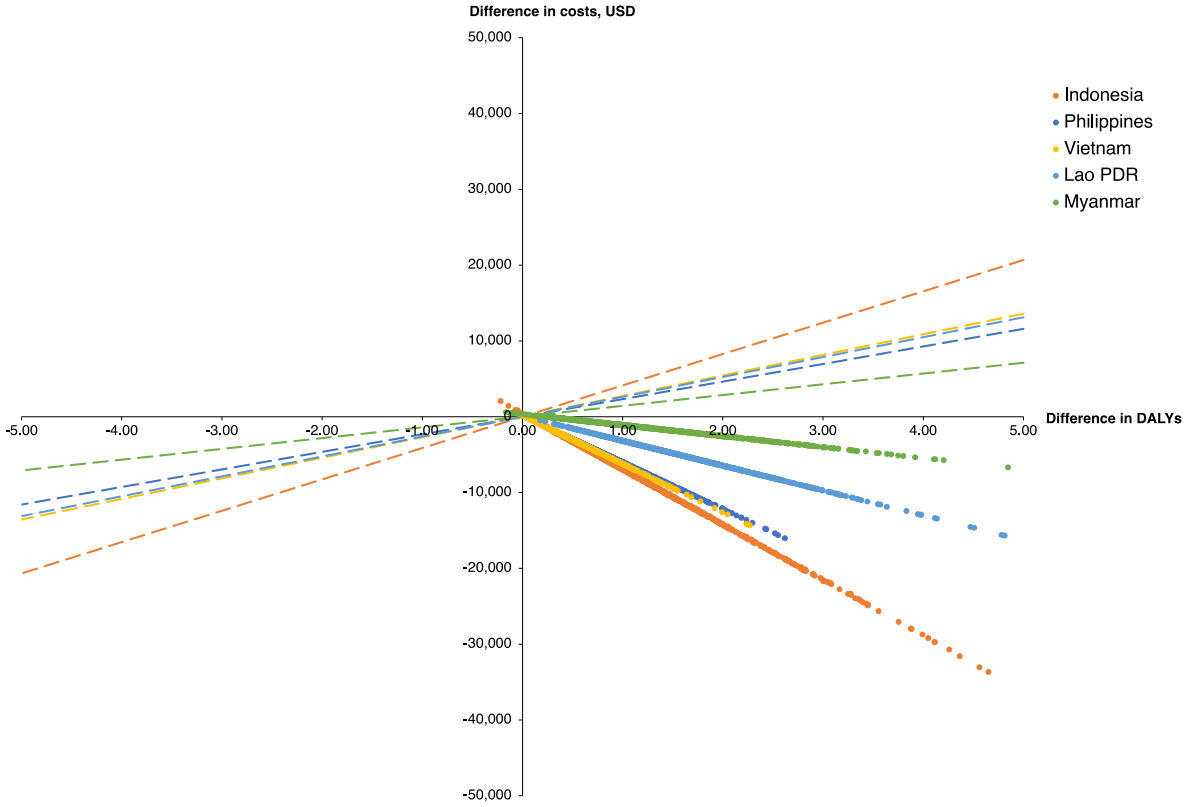


Figure C4 Cost-effectiveness plane of incremental costs per disability-adjusted life year (DALY) averted of improving access to snake antivenom in ASEAN countries.

Incremental costs and disability-adjusted life years (DALYs) averted of full access to snake antivenom in each ASEAN country based on a probabilistic sensitivity analysis of 1,000 iterations are presented in dots. Willingness-to-pay thresholds of each country are presented as dash lines with corresponding color.



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