ANTIVENOM CROSS-NEUTRALIZATION AND NEUTRALIZATION: A SYSTEMATIC REIVEW OF NON-CLNICAL STUDIES IN ASIA REGION

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สุธินี สู้ไพริน : การทบทวนวรรณกรรมอย่างเป็นระบบของข้อมูลการศึกษาความสามารถของเซรุ่มพิษงู ในการต้านฤทธิ์ของพิษงูในภูมิภาคเอเชีย . (ANTIVENOM CROSS-NEUTRALIZATION AND NEUTRALIZATION: A SYSTEMATIC REIVEW OF NON-CLNICAL STUDIES IN ASIA REGION) อ.ที่ปรึกษาหลัก : ผศ. ภญ. ดร.สุธีรา เตชคุณวุฒิ

ที่มาและความสำคัญ: การใช้เซรุ่มต้านพิษงูที่มีประสิทธิภาพในการต้านฤทธิ์ข้าม สามารถเพิ่มการเข้าถึงเซรุ่มต้านพิษงู ซึ่งเป็นปัจจัยสำคัญในการลดการตาย และการพิการจากโรคงูพิษกัด อย่างไรก็ตาม การศึกษาประสิทธิภาพในการต้านฤทธิ์ข้ามของเซรุ่มต้านพิษงูมักทำการศึกษาในสัตว์ทดลองเนื่องจากปัญหาทางด้านจริยธรรมในการศึกษาในมนุษย์ การศึกษานี้มีวัตถุประสงค์เพื่อสืบค้นและสรุปข้อมูลที่เกี่ยวกับประสิทธิภาพในการต้านฤทธิ์ข้ามของเซรุ่มต้านพิษงูในเอเชียที่ทำการศึกษาในสัตว์ทดลอง

ระเบียบวิธีวิจัย: การทบทวนวรรณกรรมอย่างเป็นระบบได้ถูกจัดทำขึ้นเพื่อสืบค้นการศึกษาที่เกี่ยวข้องที่ตีพิมพ์ตั้งแต่เริ่มต้นจนถึงวันที่ 30 พฤษภาคม 2565 ในฐานข้อมูล PubMed, Scopus, Web of Science และ Embase นอกจากนี้ ยังมีการสืบค้นบทความจากเอกสารอ้างอิงของการศึกษาที่ผ่านการคัดเลือกเพื่อหาบทความที่เกี่ยวข้องเพิ่มเติม การศึกษาที่รายงานผลประสิทธิภาพของเซรุ่มต้านพิษงูในการต้านฤทธิ์ของพิษงูในเอเชียที่ก่อให้เกิดการเสียชีวิตในสัตว์ทดลองจะได้รับการคัดเลือกเข้ามาในการศึกษานี้ การประเมินคุณภาพของการศึกษาจะจัดทำขึ้นโดยใช้เครื่องมือประเมินความเสี่ยงต่อการเกิดอคติในการศึกษาที่ใช้สัตว์ทดลอง ที่ชื่อว่า SYRCLE และมีการประเมินการรายงานข้อมูลโดยใช้เครื่องมือที่พัฒนาจากแนวทางการรายงานผล ARRIVE สำหรับข้อมูลการต้านฤทธิ์ของพิษงู และการต้านฤทธิ์ข้ามของเซรุ่มต้านพิษงู ได้มีการสรุปข้อมูลไว้ในการศึกษา นอกจากนี้ การวิเคราะห์สถานการณ์การมีอยู่ของเซรุ่มต้านพิษงูที่มีประสิทธิภาพได้จัดทำขึ้นโดยเปรียบเทียบข้อมูลที่ได้จากการทบทวนวรรณกรรมอย่างเป็ นระบบกับฐานข้อมูลเกี่ยวกับงูกัดที่พัฒนาโดยองค์การอนามัยโลก

ผลการศึกษา: การศึกษาที่เกี่ยวข้อง 48 การศึกษาได้ผ่านการคัดเลือกจากการทบทวนวรรณกรรมอย่างเป็นระบบ การศึกษาส่วนใหญ่ศึกษาประสิทธิภาพของเซรุ่มต้านพิษงูในการต้านฤทธิ์ของงูในภูมิภาคเอเชียตะวันออกเฉียงใต้ (56%) ภูมิภาคเอเชียใต้ (36%) และภูมิภาคเอเชียตะวันออก (19%) งูพิษที่มีความสำคัญทางแพทย์ในภูมิภาคเอเชีย 22 ชนิด (49%) ถูกศึกษาเพื่อยืนยันประสิทธิภาพของเซรุ่มต้านพิษงูในการต้านฤทธิ์ของพิษงูที่ก่อให้เกิดการเสียชีวิตในสัตว์ทดลอง การวิเคราะห์สถานการณ์การมีอยู่ของเซรุ่มต้านพิษงูที่มีประสิทธิภาพในทวีปเอเชีย พบว่า เซรุ่มต้านพิษงูที่ผลิตเองในประเทศยังไม่ครอบคลุมงูพิษที่มีความสำคัญทางแพทย์ทั้งหมดในประเทศ ในกลุ่มประเทศในทวีปเอเชียที่ไม่มีการผลิตเซรุ่มต้านพิษงูภายในประเทศ มีเพียงประเทศบังกลาเทศ ศรีลังกา และมาเลเซียเท่านั้นที่พบการทำการศึกษาประสิทธิภาพของเซรุ่มต้านพิษงูในการต้านฤทธิ์ของพิษงูที่ก่อให้เกิดการเสียชีวิตในสัตว์ทดลอง สำหรับการประเมินคุณภาพของการศึกษาที่ผ่านการคัดเลือก พบว่า ไม่มีการศึกษาใดเลยที่ระบุวิธีการเลี้ยงดูสัตว์ทดลอง จำนวนสัตว์ทดลองทั้งหมดที่ใช้ ผลการทดลองทั้งกลุ่ม และอาการข้างเคียงที่พบ ทำให้ไม่สามารถประเมินความเสี่ยงของอคติในบางหัวข้อได้

สรุปผลการศึกษา: จากผลการศึกษายืนยันประสิทธิภาพในการต้านฤทธิ์ข้ามของเซรุ่มต้านพิษงูในเอเชียต่องูพิษที่มีความสำคัญทางแพทย์ในเอเชีย โดยการนำเซรุ่มต้านพิษงูที่มีประสิทธิภาพในการต้านฤทธิ์ข้ามมาใช้ จะช่วยเพิ่มการเข้าถึงเซรุ่มต้านพิษงูที่ยืนยันว่ามีประสิทธิภาพ และอาจช่วยลดการลงทุนในขั้นตอนการวิจัยและพัฒนาเซรุ่มต้านพิษงูชนิดใหม่ เนื่องจากมีเซรุ่มต้านพิษงูที่มีอยู่มีประสิทธิภาพในการใช้ข้ามสายพันธุ์ได้ โดยเฉพาะอย่างยิ่ง ในประเทศที่ไม่สามารถผลิตเซรุ่มต้านพิษงูได้เอง นอกจากนี้ ฐานข้อมูลที่เกี่ยวข้องการโรคงูกัดยังมีช่องว่างของความรู้ที่ต้องการการศึกษาและพัฒนาเพิ่มเติมเพื่อเติมเต็มฐานข้อมูลของโรคนี้

สาขาวิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อนิสิต .....
ปีการศึกษา	2564	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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KEYWORD: Anti-venom, Snakebite, Snakebite envenoming, Cross-neutralization, Neutralization, Cross-reactivity, Asia

Sutinee Soopairin : ANTIVENOM CROSS-NEUTRALIZATION AND NEUTRALIZATION: A SYSTEMATIC REIVEW OF NON-CLNICAL STUDIES IN ASIA REGION. Advisor: Asst. Prof. Suthira Taychakhoonavudh, Ph.D.

Background: Cross-neutralizing strategy has been applied to improve access to antivenoms which is a key to reduce mortality and disability of snakebite envenoming. However, preclinical studies have been conducted to discover antivenom's cross-neutralizing ability when clinical studies may not be ethically applicable. This study aimed to identify and summarize scattered evidence regarding Asia antivenom's preclinical efficacy.

Methods: We performed a systematic review to search for articles published up to May 30, 2022, in PubMed, Scopus, Web of Science, and Embase. Reference searching of eligible articles was done. Preclinical studies reported the available Asia antivenom's neutralizing ability against Asia snake lethality were included. Quality assessment was performed using the SYRCLE's risk of bias tool and the adapted ARRIVE guideline. Cross-neutralizing and neutralizing ability were summarized. Availability of Asia antivenoms was analyzed by comparing data from included studies with Snakebite Information and Data Platform developed by the World Health Organization.

Results: Forty-eight studies were included. Most studies assessed antivenom efficacy against snakes from Southeast Asia (56%), followed by South Asia (36%) and East Asia (19%). Twenty-two (49%) medically important snakes had antivenom(s) with confirmed neutralizing ability against their lethality. Situation analysis of availability of effective antivenom in Asia demonstrated that locally produced antivenoms did not cover all medically important snakes in each country. Among countries without local antivenom production, preclinical studies were conducted only in Bangladesh, Sri Lanka, and Malaysia. Husbandry, total number of animals used, group outcome reporting, and adverse events were not reported in any studies which limited risk of bias assessment.

Conclusions: Cross-neutralizing of antivenoms against some medically important snakes in Asia was confirmed. This strategy may improve access to geographically effective antivenoms and bypass investment in new antivenom development, especially in countries without local antivenom production. Database should be developed to fulfill a lacking snakebite-information system.

Field of Study:	Social and Administrative Pharmacy	Student's Signature .....
Academic Year:	2021	Advisor's Signature .....

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Sutinee Soopairin

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER I
INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Snakebite envenoming is considered by World Health Organization (WHO) as a neglected tropical disease because of its high morbidity, disability, and mortality. It usually occurs in rural areas of low to middle income countries with insufficient financial support for patient suffering from snakebite envenoming. Moreover, antivenom, the only effective treatment for snakebite envenoming, can reduce morbidity, disability, and mortality of this public health problem yet its high cost leading to unaffordability, lower demand, and eventual antivenom discontinuation. Consequently, patients are left behind and cannot access to appropriate treatment. Hence, enhancement of antivenom accessibility is a key factor resulting in effective treatment and increasing patient's outcomes. Unfortunately, many developing countries with high incidence of snakebite cannot access to antivenom because they have no local antivenom production and no specific antivenoms are available in those regions. To improve access to snakebite envenoming treatment, antivenoms have to be imported from other countries. However, the effectiveness of imported antivenoms is uncertain because the products are not raised against snakes in the designation area.

Some antivenoms were able to neutralize against the toxic effects of the venom of different snake species not included in the immunizing venom mixture, especially those closely related species, called cross-neutralization or para-specific activity. In some antivenom-deficient countries, alternative antivenoms with para-specific activity with snakes in their region have been used. Hence, cross-neutralization between antivenom and snake venoms is one of the strategies applied to increase antivenom accessibility.

Most antivenoms available in the market have been registered without prior clinical studies. However, plenty of non-clinical studies have been conducted to assess the efficacy of antivenoms against snake venoms since antivenom neutralization of lethal activity is essential in non-clinical assay before any use in humans according to WHO guidelines for the production, control, and regulation of snake antivenom immunoglobulins. In earlier study, systematic review of non-clinical efficacy of antivenoms in sub-Saharan Africa region

was conducted. Unfortunately, no systematic review about this topic has been conducted to summarize this scattered evidence in Asia region.

1.2 RESEARCH QUESTION

What is the non-clinical evidence of cross-neutralization and neutralization between available antivenoms and snake venoms in Asia region?

1.3 OBJECTIVE

To identify, review, and summarize the information about cross-neutralization and neutralization between available antivenoms and snake venoms in Asia region reporting in non-clinical studies.

1.4 EXPECTED BENEFITS

Antivenom is a product in which access is an issue. Results from the systematic review will provide information on the cross-neutralization and neutralization between available antivenoms and snake venoms in Asia region reporting in non-clinical studies. These results can be used to guide the regulatory guidance for antivenom in which full clinical studies may not applicable. This could be the first step toward the improvement of equal access to antivenom across the Asia region.

CHAPTER II
LITERATURE REVIEW

2.1 BURDEN OF SNAKEBITE ENVENOMING

2.1.1 WHAT IS SNAKEBITE ENVENOMING?

Snakebite envenoming is a disease caused by injection of venom by a venomous snake.(1) However, some bites of venomous snakes do not cause envenoming called dry bites and some bites caused by non-venomous snakes. Hence, about 50% of snakebite were envenoming, a figure depends on snake species.(2) Since snake venoms consist of different kind of toxic components, people who were bitten by different snake species may develop vary signs and symptoms. Snakes can be classified into 2 families, Viperidae (viperids) and Elapidae (elapids). Snake venoms from family Viperidae (Viperids) mainly consist of snake venom metalloproteinase (SVMP), especially class PIII, which predominately cause signs and symptoms associated with cardiovascular and hemostasis disturbance. SMVP causes hemostasis disturbance due to coagulopathy, generates bleeding local effect, and induces systemic hemorrhage resulting in cardiovascular shock. On the other hand, snake venoms from family Elapidae (elapids) mainly cause neurotoxicity due to alpha-neurotoxin and beta-neurotoxin, especially phospholipase A2 (PLA2), main neurotoxins found in elapid snake venoms. These neurotoxins induce flaccid neuromuscular paralysis leading to blockage of respiratory muscles which can be life-threatening. Moreover, sea snake venoms from both families develop rhabdomyolysis because of myotoxic PLA2s. Snakebite envenoming may also induce acute kidney injury in some snake species from both families due to renal cytotoxicity, renal blood flow reduction, and deposition of myoglobin in renal tubules.(1) Unfortunately, envenoming by venomous snake effects quality of life of patients due to long-term effects of envenoming. Survivors of snakebite envenoming may develop chronic pain, swelling, and local necrosis leading to amputation and disability as a long-term sequalae of local effects. Some patients suffering from acute kidney injury may develop chronic kidney disease. Besides, psychological effects have been reported in survivors of snakebite envenoming, for example, depression, post-traumatic stress disorder (PTSD), and somatization. Other long-tern effects have also been reported such as hypopituitarism and blindness.(3)

2.1.2 EPIDEMIOLOGY DATA OF SNAKEBITE ENVENOMING

Global incidence rate and number of snakebite envenoming had been estimated and published in the article. The results of estimation showed that around 421,000 to 1,841,000 people were envenoming per year. The incidence rate of this disease was at least 6.28 to 27.5 incidences per 100,000 people annually. South Asia region had the highest incidence of snakebite envenoming. According to country estimation, India had the highest envenoming among all countries. 81,000 people in India were envenoming per year. In addition, Southeast Asia is a region with the second highest incidence of snakebite envenoming. These demonstrated that snakebite envenoming is an important public health issue in Asia region. Global mortality rate and deaths from snakebite envenoming had also been estimated and published. Consistently, region with the highest deaths from snakebite envenoming was South Asia region since it is the region with highest incidence of snakebite envenoming. Annually, around 20,000 to 94,000 deaths from snakebite envenoming occurred. Unsurprisingly, India is the countries with the highest deaths because of snakebite envenoming. Nevertheless, incidence and mortality rate of snakebite envenoming were found to be underestimated because this disease usually occurs in rural areas or in poor countries with poor databases. Moreover, peoples living in those areas usually seek for traditional therapy rather than hospital treatment and some patients.(4)

2.1.3 ECONOMIC BURDEN OF SNAKEBITE ENVENOMING

Since snakebite envenoming usually occurs in rural areas of low to middle income countries, treatment cost of snakebite envenoming, especially antivenoms, is higher than patients' monthly income. Additionally, lack of patient financial support in some countries lead to treatment inaccessibility. Some patients have to sale their belongings which also affect their families. As state above, snakebite envenoming and its long-term effects impact on productivity. Patients lost their workdays and income resulting in financial insufficiency for themselves and their families. Moreover, snakebite envenoming has higher Disability Adjusted Life Years (DALYs) comparing with other neglected tropical diseases such as

Dengue. In spite of the higher burdens, snakebite envenoming receives less funds per DALY.(5)

2.1.4 MEDICALLY IMPORTANT VENOMOUS SNAKE CATEGORIES

Since snakebite envenoming occurs in many regions, especially rural area, with different venomous snake species in different areas. It is important to prioritize the venomous snake species that are medically important according to incidence and mortality from their bites. Hence, World Health Organization (WHO) classified some venomous snake as medically important snakes. There are 2 categories of medically important snakes. First, highest medically important snakes (category 1) are defined as deadly venomous snakes that are widespread in that area and cause a lot of snakebites leading to high morbidity, disability, or mortality. Next, secondary medically important snakes (category 2) are deadly venomous snakes causing morbidity, disability, or death, that their data might be inadequate and/or are less frequently implicated.

Two categories of venomous snakes in different regions have been reported within the WHO Guidelines on production, control, and regulation of snake antivenom immunoglobulins. Venomous snakes in both categories of medically important venomous snakes are different among countries. For example, Category 1 medically important venomous snakes in Thailand are *Bungarus candidus, Naja kaouthia, Naja siamensis, Calloselasma rhodostoma, Cryptelytrops albolabris,* and *Daboia siamensis.* While category 1 medically important venomous snakes in India are *Bungarus caeruleus, Naja kaouthia* (east), *Naja naja*, *Daboia russelii, Echis carinatus, Hypnale hypnale* (south-west). It demonstrates that each country has its own concern and these medically important venomous snakes should be the most important targets for antivenom production or seeking for available antivenoms that are able to neutralize their toxic effect in order to reduce disability and death.(6)

2.1.5 SNAKEBITE ENVENOMING, A NEGLECTED TROPICAL DISEASE

As discuss above, WHO decided to classify snakebite envenoming as a category A of the neglected tropical disease in 2017. The African Society of Venomology (ASV) suggested 4 strategies to solve the problem of snakebite envenoming. First, Epidemiological data must

be collected to specify the antivenom requirement in different regions. Second, it is important to educate populations with high risk of snakebite envenoming to avoid working in risk areas, wear boots or other protections, and immediately go to hospital rather than traditional healers after bitten by venomous snakes. Third, improve antivenom accessibility by good manufacture with efficacy and safety validation of antivenoms. Lastly, healthcare professionals need to be trained to select the appropriate antivenoms in their regions, use specific and appropriate antivenoms in individual patients, and handle with antivenom storage.(7)

Moreover, WHO aims to reduce 50% of disability and death from snakebite envenoming by 2030. To reach this goal, WHO create a snakebite envenoming roadmap for global to fight with this neglected tropical disease. As mentioned in the road map, first, it is important to have an effective and safe life-saving treatment of snakebite envenoming which is antivenom. Good quality antivenoms should be accessible for snakebite envenoming patients in terms of availability and affordability. Investment or funding in research regarding effectiveness, safety, and production technologies of antivenoms should be provided for manufacturers. With adequate investment or funding, manufacturers have potential to develop effective and specific antivenoms for the market which can improve antivenom availability. In terms of affordability, we should reduce out-of-pocket payments among patients by increasing resources or developing health policy to help vulnerable patients since this neglected tropical disease mostly affect patients with low income. Regulation and quality control of antivenoms need to be revised to develop better regulation and quality control standard ensuring quality of antivenoms. Global risk-benefit assessment of antivenoms will be evaluated to confirm antivenom quality and accessibility in each region. WHO hopes that at least 3 good quality and fit-for-use antivenoms are accessible in each area. Second, empowering communities is also the key. Educating communities about snakebite envenoming prevention and avoidance, reducing traditional-healers seeking behaviors along with the first-aid after snakebite, and improving confidence in antivenom quality and hospital treatment should be applied to empower communities. Third, strong health systems help us fight against this neglected public health issue. Community health service should be strengthened and well-prepared for snakebite envenoming patients. All facilities needed for snakebite envenoming management which consists of pre-hospital

care, ambulance transportation, effective diagnosis, vital medicines including antivenoms, and other supportive care should be accessible and well-prepared for snakebite envenoming victims. Moreover, healthcare professional training is also important to improve decision making in snakebite envenoming treatment since the less time consumes, the more chance to save patients' life. Hence, it is essential for healthcare professionals to immediately diagnose snake species and select an appropriate and effective antivenom against different bite along with other supportive treatment. Research regarding disease burden, epidemiology, clinical outcome, cost reduction, and policy development should be done to collect more data for developing country-level implementation and Improving healthcare accessibility through health policy development. Lastly, regional, and global multidisciplinary collaboration is vital to promote advocacy and harmonize data management and synthesis.(8)

2.2 ANTIVENOMS

2.2.1 WHAT IS ANTIVENOM?

Antivenom is an immunoglobulin or a part of immunoglobulin purified from plasma of animals immunized with snake venom(s). When animals are immunized with venom from one species of snake, this developed antivenom is called Monovalent (Monospecific) antivenom. On the other hand, if animals are immunized with more than one species of snake, this antivenom is called Polyvalent (Polyspecific) antivenom. These antivenoms are created specifically for each snake(s). Nevertheless, some antivenoms were able to cross-neutralize against different species of snake, especially closely related species, which is called para-specific activity or cross-neutralizing activity.(2)

2.2.2 GUIDELINE OF SNAKEBITE TREATMENT

According to WHO guidelines for the management of snakebites (2^{nd} edition), antivenom is indicated for patients proven or suspected with snakebite who develop $\geq$ 1 signs of systematic envenoming. It should be given as soon as possible when it is indicated.

Additionally, it is important for healthcare professionals not to administer antivenom to patients without medical indication in order to avoid antivenom reaction.(2)

Since antivenom is the only effective treatment for snakebite envenoming. It is crucial to use specific antivenoms to treat snakebite envenoming to reduce morbidity and mortality compared with treatment without antivenoms. According to a case study from Africa, Fav-Afrique polyvalent antivenom, an effective and safe antivenom, had been used against African snakebite envenoming. Unfortunately, Fav-Afrique polyvalent antivenom was unavailable in the first 6 months of 2013. An alternative antivenom had been used during this period. However, it was found that snakebite envenoming fatality rate increased from only 0.47% to 10% after using the alternative antivenom instead of Fav-Afrique polyvalent antivenom. This case study confirms that specific antivenoms are necessary as a potential treatment for snakebite envenoming.(9)

2.2.3 REASONS AND CONSEQUENCES OF ANTIVENOM INACCESSIBILITY

Antivenom inaccessibility in this study is clarified as antivenom unavailability and/ or unaffordability. It is the key factor resulting in ineffective treatment of snakebite envenoming in many developing countries.

Reasons and consequences that cause antivenom inaccessibility is called vicious cycle of antivenom inaccessibility. As we all known, antivenom prices are usually high which decrease antivenom access. Moreover, some patients have low confidence in product effectiveness and safety since some antivenoms are not effective due to low quality, unsafe, or ineffective production, absence of appropriate reference standards and specification, and lack of knowledge about antivenoms in healthcare professionals. Hence, they decide to seek for traditional treatment with lower price. These factors push down antivenom demand resulting in falling sales of antivenom. Manufacturers have no choice but to reduce antivenom production because of reduced income and profit. Manufacturers must increase antivenom prices to stay in the market, decrease investment in antivenom procurement causing poor quality antivenoms, or decide to exit production. All factors discussed above lead to antivenom inaccessibility. Moreover, weak healthcare system and poor antivenom distribution also caused antivenom inaccessibility. Nowadays, this vicious cycle of

antivenom inaccessibility had been unsolved and this dramatic issue needs to be untangled immediately.(10, 11)

2.3 CROSS-NEUTRALIZATION AS A STRATEGIE FACILITATING ACCESS TO ANTIVENOMS

2.3.1 OVERVIEW OF STRATEGIES FACILITATING ACCESS TO ANTIVENOMS

To improve access to antivenoms, a multicomponent strategy needs to be applied. It is important to identify the appropriate snake species and their geographical origin to represent the toxin profile of target snake species for developing effective antivenoms. Good manufacturing and quality control is also a key to develop effective antivenoms leading to enhancement of confidence in products and patient access to antivenom. Some countries with local production of antivenom can produce antivenoms for other regions or other countries which can increase access to antivenoms. Moreover, manufacturers from different regions may collaborate to develop antivenoms for international use, for example, pan-African polyvalent antivenom. Engagement of governments with national and international public health organizations is crucial to create proper health policy frameworks for improvement of access to antivenoms, for example, increase investment in the production of antivenoms and provide financial support for patients suffering from snakebite envenoming.(12, 13)

2.3.2 CROSS-NEUTRALIZATION OF LETHAL ACTIVITY

Cross-neutralization is one of the strategies to improve access to antivenoms. According to WHO guidelines for the production control and regulation of snake antivenom immunoglobulins, cross-neutralization is defined as ability of an antivenom raised against venom(s) to neutralize the toxic effects of the venom of a closely related snake species that are not included in the immunizing mixture.(2) Antivenoms with cross-neutralization ability are used for treating snakebite envenoming in antivenom shortage areas. For example, Malaysia, which has no local production of antivenoms, uses antivenom supplied from The Queen Saovabha Memorial Institute (QSMI), Thailand.(14) However, assessment of antivenom ability to neutralize toxic effects against snake venoms using preclinical testing is required for antivenoms that will be used in new geographical areas in human. A

compulsory and essential assay for preclinical testing of antivenoms is a neutralization of lethality of snake venoms as a routine quality control of antivenom effectiveness. While other preclinical tests are additional assays which are not a routine quality control of antivenoms.(2)

Neutralization of lethal activity or lethality, a compulsory assay of preclinical testing of antivenoms, determines the effectiveness of the antivenom whether it can neutralize lethal activity of the snake venom(s). First, the median lethal dose (LD50) assay should be held in order to calculate the lethal activity of snake venom. Median lethal dose (LD50) is defined as the smallest amount of snake venom that cause 50% death in the mice injected with solutions of venom. Groups of at least 5 mice are inject intravenously in the tail vein with 0.2 – 0.5 ml of solutions with various doses of snake venoms or inject intraperitoneally with 0.5 ml of solutions. Deaths of mice are recorded at 24 hours in intravenous injection assay or at 48 hours in intraperitoneal injection assay. LD50 will be calculated using statistical analysis, e.g., Probit analysis. Next, the median effective dose (ED50) assay is held to assess the ability of antivenom to neutralize toxic effect of snake venoms. The median effective dose (ED50) of an antivenom is defined as the volume of antivenom that protects 50% of the mice injected with solutions of snake venom. A fixed amount of venom, which is called challenge dose (multiples of LD50), with various volumes of the antivenom is mixed, incubated for 30 minutes at 37 °C, and adjusted to a constant final volume with saline solution. Then, each mixture is injected intravenously into the tail vein of groups of 5 – 6 mice or inject intraperitoneally. A control group of mice were injected intravenously or intraperitoneally with a mixture of saline solution with challenge dose of snake venom without antivenom to ensure that this challenge dose will absolutely cause 100% lethality. After injection, deaths are recorded at 24 hours in intravenous injection assay or at 48 hours in intraperitoneal injection assay. The results will be analyzed using statistical analysis, e.g., Probit analysis.(2, 15)

As preclinical test is used as a routine quality control, clinical studies in human of antivenoms have been neglected even the century use of antivenoms and they are not a requirement for antivenom aprroval.[2] Hence, there are plenty of preclinical assessment of antivenom effectiveness, especially neutralization of lethal activity. Systematic review of preclinical assessment of antivenoms in sub-Saharan Africa region was conducted.(16) The results of this study demonstrated lack of preclinical testing of antivenom effectiveness in

sub-Saharan Africa and absence of epidemiological database of snakebite envenoming. Additionally, various methods and metrics used obstruct the comprehensive meta-analysis of antivenom preclinical efficacy and it is hard for healthcare professionals in the decision making for snakebite envenoming treatment.

CHAPTER III
METHODOLOGY

This study consisted of 2 parts; Part A: a systematic review conducted to summarize cross-neutralization and neutralization data of Asia antivenoms against Asia snakes and database searching to search for a list of available antivenoms in Asia and Part B: an analysis of antivenom availability in Asia

3.1 PART A: A SYSTEMATIC REVIEW CONDUCTED TO RETRIEVE CROSS-NEUTRALIZATION AND NEUTRALIZATION DATA OF ASIA ANTIVENOMS AGAINST ASIA SNAKES

The systematic review methods were conducted following the Methodological Expectations of Cochrane Intervention Reviews (MECIR) and be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.(17, 18) Study protocol was registered at PROSPERO (CRD42022284543).(19)

3.1.1 Definition of terms

The following terms in this review are defined below.

Cross-neutralization

Some antivenoms were able to cross-neutralize against the toxic effects of the venom of different snake species not included in the immunizing venom mixture, especially closely related species, also called para-specific activity.

Median effective dose (or effective dose 50%) (ED50)

The volume of antivenom that can protect 50% of mouses injected intravenously or intraperitoneally with a challenge dose of snake venom (Multiples of LD50 of venom).

Median lethal dose or lethal dose 50% (LD50)

The amount of snake venoms that are injected intravenously or intraperitoneally causing 50% of death in mouses in a group after 24–48 hours.

Monospecific antivenom

Antivenoms that are raised from venom of a single species and are limited in use to that species or to a few closely related species (typically from the same genus) whose venoms show clinically effective cross-neutralization with the antivenom. The term “monovalent” is often used and has the same meaning.

Neutralization

Antivenoms that were able to neutralize against the toxic effects of the venom of snake specie(s) in the immunizing venom mixture.

Polyspecific antivenom

Antivenoms that are obtained by fractionating the plasma from animals immunized with a mixture of venoms from more than one species of venomous snakes. The term “polyvalent” is often used and has the same meaning.

3.1.2 Search strategy and eligibility criteria

The following electronic bibliographic databases: PubMed; Scopus; Web of Science; and EMBASE, were used to search for published articles related to cross-neutralization and neutralization between antivenoms and snake venoms. The search term used in this review was ((Antivenom OR Antivenin OR Antivenene OR Anti-venom) AND Snake* AND Neutrali*). The search term for Scopus was (Antivenom OR Antivenin OR Antivenene OR Anti-venom) AND Snake AND Neutralize. The search term for Web of Scinece was TS = (Antivenins OR Antivenom OR Antivenin OR Antivenene OR Anti-venom) AND TS=Snake* AND TS=neutrali*. Lastly, the search term for Embase was (‘snake venom antiserum’/exp/mj OR antivenom OR antivenin OR amtivenene OR ‘anti venom’) AND snake* AND neutrali*. All search terms were developed by SS under supervision by CP and ST. Full search strategy with results was provided in the Appendix. We initially searched for published articles from inception up to 30 May 2022. Reference searching was done to search for some related articles that were not included in searches. Grey literature was not searched in this review.

Inclusion criteria for this systematic review were preclinical studies conducted following WHO guideline, using murine subjects, and demonstrating *in vivo* cross-neutralizing activity

and/or neutralizing ability of available antivenoms in Asian market against lethal activity of snake venoms originating from Asia. Case studies, cross-over studies, studies in other species which was not murine, *in vitro* studies, *ex vivo* studies, and in sillico studies were excluded. Studies using non-Asia and unavailable antivenoms were excluded. Moreover, studies reporting only parameters indicating neutralization of toxic effects of snake venoms other than lethality were also excluded since they were supplementary preclinical assays which were not required.(15) There was no language restriction in this systematic review.

3.1.3 Study selection and data extraction

Titles and abstracts of studies identified using the search strategy were screened independently by two reviewers (SS and CP) to select relevant studies. The full texts of all relevant studies were retrieved and independently assessed for eligibility by two reviewers (SS and CP). Any discrepancy between both reviewers over the eligibility of any studies was resolved through discussion with the third reviewer (ST).

A standardized, pre-piloted data extraction form was used to independently extract data from the included studies using Microsoft® Excel spreadsheet for Mac (Microsoft, Redmond, WA, USA) by two reviewers (SS and CP). Discrepancies between both reviewers were resolved through discussion with the third reviewer (ST). Extracted information included:

1. General information of included studies: authors, publication year, title, DOI, reference
2. Snake information: snake species, origin of snakes
3. Antivenom information: antivenom, manufacturer, country manufacturer located, snake venom(s) in the immunizing mixture in antivenom development, type of antivenom, animal source, manufacturing information, marketed neutralizing potency
4. Parameters indicating neutralization of lethality between antivenoms and snake venoms: route of administration, LD50, challenge dose, ED50, potency, normalized potency, recommendation in the articles, recommendation of number of antivenom vial(s) used, volume of antivenom to neutralize 100 mg of snake venom, protein concentration

5. Information for assessment of the risk of bias.

3.1.4 Quality assessment

Two review authors (SS and CP) independently assessed the risk of bias of the included studies by using Systematic Review Centre for Laboratory animal Experimentation's (SYRCLE) risk of bias tool for animal studies.(20) Moreover, adapted Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines, a guideline for reporting an *in vivo* experiment, was used to assess the reporting quality of the included studies in four domains: Experimental set up:

   a. Antivenom batch
   b. Antivenom total protein content
   c. Geographical origin of snake species
   d. Ethical compliance statement
   e. Conflict of interest statement

2. Animals:
   a. Source of animals
   b. Mouse strain
   c. Weight
   d. Mouse sex
   e. Husbandry
3. Procedure:
   a. Stating of control groups.
   b. Multiples of LD50 used in neutralization of lethality experiment
   c. Number of mouses per group
   d. Total number of animals and number of groups used in the experiment
   e. Antivenom and snake venom pre-incubation
   f. Route of administration
   g. Volume of mixture injected
   h. Experiment length
4. Result reporting:
   a. Mouse group outcome
   b. Adverse events
   c. Description of statistical analysis

d. Calculation method

e. Units used to report ED50s.(16)

3.1.5 Data synthesis

The extracted data were qualitatively synthesized using a content analysis to generate the summary of the methodological characteristics of the included studies. The summary showed how well the preclinical studies assessing neutralization of lethality of available antivenoms in Asia and Asian snake venoms had been conducted.

Extracted parameters indicating neutralization of lethal activity between available antivenoms and snake venoms, such as median lethal dose (LD50), the amount of snake venoms that are injected intravenously or intraperitoneally causing 50% of death in mouses in a group after 24–48 hours; median effective dose (ED50), the volume of antivenom that can protect 50% of mouses injected intravenously or intraperitoneally with a challenge dose of snake venom (Multiples of LD50 of venom); and potency from each study, were summarized and presented. Cross-neutralizing and neutralizing ability from the included studies was demonstrated in heat map to depict the efficacy of available antivenoms in Asia that was able to neutralize against lethality of snake venoms in Asia.

3.2 PART B: AN ANALYSIS OF ANTIVENOM AVAILABILITY IN ASIA

To gain insights on the situation of antivenom availability in Asia, data from the first part were combined with a list of available antivenoms in Asia from Snakebite Information and Data Platform, a new snakebite database developed by WHO.(21) We also identified medically important venomous snakes in Asia from WHO guideline.(15) Medically important venomous snakes were categorized in 2 categories. First, category 1 medically important venomous snakes (Highest medical important) defined as those highly venomous snakes which were common or widespread in areas with large human population and caused numerous snake-bites, resulting in high levels of morbidity, disability, or mortality. For category 2 medically important venomous snakes, they were defined as highly venomous snakes that can cause morbidity, disability, or death but they were poorly known species and/or not a common cause of bites.(15) Next, we compared a list of Asia available

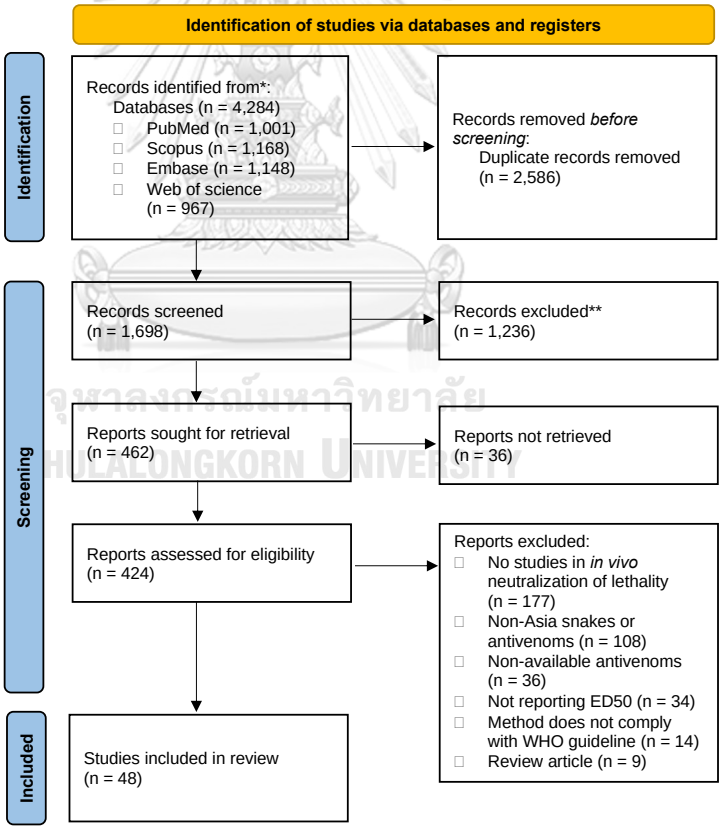
antivenoms with a list of medically important venomous snakes to analyze the situation of effective antivenom availability against medically important venomous snakes in Asia. We also summarized several Asia medically venomous snakes with studies reported antivenom cross-neutralizing ability and neutralizing ability included in this systematic review.

CHAPTER IV
RESULTS

4.1 PART A: A SYSTEMATIC REVIEW CONDUCTED TO RETRIEVE CROSS-NEUTRALIZATION AND NEUTRALIZATION DATA OF ASIA ANTIVENOMS AGAINST ASIA SNAKES

4.1.1 Study selection

A total of 4,284 articles were identified from four electronic databases using discreet search strategy. A total of 2,586 duplicated articles were removed. Titles and abstracts of 1,698 articles were screened and 426 full-text articles were assessed for eligibility. Eventually, 48 eligible articles were included as shown in Figure 1. No studies were retrieved from reference searching.



Abbreviation: ED50 – Median effective dose; WHO – World Health organization.

Figure 1 Study selection flow diagram

4.1.2 Study characteristics

Snake species inhabited in Asia region which had been studied to assess antivenom cross-neutralizing and neutralizing ability against them are summarized in Table 1.

Table 1 Study characteristics

Author, year	Family	Snake species	Country	Route of administra-tion	LD50	Antivenom	Manufacturer	Challenge dose	ED50 (mcl)	ER50 (mg venom/ ml antivenom)	Potency	Protein concentration (mg/ml)
Tan KY, 2022 (22)	Viperidae	*Deinagkistrodon acutus*	Taiwan	I.V.	8.27 (7.03-9.72) mcg/g	Deinagkistrodon acutus Monovalent Antivenoms	Central for Disease Control	2	2.78	136.84 (116.32-160.83)	68.42	Not reported
Tan KY, 2022 (22)	Viperidae	*Deinagkistrodon acutus*	China	I.V.	3.00 (2.74-3.28) mcg/g	Deinagkistrodon acutus Monovalent Antivenoms	Central for Disease Control	2	5.00	27.60 (25.21-30.18)	13.80	Not reported
Tan KY, 2022 (22)	Viperidae	*Deinagkistrodon acutus*	Taiwan	I.V.	8.27 (7.03-9.72) mcg/g	Deinagkistrodon acutus Monovalent Antivenoms	Shanghai Serum Bio-Technology Co., Ltd	2	6.88	60.15 (51.13-70.69)	30.07	Not reported
Tan KY, 2022 (22)	Viperidae	*Deinagkistrodon acutus*	China	I.V.	3.00 (2.74-3.28) mcg/g	Deinagkistrodon acutus Monovalent Antivenoms	Shanghai Serum Bio-Technology Co., Ltd	2	32.00	32.00 (29.23-34.99)	16.00	Not reported
Chanhome O, 2022 (23)	Viperidae	*Protobothrops kelomohy*	Thailand (Northern Thailand)	I.V.	0.67 (0.58-0.78) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute	3	39.70 (32.13-49.08)	1.02 (0.83-1.26)	Not reported	Not reported
Chanhome O, 2022 (23)	Viperidae	*Protobothrops kelomohy*	Thailand (Northern Thailand)	I.V.	0.67 (0.58-0.78) mcg/g	Russell's viper antivenin	Queen Saovabha Memorial Institute	3	111.33 (85.23-145.41)	0.36 (0.28-0.48)	Not reported	Not reported
Chanhome O, 2022 (23)	Viperidae	*Protobothrops kelomohy*	Thailand (Northern Thailand)	I.V.	0.67 (0.58-0.78) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute	2.5	293.38 (234.96-356.59)	0.12 (0.09-0.14)	Not reported	Not reported
Chanhome O, 2022 (23)	Viperidae	*Protobothrops kelomohy*	Thailand (Northern Thailand)	I.V.	0.67 (0.58-0.78) mcg/g	Malayan pit viper antivenin	Queen Saovabha Memorial Institute	2	Not effective	Not effective	Not reported	Not reported

Wong KY, 2021 (24)	Elapidae	*Naja naja*	Sri Lanka (Colombo)	I.V.	0.75 (0.48-1.18) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd.	2.5	35.00	1.23 (1.11-1.37)	Not reported	Not reported
Faisal T, 2021 (25)	Viperidae	*Daboia russelii*	Sri Lanka	I.V.	0.24 (0.22-0.39) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd.	5	6.25 (5.04-7.75)	4.61 (3.65-11.90)	3.69	84.93 ± 4.3
Faisal T, 2021 (25)	Viperidae	*Daboia russelii*	India	I.V.	0.32 (0.27-0.46) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd.	5	7.83 (6.40-9.58)	4.70 (3.97-6.76)	3.76	84.93 ± 4.3
Attarde S, 2021 (26)	Elapidae	*Naja sagittifera*	India (Andaman Island)	I.V.	0.47 mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd.	3	Not effective	Not reported	Not effective	26.2 ± 1.2
Attarde S, 2021 (26)	Elapidae	*Naja sagittifera*	India (Andaman Island)	I.V.	0.47 mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines	3	126.00 (100.00-158.32)	Not reported	0.15	26.5 ± 0.77
Attarde S, 2021 (26)	Elapidae	*Naja sagittifera*	Andaman Island, India	I.V.	0.47 mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute	3	136.00 (117.43-157.68)	Not reported	0.14	25.9 ± 0.44
Attarde S, 2021 (26)	Elapidae	*Naja naja*	India	I.V.	0.84 mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd.	5	151.74 (123.78-186.00)	Not reported	0.44	26.2 ± 1.2
Attarde S, 2021 (26)	Elapidae	*Naja naja*	India	I.V.	0.84 mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines	5	198.46 (140.51-280.32)	Not reported	0.34	26.5 ± 0.77
Tan CH, 2021 (27)	Elapidae	*Naja philippinensis*	Philippines	I.V.	0.18 (0.12-0.27) mcg/g	Philippine Cobra antivenom	Research Institute for Tropical Medicine in the Philippines, Philippines	5	44.94 (20.6-69.23)	0.5 (0.33- 0.75)	0.40	16.2 ± 1.1
Tan CH, 2021 (27)	Elapidae	*Naja samarensis*	Philippines	I.V.	0.2 (0.16-0.25) mcg/g	Philippine Cobra antivenom	Research Institute for Tropical Medicine in the Philippines, Philippines	5	120.86 (104.79-139.40)	0.21 (0.17-0.26)	0.17	16.2 ± 1.1

Oh AMF, 2021 (28)	Elapidae	*Bungarus multicinctus*	China	I.V.	0.027 (0.026-0.028) mcg/g	Bungarus multicinctus monovalent antivenom	Shanghai Serum Biological Technology Co., Ltd., China	5	1.65	1.88 (1.81-1.95)	1.50	77
Oh AMF, 2021 (28)	Elapidae	*Bungarus multicinctus*	Taiwan	I.V.	0.087 (0.084-0.091) mcg/g	Bungarus multicinctus monovalent antivenom	Shanghai Serum Biological Technology Co., Ltd., China	5	4.13	2.49 (2.41-2.61)	2.00	77
Oh AMF, 2021 (28)	Elapidae	*Bungarus multicinctus*	China	I.V.	0.027 (0.026-0.028) mcg/g	Neuro bivalent antivenom	Centres for Disease Control, Taiwan	5	8.92	0.35 (0.34-0.36)	0.28	27
Oh AMF, 2021 (28)	Elapidae	*Bungarus multicinctus*	Taiwan	I.V.	0.087 (0.084-0.091) mcg/g	Neuro bivalent antivenom	Centres for Disease Control, Taiwan	5	33.39	0.31 (0.30-0.32)	0.25	27
Laxme RRS, 2021 (29)	Viperidae	*Daboia russelii*	India (Punjab, North India)	I.V.	2.97 (2.46 – 3.58) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	29.99 (24.99-36)	Not reported	0.40	26.2 ± 1.2
Laxme RRS, 2021 (29)	Viperidae	*Daboia russelii*	India (Andhra Pradesh, Southeast India)	I.V.	3.65 (3.37-3.95) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	16.07 (13.39-19.30)	Not reported	0.91	26.2 ± 1.2
Laxme RRS, 2021 (29)	Viperidae	*Daboia russelii*	India (Wast Bengal, East India)	I.V.	6.9 (6.23-7.62) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	27.66 (20.47-37.37)	Not reported	1.00	26.2 ± 1.2
Laxme RRS, 2021 (29)	Viperidae	*Daboia russelii*	India (Maharashtra, Southwest India)	I.V.	3.8 (3.42-4.21) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	17.93 (15.52-20.71)	Not reported	0.85	26.2 ± 1.2
Laxme RRS, 2021 (29)	Viperidae	*Daboia russelii*	India (Madhya Pradesh,	I.V.	2.29 (2.11-2.48) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	10.71 (8.92-12.86)	Not reported	0.86	26.2 ± 1.2

			Central India)									
Laxme RRS, 2021 (30)	Elapidae	*Naja naja*	India (Punjab, North India)	I.V.	6.53 (5.65-7.54) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	67.37	Not reported	0.39	26.2 ± 1.2
Laxme RRS, 2021 (30)	Elapidae	*Naja naja*	India (Andhra Pradesh, Southeast India)	I.V.	10.93 (9.10-13.10) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	54.24	Not reported	0.81	26.2 ± 1.2
Laxme RRS, 2021 (30)	Elapidae	*Naja naja*	India (Wast Bengal, East India)	I.V.	5.46 (4.56-6.53) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	60.45	Not reported	0.36	26.2 ± 1.2
Laxme RRS, 2021 (30)	Elapidae	*Naja naja*	India (Maharashtra, Southwest India)	I.V.	50.63 mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	Not effective	Not reported	Not effective	26.2 ± 1.2
Laxme RRS, 2021 (30)	Elapidae	*Naja naja*	India (Madhya Pradesh, Central India)	I.V.	4.36 (3.76-5.04) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	60.45	Not reported	0.29	26.2 ± 1.2
Yee KT, 2020 (31)	Viperidae	*Trimeresurus erythrurus*	Myanmar	I.V.	93.76 (74.64-116.68) mcg/mouse	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	3	71	Not reported	2.64	Not reported
Yee KT, 2020 (31)	Viperidae	*Trimeresurus erythrurus*	Myanmar	I.V.	93.76 (74.64-116.68) mcg/mouse	Russell' viper anti-venom	Myanmar Pharmaceutical Factory, Myanmar	3.5	125	Not reported	1.88	Not reported

Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	Malaysia (Seremban)	I.V.	0.9 (0.59-1.36) mcg/g	King cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	129.09 (111.99-148.94)	0.77 (0.50-1.16)	0.61	19.7 ± 0.7
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	Thailand (Bangkok)	I.V.	1.04 (0.88-1.23) mcg/g	King cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	39.37 (35.69-43.43)	2.91 (2.46-3.44)	2.32	19.7 ± 0.7
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	China (Guangzhou)	I.V.	0.51 (0.44-0.60) mcg/g	King cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	170.16 (153.72-188.37)	0.33 (0.28-0.39)	0.26	19.7 ± 0.7
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	Indonesia (East Java Island)	I.V.	0.48 (0.38-0.59 mcg/g	King cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	139.58 (104.98-185.53)	0.38 (0.30-0.47)	0.3	19.7 ± 0.7
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	Malaysia (Seremban)	I.V.	0.90 (0.59-1.36) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	2.5	97.24 (79.44-119.03)	0.53 (0.35-0.80)	0.32	102.9 ± 0.8
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	Thailand (Bangkok)	I.V.	1.04 (0.88-1.23) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	5	45.30 (43.65-47.02)	2.53 (2.14-2.99)	2.02	102.9 ± 0.8
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	China (Guangzhou)	I.V.	0.51 (0.44-0.60) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	2.5	73.45 (64.53-83.61)	0.40 (0.34-0.47)	0.24	102.9 ± 0.8
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	Indonesia (East Java Island)	I.V.	0.48 (0.38-0.59) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	5	148.41 (139.14-158.30)	0.36 (0.28-0.44)	0.29	102.9 ± 0.8
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	Malaysia (Seremban)	I.V.	0.90 (0.59-1.36 mcg/g)	Naja atra antivenom	Shanghai Institute Biological Technology Co., Ltd., China	2.5	>200	-	Not effective	255.6 ± 3.2
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	Thailand (Bangkok)	I.V.	1.04 (0.88-1.23) mcg/g	Naja atra antivenom	Shanghai Institute Biological Technology Co., Ltd., China	5	97.24 (79.44-119.03)	1.34 (1.13-1.58)	1.07	255.6 ± 3.2

Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	China (Guangzhou)	I.V.	0.51 (0.44-0.60) mcg/g	Naja atra antivenom	Shanghai Institute Biological Technology Co., Ltd., China	2.5	>200	-	Not effective	255.6 ± 3.2
Tan KY, 2020 (32)	Elapidae	*Ophiophagus hannah*	Indonesia (East Java Island)	I.V.	0.48 (0.38-0.59) mcg/g	Naja atra antivenom	Shanghai Institute Biological Technology Co., Ltd., China	2.5	>200	-	Not effective	255.6 ± 3.2
Lin B, 2020 (33)	Elapidae	*Bungarus multicinctus*	China	I.P.	0.09 mcg/g	Bungarus multicinctus monovalent antivenom	Shanghai Serum Biological Technology Co., Ltd., China	3	17.68 mcg/g	Not reported	Not reported	Not reported
Lin B, 2020 (33)	Elapidae	*Bungarus fasciatus*	China	I.P.	1.50 mcg/g	Bungarus multicinctus monovalent antivenom	Shanghai Serum Biological Technology Co., Ltd., China	3	>800 mcg/g	Not reported	Not reported	Not reported
Lin B, 2020 (33)	Elapidae	*Naja atra*	China	I.P.	0.50 mcg/g	Bungarus multicinctus monovalent antivenom	Shanghai Serum Biological Technology Co., Ltd., China	3	>800 mcg/g	Not reported	Not reported	Not reported
Lin B, 2020 (33)	Elapidae	*Ophiophagus hannah*	China	I.P.	0.44 mcg/g	Bungarus multicinctus monovalent antivenom	Shanghai Serum Biological Technology Co., Ltd., China	3	499 mcg/g	Not reported	Not reported	Not reported
Liew JL, 2020 (34)	Viperidae	*Trimeresurus purpureomaculatus*	Malaysia	I.V.	0.89 (0.59-1.36) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	5	35	2.54	2.03	20.2 ± 0.7
Liew JL, 2020 (34)	Viperidae	*Trimeresurus albolabris*	Thailand	I.V.	0.50 (0.40-0.63) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	5	10.95	5.73	4.59	20.2 ± 0.7
Lee LP, 2020 (35)	Viperidae	*Trimeresurus wiroti*	Malaysia	I.V.	0.78 (0.64-0.96) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	22.47 (14.80-34.11)	Not reported	1.05	18.07 ± 1.1
Lee LP, 2020 (35)	Viperidae	*Trimeresurus puniceus*	Indonesia	I.V.	1.21 (1.05-1.39) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	45.62 (29.15-71.40)	Not reported	0.79	18.07 ± 1.1

Hia YL, 2020 (36)	Elapidae	*Bungarus fasciatus*	Malaysia (Peninsular)	I.V.	0.91 (0.54-1.52) mcg/g	Banded krait antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	150	0.32 (0.19-0.53)	0.19	58.73 ± 0.02
Hia YL, 2020 (36)	Elapidae	*Bungarus fasciatus*	Thailand (Bangkok)	I.V.	2.55 (2.27-2.86) mcg/g	Banded krait antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	50	2.68 (2.91-3.00)	1.61	58.73 ± 0.02
Hia YL, 2020 (36)	Elapidae	*Bungarus fasciatus*	Indonesia (Java Island)	I.V.	0.45 (0.30-0.68) mcg/g	Banded krait antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	15.80	1.50 (1.00-2.26)	0.9	58.73 ± 0.02
Hia YL, 2020 (36)	Elapidae	*Bungarus fasciatus*	Myanmar	I.V.	2.44 (2.15-2.78) mcg/g	Banded krait antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	77.80	1.65 (1.45-1.88)	0.99	58.73 ± 0.02
Hia YL, 2020 (36)	Elapidae	*Bungarus fasciatus*	China (Guangdong)	I.V.	1.44 (1.15-1.81) mcg/g	Banded krait antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	100	0.76 (0.60-0.95)	0.45	58.73 ± 0.02
Choraria A, 2020 (37)	Viperidae	*Daboia russelii*	India	I.V.	10 mcg/mouse	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	3	35 (29.34-40.65)	Not reported	0.57	30
Choraria A, 2020 (37)	Viperidae	*Echis carinatus*	India	I.V.	12 mcg/mouse	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	3	40.80 (35.34-46.25)	Not reported	0.60	30
Tan CH, 2019 (38)	Viperidae	*Trimeresurus nebularis*	Malaysia	I.V.	2.00 (1.61-2.48) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	5	100	2.00 (1.61-2.48)	1.60	20.2
Pla D, 2019 (39)	Viperidae	*Daboia russelii*	Sri Lanka	I.V.	7.89 (7.16-10.90) mcg/mouse	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	3	Not reported	1.89 (1.49-2.84)	1.26	Not reported
Pla D, 2019 (39)	Viperidae	*Daboia russelii*	Sri Lanka	I.V.	7.89 (7.16-10.90) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt Ltd., India	3	Not reported	2.33 (1.62-5.12)	1.55	Not reported
Pla D, 2019 (39)	Viperidae	*Daboia russelii*	Pakistan	I.V.	3.67 (3.01-4.37) mcg/mouse	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	3	Not reported	1.86 (1.14-3.66)	1.24	Not reported

Pla D, 2019 (39)	Viperidae	*Daboia russelii*	Pakistan	I.V.	3.67 (3.01-4.37) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt Ltd., India	3	Not reported	2.66 (1.73-5.48)	1.78	Not reported
Pla D, 2019 (39)	Viperidae	*Daboia russelii*	Bangladesh	I.V.	3.69 (2.00-5.86) mcg/mouse	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	3	Not reported	<1.50	< 1.00	Not reported
Pla D, 2019 (39)	Viperidae	*Daboia russelii*	Bangladesh	I.V.	3.69 (2.00-5.86) mcg/mouse	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt Ltd., India	3	Not reported	<1.50	< 1.00	Not reported
Oh AMF, 2019 (40)	Elapidae	*Bungarus sindanus*	Pakistan	I.V.	0.04 (0.035-0.045) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	13.29	0.32 (0.24-0.41)	0.25	82
Lingam TMC, 2019 (41)	Viperidae	*Daboia siamensis*	Thailand	I.V.	0.34 (0.30-0.38) mcg/g	Russell's viper antivenin	Queen Saovabha Memorial Institute, Thailand	5	9.5	3.75 (3.31-4.20)	3.01	40.5 ± 0.6
Lingam TMC, 2019 (41)	Viperidae	*Daboia siamensis*	Indonesia	I.V.	0.22 (0.20-0.24) mcg/g	Russell's viper antivenin	Queen Saovabha Memorial Institute, Thailand	5	6.64	3.48 (3.16-3.80)	2.78	40.5 ± 0.6
Lingam TMC, 2019 (41)	Viperidae	*Daboia siamensis*	Thailand	I.V.	0.34 (0.30-0.38) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	5	Not effective	Not reported	Not reported	123.1 ± 0.2
Lingam TMC, 2019 (41)	Viperidae	*Daboia siamensis*	Indonesia	I.V.	0.22 (0.20-0.24) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	5	Not effective	Not reported	Not reported	123.1 ± 0.2
Laxme RRS, 2019 (42)	Elapidae	*Naja naja*	India (Maharashtra, West India)	I.V.	0.73 (0.50-0.88) mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	81.27 (67.30-98.13)	Not reported	0.72	8.16 ± 0.15
Laxme RRS, 2019 (42)	Elapidae	*Naja kaouthia*	India (Arunachal Pradesh,	I.V.	0.24 (0.18-0.28) mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	122.04 (101.1-147.32)	Not reported	0.16	8.16 ± 0.15

			Northeast India)									
Laxme RRS, 2019 (42)	Elapidae	*Naja kaouthia*	India (West Bengal, East India)	I.V.	1.23 (1.14-1.33) mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	Not effective	Not reported	Not effective	8.16 ± 0.15
Laxme RRS, 2019 (42)	Elapidae	*Bungarus caeruleus*	India (Punjab, North India)	I.V.	0.10 (0.03-0.31) mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	26.17 (19.36-35.37)	Not reported	0.31	8.16 ± 0.15
Laxme RRS, 2019 (42)	Elapidae	*Bungarus sindanus*	India (Rajasthan, Northwest India)	I.V.	0.02 (0.01-0.03) mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	5.43 (4.34-6.51)	Not reported	0.27	8.16 ± 0.15
Laxme RRS, 2019 (42)	Elapidae	*Bungarus fasciatus*	India (West Bengal, East India)	I.V.	1.12 (0.93-1.33) mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	138.89 (111.11-166.67)	Not reported	0.64	8.16 ± 0.15
Laxme RRS, 2019 (42)	Viperidae	*Echis carinatus*	India (Maharashtra, West India)	I.V.	0.61 (0.34-0.75) mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	92.54 (73.96-111.11)	Not reported	0.53	8.16 ± 0.15
Laxme RRS, 2019 (42)	Viperidae	*Echis carinatus sochureki*	India (Rajasthan, Northwest India)	I.V.	1.76 (0.77-2.10) mcg/g	Polyvalent snake antivenom (Asia)	Premium Serums & Vaccines Pvt. Ltd., India	5	92.54 (73.96-111.11)	Not reported	1.51	8.16 ± 0.15

Deka A, 2019 (43)	Elapidae	*Naja kaouthia*	India	Not reported	0.148 mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	4	92.68 ± 4.68 mg/g	Not reported	Not reported	Not reported
Deka A, 2019 (43)	Elapidae	*Naja kaouthia*	India	Not reported	0.148 mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	4	76.38 ± 3.48 mg/g	Not reported	Not reported	Not reported
Deka A, 2019 (43)	Elapidae	*Naja kaouthia*	India	Not reported	0.148 mcg/g	Snake antivenin I.P. (Asia)	Haffkine Biopharmaceutical Corporation Limited, India	4	112.66 ± 5.11 mg/g	Not reported	Not reported	Not reported
Deka A, 2019 (43)	Elapidae	*Naja kaouthia*	Bangladesh	Not reported	0.12 mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	4	97.28 ± 2.46 mg/g	Not reported	Not reported	Not reported
Deka A, 2019 (43)	Elapidae	*Naja kaouthia*	Bangladesh	Not reported	0.12 mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	4	94.62 ± 4.52 mg/g	Not reported	Not reported	Not reported
Deka A, 2019 (43)	Elapidae	*Naja kaouthia*	Bangladesh	Not reported	0.12 mcg/g	Snake antivenin I.P. (Asia)	Haffkine Biopharmaceutical Corporation Limited, India	4	137.23 ± 4.42 mg/g	Not reported	Not reported	Not reported
Chaisakul J, 2019 (44)	Viperidae	*Daboia siamensis*	Thailand	I.V.	10.40 (5.61-19.26) mcg/mouse	Russell's viper antivenin	Queen Saovabha Memorial Institute, Thailand	6	17 (10.88-26.56)	Not reported	Not reported	Not reported
Chaisakul J, 2019 (44)	Viperidae	*Daboia siamensis*	Myanmar	I.V.	6.00 (3.26-11.04) mcg/mouse	Russell's viper antivenin	Queen Saovabha Memorial Institute, Thailand	6	60 (40.58-88.70)	Not reported	Not reported	Not reported
Chaisakul J, 2019 (44)	Viperidae	*Daboia siamensis*	Taiwan	I.V.	6.70 (3.26-13.77) mcg/mouse	Russell's viper antivenin	Queen Saovabha Memorial Institute, Thailand	6	29.16 (23.75-35.79)	Not reported	Not reported	Not reported
Chaisakul J, 2019 (44)	Viperidae	*Daboia siamensis*	China	I.V.	4.89 (4.11-5.83) mcg/mouse	Russell's viper antivenin	Queen Saovabha Memorial Institute, Thailand	6	49.99 (47.23-52.90)	Not reported	Not reported	Not reported
Tan KY, 2018 (45)	Viperidae	*Daboia siamensis*	China (Guangxi)	I.V.	0.18 (0.12-0.27) mcg/g	Doboia siamensis Monovalent Snake Antivenom	Centres for Disease Control, Taiwan	5	11.24	1.76 (1.17-2.64)	1.41	19.3 ± 0.5

Tan KY, 2018 (45)	Viperidae	*Daboia siamensis*	Taiwan	I.V.	0.09 (0.06-0.14) mcg/g	Doboia siamensis Monovalent Snake Antivenom	Centres for Disease Control, Taiwan	5	4.9	2.02 (1.35-3.14)	1.62	19.3 ± 0.5
Tan KY, 2018 (45)	Viperidae	*Daboia siamensis*	China (Guangxi)	I.V.	0.18 (0.12-0.27) mcg/g	Gloydius brevicaudus Monovalent Snake Antivenom	Shanghai Serum Biological Technology Co., Ltd., China	5	91.24	0.22 (0.14-0.33)	0.17	168.5 ± 0;7
Tan KY, 2018 (45)	Viperidae	*Daboia siamensis*	China (Guangxi)	I.V.	0.18 (0.12-0.27) mcg/g	Deinagkistrodon acutus Monovalent Snake Antivenom	Shanghai Serum Biological Technology Co., Ltd., China	5	Not effective	Not effective	Not effective	181.1 ± 6.4
Liu BS, 2018 (46)	Elapidae	*Naja atra*	Taiwan	I.P.	0.67 mcg/g	Neuro bivalent antivenom	Centres for Disease Control, Taiwan	5	101.82 (86.97-119.17) mg/g	Not reported	Not reported	Not reported
Liu BS, 2018 (46)	Elapidae	*Naja atra*	Taiwan	I.P.	0.67 mcg/g	SAV-Naja	Institute of Vaccines and Biological Substances (IVAC), Vietnam	5	17.41 (14.87-20.38) mg/g	Not reported	Not reported	Not reported
Liu BS, 2018 (46)	Elapidae	*Naja atra*	Taiwan	I.P.	0.67 mcg/g	Neuro polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	9.70 (9.28-11.35) mg/g	Not reported	Not reported	Not reported
Liu BS, 2018 (46)	Elapidae	*Naja atra*	Taiwan	I.P.	0.67 mcg/g	Doboia siamensis Monovalent Snake Antivenom	Centres for Disease Control, Taiwan	5	Not effective	Not reported	Not reported	Not reported
Faisal T, 2018 (47)	Viperidae	*Daboia russelii*	Pakistan	I.V.	0.19 (0.17-0.25) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	78.29 (63.98-95.80)	0.29 (0.26-0.31)	0.23	20
Tan CH, 2017 (48)	Viperidae	*Trimeresurus insularis*	Indonesia	I.V.	0.78 (0.64-0.96) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	2.5	145.90 (129.12-164.97)	0.27 (0.11-0.33)	0.16	104.3 ± 0.5
Tan CH, 2017 (48)	Viperidae	*Trimeresurus purpureomaculatus*	Indonesia	I.V.	0.70 (0.65-0.76) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	2.5	100 (80.68-123.94)	0.35 (0.34-0.35)	0.21	104.3 ± 0.5

Tan CH, 2017 (48)	Viperidae	*Trimeresurus hageni*	Indonesia	I.V.	0.50 (0.40-0.63) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	2.5	70.68 (54.11-92.31)	0.35 (0.28-0.45)	0.21	104.3 ± 0.5
Tan CH, 2017 (48)	Viperidae	*Trimeresurus puniceus*	Indonesia	I.V.	1.10 (0.73-1.69) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	2.5	141 (104.04-191.2)	0.39 (0.25-0.60)	0.23	104.3 ± 0.5
Tan CH, 2017 (48)	Viperidae	*Trimeresurus insularis*	Indonesia	I.V.	0.78 (0.64-0.96) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	13.78 (8.70-21.80)	2.83 (1.23-3.48)	1.7	20.22 ± 0.7
Tan CH, 2017 (48)	Viperidae	*Trimeresurus purpureomaculatus*	Indonesia	I.V.	0.70 (0.65-0.76) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	5	38.13 (28.03-51.86)	1.84 (1.78-1.89)	1.47	20.22 ± 0.7
Tan CH, 2017 (48)	Viperidae	*Trimeresurus hageni*	Indonesia	I.V.	0.50 (0.40-0.63) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	8 (5.50-11.60)	3.13 (2.50-3.94)	1.88	20.22 ± 0.7
Tan CH, 2017 (48)	Viperidae	*Trimeresurus puniceus*	Indonesia	I.V.	1.10 (0.73-1.69) mcg/g	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	55.63 (36.60-84.40)	0.99 (0.66-1.52)	0.59	20.22 ± 0.7
Oh AMF, 2017 (49)	Elapidae	*Bungarus caeruleus*	Sri Lanka	I.V.	0.06 (0.04-0.08) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	9.44	0.56 (0.43-0.72)	0.44	Not reported
Oh AMF, 2017 (49)	Elapidae	*Bungarus caeruleus*	India	I.V.	0.10 (0.08-0.12) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	17.14	0.60 (0.48-0.74)	0.48	Not reported
Oh AMF, 2017 (49)	Elapidae	*Bungarus caeruleus*	Pakistan	I.V.	0.06 (0.05-0.07) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	16.53	0.37 (0.32-0.42)	0.3	Not reported
Wong KY, 2016 (50)	Elapidae	*Naja naja*	Pakistan	I.V.	0.22 (0.12-0.40) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	32.77	0.77 (0.69-0.85)	0.61	Not reported
Wong KY, 2016 (50)	Elapidae	*Naja naja*	Pakistan	I.V.	0.22 (0.12-0.40) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	18	1.39 (1.25-1.55)	1.11	Not reported
Wong KY, 2016 (50)	Elapidae	*Naja naja*	Pakistan	I.V.	0.22 (0.12-0.40) mcg/g	Neuro bivalent antivenom	Centres for Disease Control, Taiwan	5	75	0.34 (0.32-0.35)	0.27	Not reported

Villalta M, 2016 (51)	Viperidae	*Daboia russelii*	Sri Lanka	I.V.	7.80 (7.00-8.60) mcg/mouse	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	3	Not reported	1.90 (1.50-2.80)	Not reported	41.90 ± 0.04
Villalta M, 2016 (51)	Elapidae	*Echis carinatus*	Sri Lanka	I.V.	8.80 (6.50-11.40) mcg/mouse	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	3	Not reported	0.80 (0.50-1.30)	Not reported	41.90 ± 0.04
Villalta M, 2016 (51)	Viperidae	*Hypnale hynale*	Sri Lanka	I.V.	17.30 (15.60-19.40) mcg/mouse	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	3	Not reported	0.60 (0.30-0.90)	Not reported	41.90 ± 0.04
Villalta M, 2016 (51)	Elapidae	*Naja naja*	Sri Lanka	I.V.	22.60 (15.90-29.70) mcg/mouse	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	3	Not reported	0.70 (0.60-0.90)	Not reported	41.90 ± 0.04
Tan KY, 2016 (52)	Elapidae	*Naja kaouthia*	Thailand	I.V.	0.18 (0.12-0.27) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	18.75	1.15 (0.77-1.73)	0.92	45.00 ± 0.60
Tan CH, 2016 (53)	Elapidae	*Naja sputatrix*	Indonesia (Java Island)	I.V.	0.90 (0.59-1.36) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	2.5	111.25	0.51 (0.33-0.76)	0.3	104.3 ± 0.5
Tan CH, 2016 (53)	Elapidae	*Bungarus fasciatus*	Indonesia (Java Island)	I.V.	0.45 (0.30-0.68) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	5	44.94	1.10 (0.73-1.66)	0.88	104.3 ± 0.5
Tan CH, 2016 (53)	Viperidae	*Calloselasma rhodostoma*	Indonesia (Java Island)	I.V.	1.35 (0.78-2.06) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	5	9.38	15.83 (9.15-24.16)	12.67	104.3 ± 0.5
Tan CH, 2016 (53)	Elapidae	*Naja sputatrix*	Indonesia (Java Island)	I.V.	0.90 (0.59-1.36) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	50	1.04 (0.68-1.56)	0.62	75.3 ± 0.6
Tan CH, 2016 (53)	Elapidae	*Bungarus fasciatus*	Indonesia (Java Island)	I.V.	0.45 (0.30-0.68) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	43.75	1.08 (0.72-1.63)	0.86	75.3 ± 0.6
Tan CH, 2016 (53)	Viperidae	*Calloselasma rhodostoma*	Indonesia (Java Island)	I.V.	1.35 (0.78-2.06) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	18.75	7.92 (4.58-12.09)	6.34	43 ± 0.5
Tan CH, 2016 (53)	Elapidae	*Naja sumatrana*	Indonesia	I.V.	0.39 (0.32-0.48) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	5	156.57	0.24 (0.19-0.29)	0.19	104.3 ± 0.5

			(Sumatra)									
Tan CH, 2016 (53)	Elapidae	*Bungarus candidus*	Indonesia (Java Island)	I.V.	0.11 (0.07-0.17) mcg/g	Serum Anti Bisa Ular (Biosave)	Bio Farma, Indonesia	5	111.25	0.12 (0.00-0.19)	0.10	104.3 ± 0.5
Tan CH, 2016 (53)	Elapidae	*Naja sumatrana*	Indonesia (Sumatra)	I.V.	0.39 (0.32-0.48) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	55.63	0.67 (0.55-0.82)	0.53	75.3 ± 0.6
Tan CH, 2016 (53)	Elapidae	*Bungarus candidus*	Indonesia (Java Island)	I.V.	0.11 (0.07-0.17) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	5.56	2.18 (1.39-3.36)	1.74	75.3 ± 0.6
Maduwage K, 2016 (54)	Viperidae	*Daboia russelii*	Sri Lanka	I.V.	0.10 (0.08-0.12) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	Not reported	2.06	Not reported	198 (mg/vial)
Maduwage K, 2016 (54)	Viperidae	*Echis carinatus*	Sri Lanka	I.V.	0.66 (0.52-0.81) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	Not reported	2.79	Not reported	198 (mg/vial)
Maduwage K, 2016 (54)	Elapidae	*Naja naja*	Sri Lanka	I.V.	0.66 (0.48-0.98) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	Not reported	4.32	Not reported	198 (mg/vial)
Maduwage K, 2016 (54)	Elapidae	*Bungarus caeruleus*	Sri Lanka	I.V.	0.20 (0.15-0.25) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	Not reported	3.92	Not reported	198 (mg/vial)
Maduwage K, 2016 (54)	Viperidae	*Daboia russelii*	Sri Lanka	I.V.	0.10 (0.08-0.12) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	5	Not reported	1.24	Not reported	98 (mg/vial)
Maduwage K, 2016 (54)	Viperidae	*Echis carinatus*	Sri Lanka	I.V.	0.66 (0.52-0.81) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	5	Not reported	2.82	Not reported	98 (mg/vial)
Maduwage K, 2016 (54)	Elapidae	*Naja naja*	Sri Lanka	I.V.	0.66 (0.48-0.98) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	5	Not reported	2.42	Not reported	98 (mg/vial)
Maduwage K, 2016 (54)	Elapidae	*Bungarus caeruleus*	Sri Lanka	I.V.	0.20 (0.15-0.25) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	5	Not reported	2.93	Not reported	98 (mg/vial)
Yap MK, 2015 (55)	Elapidae	*Naja sputatrix*	Not reported (Studies from	I.V.	0.90 (0.59-1.36) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	136.72	Not reported	Not reported	Not reported

			Malaysia)									
Tan KY, 2015 (56)	Elapidae	*Naja kaouthia*	Malaysia	I.V.	0.90 (0.59-1.36) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	78.29	1.38 (0.90-2.08)	1.10	Not reported
Tan KY, 2015 (56)	Elapidae	*Naja kaouthia*	Thailand	I.V.	0.18 (0.12-0.27) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	18.75	1.15 (0.77-1.73)	0.92	Not reported
Tan KY, 2015 (56)	Elapidae	*Naja kaouthia*	Vietnam	I.V.	0.90 (0.59-1.36) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	120.86	0.87 (0.57-1.32)	0.70	Not reported
Tan KY, 2015 (56)	Elapidae	*Naja kaouthia*	Malaysia	I.V.	0.90 (0.59-1.36) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	70.68	1.43 (0.94-2.16)	1.14	Not reported
Tan KY, 2015 (56)	Elapidae	*Naja kaouthia*	Thailand	I.V.	0.18 (0.12-0.27) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	17.67	1.17 (0.78-1.76)	0.94	Not reported
Tan KY, 2015 (56)	Elapidae	*Naja kaouthia*	Vietnam	I.V.	0.90 (0.59-1.36) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	89.89	1.10 (0.72-1.66)	0.88	Not reported
Tan CH, 2015 (57)	Elapidae	*Hydrophis schistosus*	Malaysia	I.V.	0.07 (0.05-0.09) mcg/g	Neuro bivalent antivenom	Centres for Disease Control, Taiwan	2.5	141.36	0.03 (0.02-0.04)	0.02	Not reported
Tan CH, 2015 (57)	Elapidae	*Hydrophis curtus*	Malaysia	I.V.	0.11 (0.07-0.17) mcg/g	Neuro bivalent antivenom	Centres for Disease Control, Taiwan	2.5	200	0.03 (0.02-0.05)	0.02	Not reported
Tan CH, 2015 (57)	Elapidae	*Hydrophis schistosus*	Malaysia	I.V.	0.07 (0.05-0.09) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	89.89	0.05 (0.03-0.06)	0.03	Not reported
Tan CH, 2015 (57)	Elapidae	*Hydrophis curtus*	Malaysia	I.V.	0.11 (0.07-0.17) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	2.5	89.89	0.07 (0.05-0.11)	0.04	Not reported

Tan CH, 2015 (57)	Elapidae	*Hydrophis schistosus*	Malaysia	I.V.	0.07 (0.05-0.09) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	100	0.07 (0.05-1.00)	0.06	Not reported
Tan CH, 2015 (57)	Elapidae	*Hydrophis curtus*	Malaysia	I.V.	0.11 (0.07-0.17) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	125	0.09 (0.06-0.14)	0.07	Not reported
Leong PK, 2015 (58)	Elapidae	*Naja sumatrana*	Malaysia	I.V.	0.50 (0.40-0.62) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	25	2.30 (1.86-2.85)	1.84	Not reported
Leong PK, 2015 (58)	Elapidae	*Naja kaouthia*	Thailand	I.V.	0.23 (0.15-0.34) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	22.47	1.18 (0.78-1.79)	0.94	Not reported
Leong PK, 2015 (58)	Elapidae	*Naja sputatrix*	Indonesia	I.V.	0.90 (0.59-1.36) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	111.25	0.93 (0.61-1.41)	0.74	Not reported
Leong PK, 2014 (59)	Viperidae	*Calloselasma rhodostoma*	Malaysia	I.V.	1.48 (0.92-2.56) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	22.47	9.09 (5.88-14.29)	7.27	Not reported
Leong PK, 2014 (59)	Viperidae	*Calloselasma rhodostoma*	Indonesia	I.V.	1.35 (0.78-2.06) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	11.2	12.50 (7.69-20.00)	10.00	19.82 ± 1.39
Leong PK, 2014 (59)	Viperidae	*Trimeresurus albolabris*	Not reported	I.V.	0.50 (0.40-0.63) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	11.24	4.55 (2.94-6.67)	3.64	19.82 ± 1.39
Leong PK, 2014 (59)	Viperidae	*Trimeresurus purpureomaculatus*	Not reported	I.V.	1.10 (0.75-1.68) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	21.55	5.26 (2.04-14.28)	4.21	19.82 ± 1.39
Leong PK, 2014 (59)	Viperidae	*Trimeresurus popeiorum*	Not reported	I.V.	2.00 (1.61-2.48) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	21.81	8.33 (5.56-12.50)	6.66	19.82 ± 1.39

Leong PK, 2014 (59)	Viperidae	*Tropidolaemus wagleri*	Not reported	I.V.	1.50 (1.37-1.64) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	Not effective	Not effective	Not effective	19.82 ± 1.39
Leong PK, 2014 (59)	Viperidae	*Daboia siamensis*	Thailand	I.V.	0.13 (0.10-0.15) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	11.24	1.27 (0.84-1.92)	1.02	19.82 ± 1.39
Leong PK, 2014 (59)	Viperidae	*Daboia siamensis*	Myanmar	I.V.	0.34 (0.08-0.81) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	35.36	5.00 (2.38-11.00)	4.00	19.82 ± 1.39
Leong PK, 2014 (59)	Viperidae	*Calloselasma rhodostoma*	Malaysia	I.V.	1.48 (0.92-2.56) mcg/g	Malayan pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	5	Not reported	4.00 (1.87-8.33)	Not reported	14.53 ± 0.74
Danpaiboon W, 2014 (60)	Elapidae	*Ophiophagus hannah*	Thailand	I.P.	1.10 mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	1.5	19.60 mg/kg	Not reported	Not reported	Not reported
Pakmanee N, 2013 (61)	Viperidae	*Daboia siamensis*	Thailand	I.V.	3.71 mcg/mouse	Russell's viper antivenin	Queen Saovabha Memorial Institute, Thailand	2	Not reported	12.40 (12.00-12.70)	0.60	Not reported
Leong PK, 2012 (62)	Elapidae	*Naja sputatrix*	Not reported	I.V.	0.90 (0.59-1.36) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	2.5	156.60 (128-191.6)	0.33 (0.27-0.40)	0.20	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja siamensis*	Not reported	I.V.	0.28 (0.18-0.42) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	50 (40.30-62.00)	0.65 (0.53-0.80)	0.52	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja kaouthia*	Thailand	I.V.	0.23 (0.15-0.34) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	75 (68.50-82.10)	0.35 (0.32-0.39)	0.28	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja kaouthia*	Malaysia	I.V.	0.89 (0.59-1.35) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	2.5	70.70 (64.10-92.30)	0.36 (0.32-0.39)	0.22	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja sumatrana*	Malaysia	I.V.	0.50 (0.40-0.62) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	39.10 (32.00-47.90)	1.47 (1.20-1.79)	1.18	19.47 ± 1.71

Leong PK, 2012 (62)	Elapidae	*Naja philippinensis*	Not reported	I.V.	0.18 (0.12-0.27) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	2.5	156.60 (128.00-191.60)	0.07 (0.05-0.08)	0.04	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Ophiophagus hannah*	Not reported	I.V.	1.00 (0.81-1.24) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	2.5	156.60 (128.00-191.60)	0.37 (0.30-0.45)	0.22	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Bungarus fasciatus*	Not reported	I.V.	1.67 (1.10-2.53) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	Not report	Not effective	Not effective	Not effective	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Bungarus candidus*	Not reported	I.V.	0.11 (0.07-0.17) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	44.90 (29.60-68.20)	0.28 (0.19-0.43)	0.22	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja naja*	India	I.V.	1.80 (1.18-2.73) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	2.5	55.60 (36.60-84.50)	2.86 (1.92-4.35)	1.71	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja naja*	India	I.V.	1.08 (0.71-1.64) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	2.5	37.50 (34.30-41.00)	1.85 (1.22-2.86)	1.11	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja naja*	Sri Lanka	I.V.	1.13 (0.54-2.38) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	2.5	22.50 (14.80-34.10)	1.67 (1.52-1.82)	1.00	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja naja*	Sri Lanka	I.V.	1.08 (0.71-1.64) mcg/g	Snake Venom Antiserum I.P. (Asia)	VINS Bioproducts Ltd., India	5	150 (137.10-164.20)	0.83 (0.75-0.91)	0.66	19.47 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja sputatrix*	Not reported	I.V.	0.90 (0.59-1.36) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	Not report	Not effective	Not effective	Not effective	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja siamensis*	Not reported	I.V.	0.28 (0.18-0.42) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	2.5	70.70 (54.10-92.30)	0.23 (0.17-0.30)	0.14	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja kaouthia*	Thailand	I.V.	0.23 (0.15-0.34) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	5	55.60 (36.60-84.50)	0.46 (0.30-0.70)	0.37	7.04 ± 1.71

Leong PK, 2012 (62)	Elapidae	*Naja kaouthia*	Malaysia	I.V.	0.89 (0.59-1.35) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	Not report	Not effective	Not effective	Not effective	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja sumatrana*	Malaysia	I.V.	0.50 (0.40-0.62) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	5	150 (137.10-164.20)	0.38 (0.36-0.42)	0.30	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja philippinensis*	Not reported	I.V.	0.18 (0.12-0.27) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	Not report	Not effective	Not effective	Not effective	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Ophiophagus hannah*	Not reported	I.V.	1.00 (0.81-1.24) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	Not report	Not effective	Not effective	Not effective	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Bungarus fasciatus*	Not reported	I.V.	1.67 (1.10-2.53) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	Not report	Not effective	Not effective	Not effective	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Bungarus candidus*	Not reported	I.V.	0.11 (0.07-0.17) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	2.5	26.70 (12.70-56.40)	0.24 (0.11-0.50)	0.14	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja naja*	India	I.V.	1.80 (1.18-2.73) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	Not report	Not effective	Not effective	Not effective	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja naja*	India	I.V.	1.08 (0.71-1.64) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	Not report	Not effective	Not effective	Not effective	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja naja*	Sri Lanka	I.V.	1.13 (0.54-2.38) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	Not report	Not effective	Not effective	Not effective	7.04 ± 1.71
Leong PK, 2012 (62)	Elapidae	*Naja naja*	Sri Lanka	I.V.	1.08 (0.71-1.64) mcg/g	Polyvalent Snake Antivenom (Asia)	Bharat Serums & Vaccines, India	2.5	200	0.31	0.19	7.04 ± 1.71
Leong PK, 2012 (63)	Elapidae	*Naja sputatrix*	Not reported	I.V.	0.90 (0.59-1.36) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	111.25	0.93 (0.61-1.41)	0.74	20.3
Leong PK, 2012 (63)	Elapidae	*Naja siamensis*	Not reported	I.V.	0.28 (0.18-0.42) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	22.47	1.43 (0.94-2.18)	1.15	20.3
Leong PK, 2012 (63)	Elapidae	*Naja sumatrana*	Malaysia	I.V.	0.50 (0.40-0.62) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	25	2.30 (1.86-2.85)	1.84	20.3

Leong PK, 2012 (63)	Elapidae	*Naja kaouthia*	Thailand	I.V.	0.23 (0.15-0.34) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	22.47	1.18 (0.78-1.79)	0.94	20.3
Leong PK, 2012 (63)	Elapidae	*Naja kaouthia*	Malaysia	I.V.	0.89 (0.59-1.35) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	150	0.68 (0.62-0.75)	0.55	20.3
Leong PK, 2012 (63)	Elapidae	*Naja philippinensis*	Not reported	I.V.	0.18 (0.12-0.27) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	156.57	0.13 (0.11-0.16)	0.10	20.3
Leong PK, 2012 (63)	Elapidae	*Naja atra*	Not reported	I.V.	0.56 (0.37-0.84) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	56	0.86 (0.79-0.94)	0.52	20.3
Leong PK, 2012 (63)	Elapidae	*Naja oxiana*	Not reported	I.V.	1.11 (0.73-1.69) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	37.5	1.70 (1.56-1.85)	1.01	20.3
Leong PK, 2012 (63)	Elapidae	*Naja naja*	India	I.V.	1.80 (1.18-2.73) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	200	0.52	0.31	20.3
Leong PK, 2012 (63)	Elapidae	*Naja naja*	India	I.V.	1.08 (0.71-1.64) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	156.57	0.40 (0.32-0.49)	0.24	20.3
Leong PK, 2012 (63)	Elapidae	*Naja naja*	Sri Lanka	I.V.	1.13 (0.54-2.38) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	100	0.65 (0.52-0.84)	0.39	20.3
Leong PK, 2012 (63)	Elapidae	*Naja naja*	Sri Lanka	I.V.	1.08 (0.71-1.64) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	89.88	1.39 (0.91-2.08)	1.11	20.3
Leong PK, 2012 (63)	Elapidae	*Naja haje*	Not reported	I.V.	0.09 (0.05-1.40) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	78.29	0.13 (0.11-0.16)	0.10	20.3

Leong PK, 2012 (63)	Elapidae	*Naja melanoleuca*	Not reported	I.V.	0.33 (0.22-0.51) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	55.63	0.68 (0.44-1.03)	0.54	20.3
Leong PK, 2012 (63)	Elapidae	*Naja nigricollis*	Not reported	I.V.	0.75 (0.69-0.82) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	55.63	0.78 (0.49-1.18)	0.47	20.3
Leong PK, 2012 (63)	Elapidae	*Naja nubiae*	Not reported	I.V.	0.28 (0.22-0.37) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	78.29	0.41 (0.34-0.50)	0.33	20.3
Leong PK, 2012 (63)	Elapidae	*Naja katiensis*	Not reported	I.V.	1.20 (0.97-1.45) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	2.5	Not effective	Not effective	Not effective	20.3
Leong PK, 2012 (63)	Elapidae	*Ophiophagus hannah*	Malaysia	I.V.	1.00 (0.81-1.24) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	11.24	10.23 (6.74-15.54)	8.19	20.3
Leong PK, 2012 (63)	Elapidae	*Bungarus fasciatus*	Malaysia	I.V.	1.67 (1.10-2.53) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	111.25	1.73 (1.14-2.62)	1.38	20.3
Leong PK, 2012 (63)	Elapidae	*Bungarus candidus*	Malaysia	I.V.	0.11 (0.07-0.17) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	13.91	0.91 (0.60-1.38)	0.73	20.3
Leong PK, 2012 (63)	Elapidae	*Bungarus flaviceps*	Malaysia	I.V.	0.18 (0.09-0.21) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	11.24	1.84 (1.21-2.80)	1.47	20.3
Leong PK, 2012 (63)	Elapidae	*Bungarus multicinctus*	Not reported	I.V.	0.11 (0.05-0.22) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	37.5	0.34 (0.31-0.37)	0.27	20.3
Leong PK, 2012 (63)	Elapidae	*Bungarus caeruleus*	Not reported	I.V.	0.17 (0.11-0.25) mcg/g	Neuro-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	78.29	0.12 (0.10-0.15)	0.07	20.3

Leong PK, 2012 (63)	Elapidae	*Naja sputatrix*	Not reported	I.V.	0.90 (0.59-1.36) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	111.25	0.93 (0.61-1.41)	0.74	12.5
Leong PK, 2012 (63)	Elapidae	*Naja siamensis*	Not reported	I.V.	0.28 (0.18-0.42) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	22.47	1.43 (0.94-2.18)	1.15	12.5
Leong PK, 2012 (63)	Elapidae	*Naja sumatrana*	Malaysia	I.V.	0.50 (0.40-0.62) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	50	1.15 (0.93-1.43)	0.92	12.5
Leong PK, 2012 (63)	Elapidae	*Naja kaouthia*	Thailand	I.V.	0.23 (0.15-0.34) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	22.47	1.18 (0.78-1.79)	0.94	12.5
Leong PK, 2012 (63)	Elapidae	*Naja kaouthia*	Malaysia	I.V.	0.89 (0.59-1.35) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	150	0.68 (0.62-0.75)	0.55	12.5
Leong PK, 2012 (63)	Elapidae	*Ophiophagus hannah*	Malaysia	I.V.	1.00 (0.81-1.24) mcg/g	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	44.94	3.07 (2.80-3.35)	2.46	12.5
Tan CH, 2011 (64)	Viperidae	*Calloselasma rhodostoma*	Malaysia	I.V.	1.48 (0.78-2.06) mcg/g	Malayan pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	5	41.53 (20.40-88.40)	Not reported	3.23	Not reported
Tan CH, 2011 (64)	Viperidae	*Hypnale hypnale*	Sri Lanka	I.V.	0.90 (0.42-1.84) mcg/g	Malayan pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	5	70.71 (33.70-148.40)	Not reported	0.89	Not reported
Tan CH, 2011 (64)	Viperidae	*Calloselasma rhodostoma*	Malaysia	I.V.	1.48 (0.78-2.06) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	22.47 (14.80-34.10)	Not reported	7.14	Not reported
Tan CH, 2011 (64)	Viperidae	*Hypnale hypnale*	Sri Lanka	I.V.	0.90 (0.42-1.84) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	41.53 (20.40-88.40)	Not reported	1.52	Not reported

Tan CH, 2011 (64)	Viperidae	*Daboia russelii*	Sri Lanka	I.V.	0.24 (0.19-0.62) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	7.52 (3.53-15.30)	Not reported	2.50	Not reported
Tan CH, 2011 (64)	Viperidae	*Echis carinatus sochureki*	Pakistan	I.V.	2.08 (1.02-4.42) mcg/g	Haemato-polyvalent snake antivenom	Queen Saovabha Memorial Institute, Thailand	5	> 200	Not reported	Not effective	Not reported
Chanhome L, 2002 (65)	Viperidae	*Trimeresurus albolabris*	Thailand	I.V.	10 mcg/mouse	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	4	14	Not reported	1.40	Not reported
Chanhome L, 2002 (65)	Viperidae	*Trimeresurus macrops*	Thailand	I.V.	140 mcg/mouse	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	4	112	Not reported	2.50	Not reported
Chanhome L, 2002 (65)	Viperidae	*Trimeresurus popeiorum*	Thailand	I.V.	35 mcg/mouse	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	4	112	Not reported	0.63	Not reported
Chanhome L, 2002 (65)	Viperidae	*Trimeresurus hageni*	Thailand	I.V.	10 mcg/mouse	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	4	56	Not reported	0.36	Not reported
Chanhome L, 2002 (65)	Viperidae	*Trimeresurus purpureomaculatus*	Thailand	I.V.	8 mcg/mouse	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	4	56	Not reported	0.29	Not reported
Chanhome L, 2002 (65)	Viperidae	*Trimeresurus kanburiensis*	Thailand	I.V.	60 mcg/mouse	Green pit viper antivenin	Queen Saovabha Memorial Institute, Thailand	4	114	Not reported	1.06	Not reported
Khow O, 2001 (66)	Elapidae	*Naja kaouthia*	Thailand	I.V.	6.50 (4.70-8.90) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	29.60 (24.50-37.70)	Not reported	Not reported	Not reported
Khow O, 2001 (66)	Elapidae	*Naja kaouthia*	Thailand	I.V.	6.50 (4.70-8.90) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	41.40 (33.60-52.50)	Not reported	Not reported	Not reported

Khow O, 2001 (66)	Elapidae	*Naja kaouthia*	Thailand	I.V.	6.50 (4.70-8.90) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	45.90 (36.70-59.70)	Not reported	Not reported	Not reported
Khow O, 2001 (66)	Elapidae	*Naja kaouthia*	Thailand	I.V.	6.50 (4.70-8.90) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	29.60 (24.50-37.70)	Not reported	Not reported	Not reported
Khow O, 2001 (66)	Elapidae	*Lapemis hardwickii*	Japan	I.V.	6.50 (4.70-8.90) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	91.8	Not reported	Not reported	Not reported
Khow O, 2001 (66)	Elapidae	*Lapemis hardwickii*	Japan	I.V.	6.50 (4.70-8.90) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	128.50 (102.40-166.50)	Not reported	Not reported	Not reported
Khow O, 2001 (66)	Elapidae	*Lapemis hardwickii*	Japan	I.V.	6.50 (4.70-8.90) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	118.3 (94.70-153.40)	Not reported	Not reported	Not reported
Khow O, 2001 (66)	Elapidae	*Lapemis hardwickii*	Japan	I.V.	6.50 (4.70-8.90) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	91.80 (73.40-120.00)	Not reported	Not reported	Not reported
Chanhome L, 1999 (67)	Elapidae	*Bungarus fasciatus*	Thailand	I.V.	61.70 (43.50-87.50) mcg/mouse	Banded krait antivenin	Queen Saovabha Memorial Institute, Thailand	4	432.40 (312.60-598.80)	Not reported	Not reported	Not reported
Chanhome L, 1999 (67)	Elapidae	*Bungarus candidus*	Thailand	I.V.	3.20 (2.50-4.20) mcg/mouse	Banded krait antivenin	Queen Saovabha Memorial Institute, Thailand	4	319.70 (251.80-406.00)	Not reported	Not reported	Not reported
Chanhome L, 1999 (67)	Elapidae	*Bungarus flaviceps*	Thailand	I.V.	3.40 (2.60-4.40) mcg/mouse	Banded krait antivenin	Queen Saovabha Memorial Institute, Thailand	4	178.80 (138.30-230.00)	Not reported	Not reported	Not reported
Khow O, 1997 (68)	Elapidae	*Naja kaouthia*	Thailand	I.V.	6.61 (5.20-8.39) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	37.20 (29.00-47.50)	Not reported	Not reported	Not reported

Khow O, 1997 (68)	Elapidae	*Naja siamensis*	Thailand	I.V.	21.40 (14.39-31.80) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	91.60 (66.20-126.80)	Not reported	Not reported	Not reported
Khow O, 1997 (68)	Elapidae	*Naja kaouthia*	Thailand	I.V.	6.61 (5.20-8.39) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	28.50 (20.80-39.10)	Not reported	Not reported	Not reported
Khow O, 1997 (68)	Elapidae	*Naja siamensis*	Thailand	I.V.	21.40 (14.39-31.80) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	91.60 (66.20-126.80)	Not reported	Not reported	Not reported
Khow O, 1997 (68)	Elapidae	*Naja kaouthia*	Thailand	I.V.	6.61 (5.30-8.39) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	38.40 (29.80-52.50)	Not reported	Not reported	Not reported
Khow O, 1997 (68)	Elapidae	*Naja siamensis*	Thailand	I.V.	21.40 (14.39-31.8) mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	4	135.90 (114.00-171.00)	Not reported	Not reported	Not reported
Sells PG, 1994 (69)	Elapidae	*Naja kaouthia*	Thailand	I.V.	17.50 mcg/mouse	Cobra antivenin	Queen Saovabha Memorial Institute, Thailand	5	6.80 (6.76-6.90) mg	Not reported	Not reported	Not reported

From 48 studies included in this study, snakes inhabited in Southeast Asia, South Asia and East Asia were tested in 27 studies (56%) (23, 27, 31, 32, 34-36, 38, 41, 44, 48, 52, 53, 56-69), 18 studies (36%) (24-26, 29, 30, 37, 39, 40, 42, 43, 47, 49-51, 54, 62-64), and 9 studies (19%) (22, 28, 32, 33, 36, 44-46, 66) respectively. No studies were found to assess snakes inhabited in Central Asia. Twenty-seven studies conducted in snakes inhabited in Southeast Asia were mostly conducted in venomous snakes from Thailand (23, 32, 34, 36, 41, 44, 52, 56, 58-63, 65-69) and Malaysia (32, 34-36, 38, 56-59, 62-64) while all studies conducted in snakes from South Asia were conducted with venomous snakes inhabited in India (10 studies) (25, 26, 29, 30, 37, 42, 43, 49, 62, 63) and Sri Lanka (9 studies).(24, 25, 39, 49, 51, 54, 62-64)

In terms of snake family, twenty-nine studies (60%) (24, 26-28, 30, 32, 33, 36, 42, 43, 46, 49-58, 60, 62, 63, 66-69) include antivenom cross-neutralizing and neutralizing ability against snakes in Elapidae family and 23 (48%) studies (22, 23, 25, 29, 31, 34, 35, 37-39, 41, 42, 44, 45, 47, 48, 51, 53, 54, 59, 61, 64, 65) include antivenom cross-neutralizing and neutralizing ability against snakes in Viperidae family. The most frequently tested snake venom was *Naja kaouthia* venom (10 from 48 studies (21%) included in this study).(42, 43, 52, 56, 58, 62, 63, 66, 68, 69)

Among Asia polyvalent antivenoms demonstrated in the included articles, neuro-polyvalent snake antivenom from Queen Saovabha Memorial Institute (QSMI), Thailand was the most frequently tested polyvalent antivenom which was reported in 7 (15%) studies.(46, 53, 55-58, 63) While cobra antivenom from QSMI, Thailand was the most frequently tested monovalent antivenom reported in 10 (21%) studies among Asia monovalent antivenoms tested in the included articles.(26, 50, 52, 56, 57, 60, 63, 66, 68, 69)

4.1.3 Neutralizing and cross-neutralizing ability of available antivenom in Asia against lethality of medically important venomous snakes in Asia from preclinical studies

All neutralizing and cross-neutralizing ability of antivenom against lethality of medically important venomous snakes in Asia from the included preclinical studies were summarized in **Table 2**. Neutralizing and cross-neutralizing ability were different among antivenoms and varied between snake venoms. More details of strength of these abilities, such as, ED50,

were reported in **Table 1**. Metrics of ED50 were found to be used differently across the included studies, thereby, meta-analysis of ED50 cannot be performed in our study.

Of 45 medically important venomous snakes inhabited in Asia identified by WHO, we found that only twenty-two (49%) medically important venomous snakes in Asia were tested and confirmed neutralizing ability of antivenoms against their lethality. Ineffectiveness of antivenoms against six (13%) medically important venomous snakes were found.

Table 2 Neutralizing and cross-neutralizing ability of available Asia antivenoms against lethality of medically important venomous snakes in Asia according to non-clinical evidence

Manufacturer; Country	SSBT; CN		NIPM; TW			Haffkine; IN	Bharat; IN	Premium; IN	VINS; IN	NIH; PK	Persero ; ID	MPF; MM	RITM; PH	QSMI; TH							IVAC; VN
Snake species / Antivenom	*Agkistrodon acutus* antivenin	*Bungarus multicinctus* antivenin	Antivenom *B. multicinctus*/*N.n.naja*	*Doboia siamensis* monovalent antivenom	Monovalent Antivenin Snorkel Viper	Snake antivenin I.P. (Asia)	Snake Venom Antiserum (Polyvalent)	Snake venom antiserum I.P.	Snake Venom Antiserum I.P. (Asia)	Polyvalent Antisnake Venom Serum	Serum Anti Bisa Ular Polivalen (SABU)	Anti-Viper (Russell's viper)	Monovalent (*Naja philippinensis*) Cobra	Banded krait antivenin	Cobra Antivenin	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Malayan pit viper antivenin	Neuro-polyvalent snake antivenom	Russell's viper antivenin	Refined earth tiger snake antivenom
Elapidae																					
East Asia																					
B. multicinctus		#, CN (28, 33), TW (28)	#, CN (28), TW (28)																		
N. atra		CN (33)	#, TW (46)	TW (46)															TW (46)		TW (46)
South Asia																					
B. caeruleus						#	#, LK (54)	#, IN (42)	#, LK, IN, PK (49)	#, LK (54)											
B. sindanus								IN (42)	PK (40)												
N. kaouthia						IN (43), BD (43)	IN (43), BD (43)	IN (42)	IN (43), BD (43)												

Manufacturer; Country	SSBT; CN		NIPM; TW			Haffkine; IN	Bharat; IN		Premium; IN		VINS; IN	NIH; PK	Persero ; ID	MPF; MM	RITM; PH	QSMI; TH						IVAC; VN
Snake species / Antivenom	*Agkistrodon acutus* antivenin	*Bungarus multicinctus* antivenin	Antivenom *B. multicinctus*/*N.n.naja*	*Daboia siamensis* monovalent antivenom	Monovalent Antivenin Snorkel Viper	Snake antivenin I.P. (Asia)	Snake Venom Antiserum (Polyvalent)		Snake venom antiserum I.P.		Snake Venom Antiserum I.P. (Asia)	Polyvalent Antisnake Venom Serum	Serum Anti Bisa Ular Polivalen (SABU)	Anti-Viper (Russell's viper)	Monovalent (*Naja philippinensis*) Cobra	Banded krait antivenin	Cobra Antivenin	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Malayan pit viper antivenin	Neuro-polyvalent snake antivenom	Russell's viper antivenin	Refined earth tiger snake antivenom
N. naja			PK (50)			#	#, IN (26), LK (54)	#, IN (62) LK (62)	#, IN (26, 30, 42)	#, IN (30)	#, IN (62), PK (50), LK (24, 51, 62)	#, LK (54)					PK (50)				IN (63), LK (63)		
Southeast Asia																						
B. candidus													Java island (ID) (53)			TH (67)					#, Java island (ID) (53), MY (63)		
N. kaouthia							TH (62)	MY (62)			MY (62), TH (62)						#, MY (56, 63), TH (52, 56, 63, 66, 68, 69),				#, MY (56), TH (56, 58), VN (56)		#

Manufacturer; Country	SSBT; CN		NIPM; TW			Haffkine; IN	Bharat; IN	Premium; IN	VINS; IN	NIH; PK	Persero ; ID	MPF; MM	RITM; PH	QSMI; TH						IVAC; VN
Snake species / Antivenom	*Agkistrodon acutus* antivenin	*Bungarus multicinctus* antivenin	Antivenom *B. multicinctus*/*N.n.naja*	*Daboia siamensis* monovalent antivenom	Monovalent Antivenin Snorkel Viper	Snake antivenin I.P. (Asia)	Snake Venom Antiserum (Polyvalent)	Snake venom antiserum I.P.	Snake Venom Antiserum I.P. (Asia)	Polyvalent Antisnake Venom Serum	Serum Anti Bisa Ular Polivalen (SABU)	Anti-Viper (Russell's viper)	Monovalent (*Naja philippinensis*) Cobra	Banded krait antivenin	Cobra Antivenin	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Malayan pit viper antivenin	Neuro-polyvalent snake antivenom	Russell's viper antivenin	Refined earth tiger snake antivenom
															VN (56)						
N. philippinensis													#, PH (27)								
N. samarensis													PH (27)								
N. siamensis															TH (68)						
N. sputatrix											#, Java island (ID) (53)								Java Island (ID) (53, 58), MY (55)		
N. sumatrana							MY (62)		MY (62)		Sumatra (ID) (53)								MY (58), Sumatra (ID) (53)		
Viperidae																					
East Asia																					
D. acutus	#, CN				#, CN																

Manufacturer; Country	SSBT; CN		NIPM; TW			Haffkine; IN	Bharat; IN	Premium; IN	VINS; IN	NIH; PK	Persero ; ID	MPF; MM	RITM; PH	QSMI; TH							IVAC; VN
Snake species / Antivenom	*Agkistrodon acutus* antivenin	*Bungarus multicinctus* antivenin	Antivenom *B. multicinctus*/*N.n.naja*	*Daboia siamensis* monovalent antivenom	Monovalent Antivenin Snorkel Viper	Snake antivenin I.P. (Asia)	Snake Venom Antiserum (Polyvalent)	Snake venom antiserum I.P.	Snake Venom Antiserum I.P. (Asia)	Polyvalent Antisnake Venom Serum	Serum Anti Bisa Ular Polivalen (SABU)	Anti-Viper (Russell's viper)	Monovalent (*Naja philippinensis*) Cobra	Banded krait antivenin	Cobra Antivenin	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Malayan pit viper antivenin	Neuro-polyvalent snake antivenom	Russell's viper antivenin	Refined earth tiger snake antivenom
	(22), TW (22)				(22), TW (22)																
South Asia																					
D. russelii						#	#, IN (37), LK (54)	#, BD (39), IN (29), PK (39), LK (39)	#, BD (39), IN (25), PK (39, 47), LK (25, 39, 51)	#, LK (54)							LK (64)				
E. carinatus						#	#, IN (37), LK (54)	#, IN (42)	#, LK (51)	#, LK (54)							PK (64)				
H. hypnale									LK (51)								LK (64)	LK (64)			
Southeast Asia																					
C. rhodostoma											#, Java island (ID) (53)						#, Java island (ID) (53, 59),	#, MY (59, 64)			

Manufacturer; Country	SSBT; CN		NIPM; TW			Haffkine; IN	Bharat; IN	Premium; IN	VINS; IN	NIH; PK	Persero ; ID	MPF; MM	RITM; PH	QSMI; TH						IVAC; VN
Snake species / Antivenom	*Agkistrodon acutus* antivenin	*Bungarus multicinctus* antivenin	Antivenom *B. multicinctus*/*N.n.naja*	*Daboia siamensis* monovalent antivenom	Monovalent Antivenin Snorkel Viper	Snake antivenin I.P. (Asia)	Snake Venom Antiserum (Polyvalent)	Snake venom antiserum I.P.	Snake Venom Antiserum I.P. (Asia)	Polyvalent Antisnake Venom Serum	Serum Anti Bisa Ular Polivalen (SABU)	Anti-Viper (Russell's viper)	Monovalent (*Naja philippinensis*) Cobra	Banded krait antivenin	Cobra Antivenin	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Malayan pit viper antivenin	Neuro-polyvalent snake antivenom	Russell's viper antivenin	Refined earth tiger snake antivenom
																	MY (59, 64)				
T. albolabris																#, TH (34, 65)	#				
T. erythrurus												MM (31)				MM (31)					
T. insularis											ID (48)					ID (48)					
D. siamensis											ID (41), TH (41)	#					#, MM (59), TH (59)			#, ID (41), MM (44), TH (41, 44, 61)	

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1**.

Abbreviations: BD – Bangladesh; BE – Biological E Limited; Bharat – Bharat Serums and Vaccines Limited; CN – China; Haffkine – Haffkine Biopharmaceutical Corporation Ltd; ID – Indonesia; IN – India; IVAC – Institute of Vaccines and Biological Substances; LK – Sri Lanka; MM – Myanmar; MPF – Myanmar Pharmaceutical Factory; MY – Malaysia; NIH – National Institute of Health; NIPM – National Institute of Preventive Medicine; Persero – PT Bio Farma; PH – Philippines; PK – Pakistan; Premium – Premium Serums and Vaccines Pvt. Ltd.; QSMI – Queen Saovabha Memorial Institute; RITM –Research Institute for Tropical Medicine (Biologicals Manufacturing Division); SSBT – Shanghai Serum Bio-technology Co Ltd; TH – Thailand; TW – The Republic of China (Taiwan); VINS – VINS Bioproducts Ltd; VN – Vietnam.

Elapidae medically important venomous snakes in Asia

No Elapidae medically important venomous snakes in Central Asia were found to be tested in the included studies.

For snakes inhabited in East Asia, *Bungarus multicintus* inhabited in China lethality can be neutralized by its specific antivenom, *Bungarus multicinctus* antivenin from Shanghai Serum Bio-technology Co. Ltd., China, and cross-neutralized by neurobivalent antivenom from National Institute of Preventive Medicine, Taiwan.(28) While lethality of *Bungarus multicinctus* inhabited in Taiwan can be neutralized by neurobivalent antivenom from National Institute of Preventive Medicine, Taiwan and was cross-neutralized by *Bungarus multicinctus* antivenin from Shanghai Serum Bio-technology Co. Ltd., China.(28)

Lethality of *Naja atra* inhabited in China can be cross-neutralized by *Bungarus multicinctus* antivenin from Shanghai Serum Bio-technology Co. Ltd., China.(33) Moreover, lethality of *Naja atra* inhabited in Taiwan was neutralized by neurobivalent antivenom from National Institute of Preventive Medicine, Taiwan and cross-neutralized by neuro-polyvalent snake antivenom from QSMI, Thailand and refined earth tiger snake antivenom from Institute of Vaccines and Biological Substances (IVAC), Vietnam.(46) However, *Daboia siamensis* monovalent antivenom from Center of disease control, Taiwan was found to be ineffective against lethality of *Naja atra* inhabited in Taiwan.(46)

In South Asian snakes, *Bungarus caeruleus* inhabited in India lethality was neutralized by snake venom antiserum I.P. from Premium Serums and Vaccines Pvt. Ltd., India,(42) and snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India.(54) While lethality of *Bungarus caeruleus* inhabited in Sri Lanka was cross-neutralized by snake venom antiserum (polyvalent) from Bharat Serums and Vaccines Limited, India, snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India,(49) and polyvalent antisnake venom serum from National Institute of Health, Pakistan.(54) Moreover, Lethality of *Bungarus caeruleus* inhabited in Pakistan can be cross-neutralized by snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India.(49)

Bungarus sindanus inhabited in India lethality was found to be cross-neutralized by snake venom antiserum I.P. from Premium Serums and Vaccines Pvt. Ltd., India.(42) While

Bungarus sindanus from Pakistan can be cross-neutralized by snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India.(40)

In *Naja kaouthia* inhabited in India and Bangladesh, their lethality was cross-neutralized by snake antivenin I.P. (Asia) from Haffkine Biopharmaceutical Co. Ltd., snake venom antiserum (Polyvalent) from Bharat Serums and Vaccines Limited, India, and snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India.(43) However, lethality of *Naja kaouthia* inhabited in India cannot be cross-neutralized by snake venom antiserum I.P. from Premium Serums and Vaccines Pvt. Ltd., India.(42)

For *Naja naja* inhabited in India, its lethality can be neutralized by snake venom antiserum (Polyvalent) from Bharat Serums and Vaccines Limited, India,(26) snake venom antiserum I.P. from Premium Serums and Vaccines Pvt. Ltd., India,(26, 30, 42) and snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India.(62) However, snake venom antiserum I.P. from Premium Serums and Vaccines Pvt. Ltd., India showed ineffectiveness against lethality of *Naja naja* inhibited in different area in India.(30) Furthermore, another study found that snake venom antiserum (Polyvalent) from Bharat Serums and Vaccines Limited, India was ineffective against lethality of *Naja naja* inhabited in India.(62) Indian *Naja naja* lethality also can be cross-neutralized by neuro-polyvalent snake antivenom from QSMI, Thailand.(63) Lethality of *Naja naja* in Pakistan was cross-neutralized by neurobivalent antivenom from National Institute of Preventive Medicine, Taiwan, snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India, and cobra antivenin from QSMI, Thailand.(50) Moreover, lethality of *Naja naja* inhabited in Sri Lanka can be cross-neutralized by snake venom antiserum (Polyvalent) from Bharat Serums and Vaccines Limited, India,(54) snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India,(24, 51, 62) polyvalent antisnake venom serum from National Institute of Health, Pakistan,(54) and neuro-polyvalent snake antivenom from QSMI, Thailand.(63) Nevertheless, there is a study found that snake venom antiserum (Polyvalent) from Bharat Serums and Vaccines Limited, India was not effective against *Naja naja* from Sri Lanka.(62)

In Southeast Asia, lethality of *Bungarus candidus* inhabited in Thailand was cross-neutralized by banded krait antivenin from QSMI, Thailand.(67) *Bungarus candidus*

inhabited in Java Island, Indonesia was found to be cross-neutralized against its lethality by serum anti bisa ular polivalen (Bio Save) from PT Bio Farma (Persero), Indonesia and neuro-polyvalent snake antivenom from QSMI, Thailand.(53) Lethality of *Bungarus candidus* inhabited in Malaysia can be cross-neutralized by neuro-polyvalent snake antivenom from QSMI, Thailand.(63)

For *Naja kaouthia*, there were studies confirmed that Thai *Naja kaouthia* lethality can be neutralized by cobra antivenin (52, 56, 63, 66, 68, 69) and neuro-polyvalent snake antivenom from QSMI, Thailand.(56, 58) These two antivenoms can also cross-neutralized against lethality of *Naja kaouthia* inhabited in Malaysia and Vietnam.(56, 63) Moreover, snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India, can cross-neutralized against lethality *Naja kaouthia* venom inhabited in Thailand and Malaysia.(62) On the other hand, another antivenom developed in India, snake venom antiserum (Polyvalent) from Bharat Serums and Vaccines Limited, can cross-neutralized against only lethality of *Naja kaouthia* venom inhabited in Thailand but it is not effective against lethality of *Naja kaouthia* venom from Malaysia.(62)

For *Naja philippinensis* inhabited in the Philippines, it was found that its specific antivenom, monovalent (*Naja philippinensis*) cobra antivenin from Biologicals Manufacturing Division (Research Institute for Tropical Medicine), Philippines can neutralize against its lethality.(27) Moreover, this antivenom can also cross-neutralized against lethality of *Naja samarensis*.(27)

For *Naja siamensis* in Thailand, cobra antivenin from QSMI, Thailand can cross-neutralized against its lethality.(68)

Naja sputatrix inhabited in Indonesia can be neutralized by its specific antivenom, serum anti bisa ular polivalen (Bio Save) from PT Bio Farma (Persero), Indonesia, (53) and can be cross-neutralized by neuro-polyvalent snake antivenom from QSMI, Thailand, (53, 58) which is similar to *Naja sputatrix* inhabited in Malaysia.(55)

Lastly, *Naja sumatrana* inhabited in Sumatra Island, Indonesia can be cross-neutralized by serum anti bisa ular polivalen (Bio Save) from PT Bio Farma (Persero), Indonesia and neuro-polyvalent snake antivenom from QSMI, Thailand, (53) which is like *Naja sumatrana* inhabited in Malaysia that can also be cross-neutralized by neuro-polyvalent snake

antivenom from QSMI, Thailand.(58) Additionally, two antivenoms from India, snake venom antiserum (Polyvalent) from Bharat Serums and Vaccines Limited and snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., were found to be cross-neutralized against lethality of *Naja sumatrana* in Malaysia.(62)

Viperidae medically important venomous snakes in Asia

No Viperidae medically important venomous snakes in Central. *Deinagkistrodon acutus* inhabited in China and Taiwan were found to be tested against *Agkistrodon acutus* antivenin from Shanghai Serum Bio-technology Co Ltd. and Monovalent Antivenin Snorkel Viper from National Institute of Preventive Medicine, Taiwan. The results showed that both antivenoms can neutralized against lethality of both *Deinagkistrodon acutus* from China and Taiwan.(22)

In South Asia, three medically important venomous snakes in Viperidae family were tested in the included studies. There were studies confirmed that snake venom antiserum (polyvalent) from Bharat Serums and Vaccines Limited, India,(37) snake venom antiserum I.P. from Premium Serums and Vaccines Pvt. Ltd., India,(29) and snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India,(25) specific antivenoms against *Daboia russelii* inhabited in India, can neutralize against its lethality. While lethality of *Daboia russelii* inhabited in Sri Lanka can be cross-neutralized by snake venom antiserum (polyvalent) from Bharat Serums and Vaccines Limited, India,(54) snake venom antiserum I.P. from Premium Serums and Vaccines Pvt. Ltd., India,(39) snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India,(25, 39, 51) polyvalent antisnake venom serum from National Institute of Health, Pakistan,(54) and haemato-polyvalent snake antivenom from QSMI, Thailand.(64) Moreover, *Daboia russelii* from Bangladesh can be cross-neutralized by snake venom antiserum (polyvalent) from snake venom antiserum I.P. from Premium Serums and Vaccines Pvt. Ltd.(39) and snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India,(39) which is similar to *Daboia russelii* inhabited in Pakistan.(39, 47)

Echis carinatus inhabited in India lethality can be neutralized by its specific antivenom, snake venom antiserum (Polyvalent) from Bharat Serums and Vaccines Limited, India,(37) and snake venom antiserum I.P. from Premium Serums and Vaccines Pvt. Ltd., India.(42) While lethality of *Echis carinatus* inhabited in Sri Lanka was found to be cross-neutralized by snake venom antiserum (Polyvalent) from Bharat Serums and Vaccines Limited, India,(54) snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd. India,(51) and polyvalent antisnake venom serum from National Institute of Health, Pakistan.(54) Moreover, it was

found that lethality of *Echis carinatus* inhabited in Pakistan cannot be cross-neutralized by haemato-polyvalent snake antivenom from QSMI, Thailand.(64)

Hypnale hypnale inhabited in Sri Lanka can be cross-neutralized by snake venom antiserum I.P. (Asia) from VINS Bioproducts Ltd., India,(51) haemato-polyvalent snake antivenom, and Malayan pit viper antivenin from QSMI, Thailand.(64)

For Southeast Asian Viperidae snakes, *Calloselasma rhodostoma* in habited in Java Island, Indonesia was neutralized by its specific polyvalent antivenom, serum anti bisa ular polivalen (Bio Save) from PT Bio Farma (Persero), Indonesia,(53) and cross-neutralized by haemato-polyvalent snake antivenom from QSMI, Thailand.(53, 59) Lethality of *Calloselasma rhodostom*a inhabited in Malaysia can also cross-neutralized by haemato-polyvalent snake antivenom from QSMI, Thailand,(59, 64) and Malayan pit viper antivenin from QSMI.(59, 64)

Trimeresurus albolabris inhabited in Thailand had a specific antivenom, green pit viper antivenin from QSMI, Thailand, which had been confirmed its efficacy against lethality of this snake species.(34, 65)

For lethality of *Trimeresurus erythrurus* inhabited in Myanmar, it can be cross-neutralized by anti-Viper (Russell's viper) from Myanmar Pharmaceutical Factory, Myanmar,(31) and green pit viper antivenin from QSMI, Thailand.(31)

Lethality of *Trimeresurus insularis* inhabited in Indonesia can also be cross-neutralized by green pit viper antivenin from QSMI, Thailand,(48) and serum anti bisa ular polivalen (Bio Save) from PT Bio Farma (Persero), Indonesia.(48)

Lastly, *Daboia siamensis* inhabited in Myanmar can be cross-neutralized haemato-polyvalent snake antivenom (59) and Russell's viper antivenin from QSMI, Thailand.(44) *Daboia siamensis* inhabited in Thailand had specific antivenoms, haemato-polyvalent snake antivenom and Russell's viper antivenin from QSMI, Thailand, which were confirmed to be neutralized against its lethality.(41, 44, 59, 61) However, serum anti bisa ular polivalen (Bio Save) from PT Bio Farma (Persero), Indonesia was ineffective against Thai *Daboia siamensis* lethality.(41) In accordance with *Daboia siamensis* inhabited in Indonesia, Russell's viper antivenin from QSMI, Thailand can cross-neutralized against its lethality but

serum anti bisa ular polivalen (Bio Save) from PT Bio Farma (Persero), Indonesia was ineffective.(41)

4.1.4 Quality assessment

Risk of bias of the included studies was assessed and presented in **Table 3**. Some information was not mentioned which limited risk of bias assessment. For selection bias, no information regarding allocation sequence was mentioned in any studies. In terms of performance bias, random housing, and care giver and/or investigator blinding were also not mentioned in the included studies. Random outcome assessment and outcome assessor blinding were not mentioned in any included preclinical studies which limited the assessment of detection bias. Incomplete outcome data was not addressed in all included studies which limited assessment of attrition bias. However, reporting bias was not found since reports of all included studies were free of selective outcome reporting.

Table 3 Risk of bias assessment using Systematic Review Centre for Laboratory animal Experimentation's (SYRCLE) risk of bias tool for animal studies.

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Tan KY, 2022 (22)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Chanhome O, 2022 (23)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Wong KY, 2021 (24)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Faisal T, 2021 (25)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Attarde S, 2021 (26)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan CH, 2021 (27)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Oh AMF, 2021 (28)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Laxme RRS, 2021 (29)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Laxme RRS, 2021 (30)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Yee KT, 2020 (31)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan KY, 2020 (32)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Lin B, 2020 (33)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Liew JL, 2020 (34)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Lee LP, 2020 (35)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Hia YL, 2020 (36)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Choraria A, 2020 (37)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan CH, 2019 (38)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Pla D, 2019 (39)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Oh AMF, 2019 (40)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Lingam TMC, 2019 (41)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Laxme RRS, 2019 (42)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Deka A, 2019 (43)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Chaisakul J, 2019 (44)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan KY, 2018 (45)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Liu BS, 2018 (46)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Faisal T, 2018 (47)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan CH, 2017 (48)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Oh AMF, 2017 (49)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Wong KY, 2016 (50)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Villalta M, 2016 (51)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan KY, 2016 (52)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan CH, 2016 (53)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Maduwage K, 2016 (54)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Yap MK, 2015 (55)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan KY, 2015 (56)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan CH, 2015 (57)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Leong PK, 2015 (58)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Leong PK, 2014 (59)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Danpaiboon W, 2014 (60)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Pakmanee N, 2013 (61)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Leong PK, 2012 (62)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Leong PK, 2012 (63)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Tan CH, 2011 (64)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Chanhome L, 2002 (65)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Khow O, 2001 (66)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Chanhome L, 1999 (67)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Author, year	1. Was the allocation sequence adequately generated and applied?	2. Were the group similar at baseline or were they adjusted for confounders in the analysis?	3. Was the allocation adequately concealed?	4. Were the animals randomly housed during the experiment?	5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6. Were animals selected at random from outcome assessment?	7. Was the outcome assessor blinded?	8. Were incomplete outcome data adequately addressed?	9. Are reports of the study free of selective outcome reporting?	10. Was the study apparently free of other problems that could result in high risk of bias?
Khow O, 1997 (68)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Sells PG, 1994 (69)	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes

Assessment of reporting guideline for in vivo neutralization of lethality of antivenom assessment in 43 studies had been reported in **Table 4**. In experiment set up section, 44 (92%) studies reported antivenom batch number. (22-38, 40-59, 62-68) Only 28 (58%) studies reported total protein concentration of antivenoms.(25-38, 40-45, 48, 51-54, 59, 62, 63) Four (8%) studies did not provide any information of origin of some snake venoms used in the studies.(55, 59, 62, 63) Ethical statement was not mentioned in six (13%) studies.(24, 65-69)

In animal section, source of animals, mouse strains, and mouse weight were mentioned in 34, 45, 45 studies, respectively. However, information regarding husbandry was not mentioned in all studies which limited the risk of bias assessment in some factors.

In procedure section, numbers of LD50 used in the experiment, route of administration, and pre-incubation process were informed in all studies. Multiples of LD50 used in the experiment were between 2.5 to 6 folds. For route of administration, intravenous (92%) (22-32, 34-42, 44, 45, 47-59, 61-69) and intraperitoneal (8%) (33, 43, 46, 60) route were used. Number of mouses per group and experiment length were mentioned in 45 (94%) (22-24, 26-46, 48-61, 63-69) and 46 (96%) studies.(22-64, 66, 68, 69) Nevertheless, total numbers of mouses used in each experiment were not provided in any studies which also limited the risk of selection bias assessment of the included studies. Control groups were stated only in ten (21%) studies.(23, 30, 31, 39, 42, 43, 51, 55, 60, 61)

In reported results section, no group outcomes and adverse events were mentioned in any studies. However, these outcomes were not pre-specified in any studies. Forty-five (94%) studies mentioned a statistical method used in ED50 calculation.(22-25, 27-30, 32-59, 61-69) Probit analysis, one of statistical methods, was used the most (77%).(22, 24, 25, 27-30, 32, 34-45, 47-59, 62-64, 69) However, its description of statistical analysis was reported only in 25 (52%) studies. All studies reported ED50 in different units, such as, mcl, mcl/mg, mcl/mice, mg, mg/ml, mg/g, and mcg/g, which limited meta-analysis of ED50 in our study.

Table 4 Assessment of reporting guideline for In vivo neutralization of lethality of antivenom assessment

Author, year	Experiment set up					Animals					Procedure								Reported results				
	Antivenom batch	Total protein concentration	Geographic origin	Ethical statement	Conflicts of interest	Source of animals	Mouse strain	Weight (g)	Mouse sex	Husbandry	Control groups stated	LD50 used for ED50	Number per group	Total number of animals used	Pre-incubation	Route of administration	Injection Volume	Experiment length	Group outcome reporting	Adverse events	Description of statistical	ED50 calculation method	ED50 reporting
Tan KY, 2022 (22)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
Chanhome O, 2022 (23)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Wong KY, 2021 (24)	Yes	No	Yes	No	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Faisal T, 2021 (25)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
Attarde S, 2021 (26)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Tan CH, 2021 (27)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
Oh AMF, 2021 (28)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Laxme RRS, 2021 (29)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
Laxme RRS, 2021 (30)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
Yee KT, 2020 (31)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Tan KY, 2020 (32)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes

Author, year	Experiment set up					Animals					Procedure								Reported results				
	Antivenom batch	Total protein concentration	Geographic origin	Ethical statement	Conflicts of interest	Source of animals	Mouse strain	Weight (g)	Mouse sex	Husbandry	Control groups stated	LD50 used for	Number per group	Total number of animals used	Pre-incubation	Route of administration	Injection Volume	Experiment	Group outcome reporting	Adverse events	Description of statistical	ED50 calculation method	ED50 reporting
Lin B, 2020 (33)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Liew JL, 2020 (34)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Lee LP, 2020 (35)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes
Hia YL, 2020 (36)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Choraria A, 2020 (37)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Tan CH, 2019 (38)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
Pla D, 2019 (39)	No	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Oh AMF, 2019 (40)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Lingam TMC, 2019 (41)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Laxme RRS, 2019 (42)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes

Author, year	Experiment set up					Animals					Procedure								Reported results				
	Antivenom batch	Total protein concentration	Geographic origin	Ethical statement	Conflicts of interest	Source of animals	Mouse strain	Weight (g)	Mouse sex	Husbandry	Control groups stated	LD50 used for ED50	Number per group	Total number of animals used	Pre-incubation	Route of administration	Injection Volume	Experiment length	Group outcome reporting	Adverse events	Description of statistical	ED50 calculation method	ED50 reporting
Deka A, 2019 (43)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Chaisakul J, 2019 (44)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Tan KY, 2018 (45)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes
Liu BS, 2018 (46)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Faisal T, 2018 (47)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes
Tan CH, 2017 (48)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Oh AMF, 2017 (49)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Wong KY, 2016 (50)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Villalta M, 2016 (51)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Tan KY, 2016 (52)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Tan CH, 2016 (53)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes

Author, year	Experiment set up					Animals					Procedure								Reported results				
	Antivenom batch	Total protein concentration	Geographic origin	Ethical statement	Conflicts of interest	Source of animals	Mouse strain	Weight (g)	Mouse sex	Husbandry	Control groups stated	LD50 used for ED50	Number per group	Total number of animals used	Pre-incubation	Route of administration	Injection Volume	Experiment length	Group outcome reporting	Adverse events	Description of statistical	ED50 calculation method	ED50 reporting
Maduwage K, 2016 (54)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Yap MK, 2015 (55)	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Tan KY, 2015 (56)	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Tan CH, 2015 (57)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Leong PK, 2015 (58)	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Leong PK, 2014 (59)	Yes	Yes	Both	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Danpaiboon W, 2014 (60)	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Pakmanee N, 2013 (61)	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Leong PK, 2012 (62)	Yes	Yes	Both	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Leong PK, 2012 (63)	Yes	Yes	Both	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Tan CH, 2011 (64)	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes

Author, year	Experiment set up					Animals					Procedure								Reported results				
	Antivenom batch	Total protein concentration	Geographic origin	Ethical statement	Conflicts of interest	Source of animals	Mouse strain	Weight (g)	Mouse sex	Husbandry	Control groups stated	LD50 used for	Number per group	Total number of animals used	Pre-incubation	Route of administration	Injection Volume	Experiment	Group outcome reporting	Adverse events	Description of statistical	ED50 calculation method	ED50 reporting
Chanhome L, 2002 (65)	Yes	No	Yes	No	No	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	No	No	Yes	Yes
Khow O, 2001 (66)	Yes	No	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Chanhome L, 1999 (67)	Yes	No	Yes	No	No	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Khow O, 1997 (68)	Yes	No	Yes	No	No	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Sells PG, 1994 (69)	No	No	Yes	No	No	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Number of fulfilling studies	44	28	44	41	37	34	45	45	10	0	10	48	45	0	48	48	37	46	0	0	25	45	48
Percentage	92%	58%	92%	85%	77%	71%	94%	94%	21%	0%	21%	100 %	94%	0%	100 %	100%	77%	96%	0%	0%	52%	94%	100

4.2 PART B: AN ANALYSIS OF ANTIVENOM AVAILABILITY IN ASIA

As shown in **Figure 2**, we summarized availability of local antivenom production and studies assessing efficacy of antivenom in each country in Asia. There are 12 countries in Asia with local antivenom production. Among countries with no local antivenom production, we found only three countries where studies assessing efficacy of antivenom are available, namely Bangladesh, Sri Lanka, and Malaysia. In countries with local antivenom production, studies assessing antivenom efficacy were found in ten countries except South Korea and Uzbekistan.

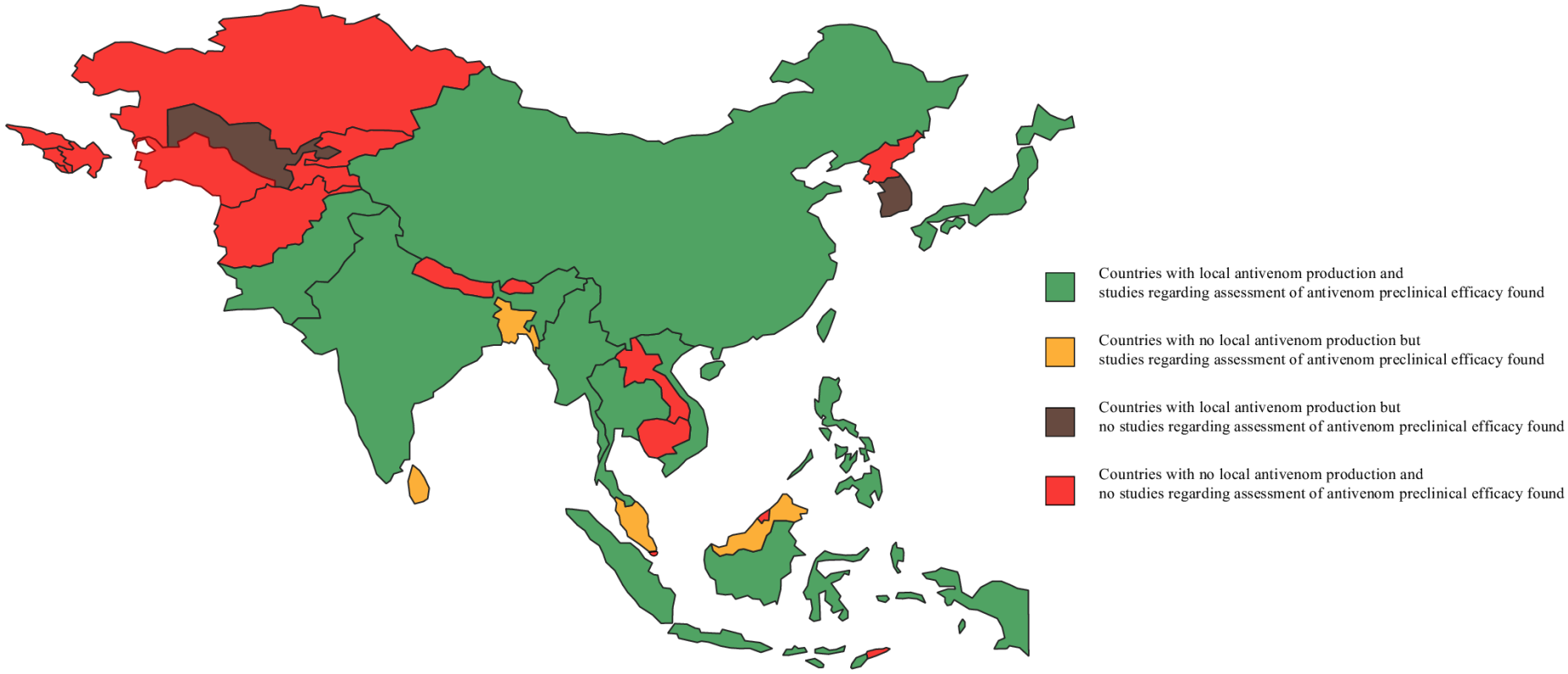


Figure 2 Heat map of availability of local antivenom production and studies assessing preclinical efficacy of antivenoms

Made with Natural Earth. Free vector and raster map data @ naturalearthdata.com

To focus more on details in each country in Asia, **Table 5** demonstrates availability of specific antivenoms against medically important venomous snakes in each country and shows snakes with preclinical studies that confirmed antivenom cross-neutralizing or neutralizing ability against their lethality.

East Asian countries, Japan, South Korea, and Taiwan have local specific antivenoms against all category 1 medically important venomous snakes in their countries. While Hong Kong and North Korea have no local specific antivenoms against category 1 medically important venomous snakes and no studies confirming antivenom cross-neutralizing or neutralizing ability were found. China has local specific antivenoms against only three (42.86%) category 1 medically important venomous snakes and one (6.25%) category 2 medically important venomous snakes but studies that confirmed antivenom efficacy against medically important venomous snakes with no local specific antivenoms were found.

India and Pakistan are the only countries in South Asia that can produce local antivenoms. However, available local antivenoms covered 66.67% and 57.14% of category 1 medically important venomous snakes in their countries, respectively.

For other countries without local antivenom production in South Asia, it has been confirmed that there are antivenoms that can cross-neutralize against lethality of category 1 medically important venomous snakes in their countries. For example, we found that available antivenoms can cross-neutralize against all (100%) category 1 medically important venomous snakes in Sri Lanka. No specific antivenoms were developed against category 2 medically important venomous snakes in South Asia. However, studies confirming antivenom efficacy against them were conducted in Bangladesh, India, and Sri Lanka.

Among countries in Southeast Asia, Brunei Darussalam, Cambodia, Malaysia, and Lao People's Democratic Republic (PDR) were countries without local antivenom production. However, studies confirming antivenom cross-neutralizing ability were found in four (100%) category 1 medically important venomous snakes in Malaysia. While no studies confirming antivenom efficacy were found in Brunei Darussalam, Cambodia, and Lao PDR.

For other countries in Southeast Asia, Thailand produced local antivenoms against five (83%) of seven category 1 medically important venomous snakes of Thailand which was the

highest among countries in Southeast Asia. For category 2 medically important venomous snakes, only Thailand and Indonesia produced specific antivenoms against two and one category 2 medically important venomous snakes, respectively. Additionally, studies confirming efficacy against category 2 medically important venomous snakes were found only in Malaysia among countries with no local antivenom production.

Table 5 Availability of specific antivenoms against category 1 and category 2 medically important venomous snakes in each country in Asia and availability of studies that confirm antivenom cross-neutralizing or neutralizing ability against their lethality

Region	Country	Category 1 Medically important venomous snakes (MIVS)			Category 2 Medically important venomous snakes (MIVS)		
		Total numbers of category 1 MIVS in each country	Total numbers of category 1 MIVS in with specific antivenom in each country	Total numbers of category 1 MIVS with antivenom with confirmed neutralizing or cross-neutralizing ability	Total numbers of category 2 MIVS in each country	Total numbers of category 2 MIVS in with specific antivenom in each country	Total numbers of category 2 MIVS with antivenom with confirmed neutralizing or cross-neutralizing ability
East Asia	China	7	3 (42.86%)	4 (57.14%)	16	1 (6.25%)	(12.50%)
	Hong Kong	3	0	0	0	0	0
	Japan	1	1 (100%)	0	3	1 (33.33%)	0
	North Korea	1	0	0	3	0	0
	South Korea	1	1 (100%)	0	3	1 (33.33%)	0
	Taiwan	4	4 (100%)	2 (50%)	2	2 (100%)	2 (100%)
South Asia	Afghanistan	3	0	0	5	0	0
	Bangladesh	5	0	1 (20%)	7	0	1 (14.29%)
	Bhutan	2	0	0	8	0	0
	India	6	4 (66.67%)	5 (83.33%)	18	0	2 (11.11%)
	Nepal	5	0	0	9	0	0
	Pakistan	7	4 (57.14%)	4 (57.14%)	3	0	0

Region	Country	Category 1 Medically important venomous snakes (MIVS)			Category 2 Medically important venomous snakes (MIVS)		
		Total numbers of category 1 MIVS in each country	Total numbers of category 1 MIVS in with specific antivenom in each country	Total numbers of category 1 MIVS with antivenom with confirmed neutralizing or cross-neutralizing ability	Total numbers of category 2 MIVS in each country	Total numbers of category 2 MIVS in with specific antivenom in each country	Total numbers of category 2 MIVS with antivenom with confirmed neutralizing or cross-neutralizing ability
	Sri Lanka	4	0	4 (100%)	4	0	1 (25%)

Region	Country	Category 1 Medically important venomous snakes (MIVS)			Category 2 Medically important venomous snakes (MIVS)		
		Total numbers of category 1 MIVS in each country	Total numbers of category 1 MIVS in with specific antivenom in each country	Total numbers of category 1 MIVS with antivenom with confirmed neutralizing or cross-neutralizing ability	Total numbers of category 2 MIVS in each country	Total numbers of category 2 MIVS in with specific antivenom in each country	Total numbers of category 2 MIVS with antivenom with confirmed neutralizing or cross-neutralizing ability
Southeast Asia	Brunei Darussalam	1	0	0	7	0	0
	Cambodia	6	0	0	4	0	0
	Indonesia	6	2 (33.83%)	5 (83.33%)	7	1 (14.29%)	3 (42.86%)
	Malaysia	4	0	4 (100%)	8	0	4 (50%)
	Myanmar	7	2 (28.57%)	2 (28.57%)	11	0	0
	Philippines	3	1 (33.33%)	2 (66.67%)	5	0	0
	Singapore	2	0	0	4	0	0
	Thailand	6	5 (83.33%)	5 (83.33%)	8	2 (25%)	4 (50%)
	Lao People's Democratic Republic	6	0	0	6	0	0
	Timor-Leste	1	0	0	1	0	0
	Vietnam	8	1 (12.50%)	1 (12.50%)	8	0	0

CHAPTER V
DISCUSSIONS

Snakebite envenoming is a neglected tropical disease with an issue in access to an effective treatment. To manage this problem, imported antivenom can be used as an alternative treatment in countries with no local antivenom production. Nonetheless, to confirm its effectiveness, assessment of antivenom efficacy is essential to be performed before using in designation areas because snake venoms are different within and between species due to geographic variation leading to different strength of antivenom neutralizing ability.(70)

As demonstrated in the results, neuro-polyvalent snake antivenom from QSMI, Thailand can cross-neutralize against lethality of many medically important venomous snakes that have no specific antivenoms within Elapidae family, for example, *Naja atra* in Taiwan, *Naja naja* in Sri Lanka, *Bungarus candidus* in Indonesia (Java Island) and Malaysia, *Naja kaouthia* in Malaysia, *Naja sputatrix* in Malaysia, *Naja sumatrana* in Indonesia (Sumatra). Consistently, haemato-polyvalent snake antivenom from QSMI, Thailand can cross-neutralized against lethality of Asia snakes without specific antivenoms in Viperidae Family which are *Daboia russelii* in Sri Lanka, *Hypnale hypnale* in Sri Lanka, *Calloselasma rhodostoma* in Malaysia, and *Daboia siamensis* in Myanmar. It showed that polyvalent antivenoms may cross-neutralize against different snake species within similar family and different region.

In terms of monovalent antivenoms, they may cross-neutralize against snakes with similar genus in different area. For instance, cobra (*Naja kaouthia*) antivenom from QSMI, Thailand has cross-neutralizing ability against lethality of *Naja kaouthia* in Malaysia and *Naja siamensis* in Thailand. Furthermore, local monovalent antivenoms can cross-neutralize against lethality of snakes with similar genus in their countries, such as, monovalent (*Naja philippinensis*) Cobra Antivenin from Biologicals Manufacturing Division, Research Institute for Tropical Medicine, Malaysia can cross-neutralize against lethality of *Naja samarensis* in the Philippines.

However, no studies confirming neutralizing ability against lethality were found in more than 50% of medically important venomous snakes in Asia. In Central Asia, all medically

important venomous snakes were not tested. In East Asia, all Elapidae medically important venomous snakes were tested. While Viperidae medically important venomous snakes in East Asia; *Trimeresurus albolabris, Daboia russelii, Gloydius blomhoffii, Gloydius brevicaudus, Protobothrops flavoviridis, Protobothrops mucrosquamatus,* and *Trimeresurus stejnegeri*; were not tested. In South Asia, snakes in Elapidae family; *Bungarus ceylonicus, Bungarus niger, Bungarus walli,* and *Naja oxiana*; were not tested. While one medically important venomous snake in Viperidae family inhabited in South Asia, *Macrovipera lebetina*, was not tested. In Southeast Asia, Elapidae medically important venomous snakes in Elapidae which are *Bungarus magnimaculatus, Bungarus multicinctus, Bungarus slowinskii, Naja atra,* and *Naja mandalayensis* were not tested. While only one Viperidae medically important venomous snakes in Southeast Asia were not found to be tested which is *Deinagkistrodon acutus*. This result showed lack of information in this public health issue which was in accordance with a previous systematic review of antivenom preclinical efficacy in sub-Saharan Africa.(16) Surprisingly, snake venom polyvalent antiserum from India, which *Naja naja* venom was included in the immunizing mixture in the development process, cannot neutralize against lethality of *Naja naja* in Maharashtra, Southwest India. This finding supports that quality of antivenom is also an issue for this neglected tropical disease.

In terms of information reported in the included studies, as seen in the result, some studies included in this systematic review did not report snake origins. To report the snake origin that had been tested in the experiment is important due to geographical variation among snake venoms. Numbers of LD50 used in each experiment were different. Moreover, metrics of ED50 were found to be used differently across the included studies which limited us from performing meta-analysis in our study. It shows that universal guideline for assessment of antivenom efficacy should be developed and applied for standardization of antivenom.

Due to ethical issue, it was challenging to perform clinical trials to assess antivenom efficacy in humans.(71) Only 43 clinical trials of snake antivenoms were conducted worldwide in the past 60 years and only 22 clinical trials were performed in Asia. Additionally, results reported in the clinical trials were heterogenous. Some measured outcomes in clinical trials were not valid. Guidance for conducting and reporting outcomes in clinical trials for

snakebite envenoming was essential.(72) In contrast, WHO developed a valid and reliable guideline to conduct preclinical studies regarding assessment of antivenom efficacy.(15) Outcomes reported in preclinical studies, such as, ED50, were universal as demonstrated in the results of this study and the method conducted rely to WHO guideline. This confirmed that preclinical studies needed to be performed to ensure efficacy of antivenom since clinical trials are not applicable.

According to situation of antivenom availability demonstrated in results, each country has different situation. Countries with local antivenoms have specific antivenoms but they do not cover all medically important venomous snakes in their countries. For countries with no local antivenoms production, studies assessing efficacy of antivenom were only in few countries. We might imply that snakebite envenoming and issue of access to effective antivenoms were not prioritized as issues needed to be focused. Collaboration in Asia should be conducted to solve this public health issue collectively by, for instance, providing any policy suggestions for both countries with and without local antivenom production and developing a target product profile for snake antivenom as a guidance for countries in Asia. Moreover, snakebite-information is important and is still lacking nowadays.(73) This study is a first step in development of snakebite-information system, especially in Asia. Nevertheless, this information system should be updated continuously so that users, such as, healthcare professionals, can search which antivenom is effectively neutralize against toxic effects of snake venoms.

To summarize, access to effective antivenoms is an issue of this neglected tropical disease. Improvement of access to effective antivenom is the key to solved snakebite envenoming. In countries with no local antivenom production, antivenom with confirmed cross-neutralizing ability can be used as an alternative treatment where new antivenom development is limited. To confirm antivenom efficacy, clinical trial is limited due to ethical issue. So, non-clinical studies should be performed instead to ensure antivenom efficacy. In countries with local antivenom production, we found that some antivenoms were ineffective against snake venoms in the immunizing mixture. Those available antivenoms are also needed to be confirmed for their efficacy. Hence, regulatory guidance should be developed. It could demonstrate what antivenom should be developed, how to produce antivenom with assured

quality, what parameters should be reported to assure the reliability and validity of methods and outcomes.

There are several limitations of our review. First, we included only available antivenoms in Asia. New-generation antivenoms waiting for Food and Drug Administration (FDA) approval with cross-neutralizing and neutralizing ability assessment were not included. Second, studies assessed cross-neutralizing and neutralizing ability of antivenom against toxic effect of snake venom other than lethality were not extracted. These limitations supported that this review should be updated periodically. Third, only snakes inhabited in Asia and antivenoms in Asia were included. Further investigations are needed where snakebite envenoming is an issue to develop more crucial databases, solve this neglected tropical disease, and achieve the goal to halve disability and mortality from snakebite envenoming according to the WHO's road map.(7)

In conclusion, cross-neutralizing ability against lethality of Asia snake venom was confirmed in some snake antivenoms in Asia. This strategy can help improve equal access to geographically effective antivenoms which can improve snakebite envenoming patient outcome. It might bypass investment in new antivenom development, especially in countries without local antivenom production. This study fulfilled the snakebite-information system which is still lacking nowadays. Nevertheless, studies confirming antivenom effectiveness against lethality of some medically important venomous snakes were not found and more databases should be encouraged to be developed.

APPENDIX 1

CROSS-NEUTRALIZING ABILITY OF AVAILABLE ASIA ANTIVENOMS AGAINST ASIA MEDICALLY IMPORTANT SNAKES IN EACH COUNTRY

BANGLADESH

Manufacturer; Country	Haffkine; India	Bharat; India	Premium; India	VINS; India
Snake species / Antivenom	Snake antivenin I.P. (Asia)	Snake Venom Antiserum (Polyvalent)	Snake venom antiserum I.P.	Snake Venom Antiserum I.P. (Asia)
N. kaouthia	Bangladesh (43)	Bangladesh (43)		Bangladesh (43)
D. russelii			Bangladesh (39)	Bangladesh (39)

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.

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CHINA

Manufacturer; Country	Shanghai Serum Bio-technology; China		National Institute of Preventive Medicine; Taiwan	
Snake species / Antivenom	*Agkistrodon acutus* antivenin	*Bungarus multicinctus* antivenin	Antivenom *B. multicinctus/N. naja* (Neurobivalent antivenom)	Monovalent Antivenin Snorkel Viper
B. multicinctus		#, China (28, 33)	China (28)	
N. atra		China (33)		
D. acutus	#, China (22)			China (22)

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.

INDIA

Manufacturer; Country	Haffkine; India	Bharat; India	Premium; India	VINS; India	Queen Saovabha Memorial Institute; Thailand
Snake species / Antivenom	Snake antivenin I.P. (Asia)	Snake Venom Antiserum (Polyvalent)	Snake venom antiserum I.P.	Snake Venom Antiserum I.P. (Asia)	Neuro-polyvalent snake antivenom
B. caeruleus	#	#	#, India (42)	#, India (49)	
B. sindanus			India (42)		
N. kaouthia	India (43)	India (43)	India (42)	India (43)	
N. naja	#	#, India (26) / #, India (62)	#, India (26, 30, 42) / #, India (30)	#, India (62)	India (63)
D. russelii	#	#, India (37)	#, India (29)	#, India (25, 39, 51)	
E. carinatus	#	#, India (37)	#, India (42)	#	

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Manufacturer; Country	Haffkine; India	Bharat; India	Premium; India	VINS; India	Queen Saovabha Memorial Institute; Thailand
Snake species / Antivenom	Snake antivenin I.P. (Asia)	Snake Venom Antiserum (Polyvalent)	Snake venom antiserum I.P.	Snake Venom Antiserum I.P. (Asia)	Neuro-polyvalent snake antivenom

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.

INDONESIA

Manufacturer; Country	Persero; Indonesia	Queen Saovabha Memorial Institute; Thailand			
Snake species / Antivenom	Serum Anti Bisa Ular Polivalen (SABU)	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Neuro-polyvalent snake antivenom	Russell's viper antivenin
B. candidus	Java island (Indonesia) (53)			Java island (Indonesia) (53)	
N. sputatrix	#, Java island (Indonesia) (53)			Java Island (Indonesia) (53, 58)	

Manufacturer; Country	Persero; Indonesia	Queen Saovabha Memorial Institute; Thailand			
Snake species / Antivenom	Serum Anti Bisa Ular Polivalen (SABU)	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Neuro-polyvalent snake antivenom	Russell's viper antivenin
N. sumatrana	Sumatra (Indonesia) (53)			Sumatra (Indonesia) (53)	
C. rhodostoma	#, Java island (Indonesia) (53)		Java island (Indonesia) (53, 59)		
T. insularis	Indonesia (48)	Indonesia (48)			
D. siamensis	Indonesia (41)				Indonesia (41)

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.

MALAYSIA

Manufacturer; Country	Bharat; India	VINS; India	Queen Saovabha Memorial Institute; Thailand			
Snake species / Antivenom	Snake Venom Antiserum (Polyvalent)	Snake Venom Antiserum I.P. (Asia)	Cobra Antivenin	Haemato-polyvalent snake antivenom	Malayan pit viper antivenin	Neuro-polyvalent snake antivenom
B. candidus						Malaysia (63)
N. kaouthia	Malaysia (62)	Malaysia (62)	Malaysia (56, 63)			Malaysia (56)
N. sputatrix						Malaysia (55)
N. sumatrana	Malaysia (62)	Malaysia (62)				Malaysia (58)
C. rhodostoma				Malaysia (59, 64)	Malaysia (59, 64)	

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.

MYANMAR

Manufacturer; Country	Myanmar Pharmaceutical Factory; Myanmar	Queen Saovabha Memorial Institute; Thailand		
Snake species / Antivenom	Anti-Viper (Russell's viper)	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Russell's viper antivenin
T. erythrurus	Myanmar (31)	Myanmar (31)		
D. siamensis	#		Myanmar (59)	Myanmar (44)

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.

PAKISTAN

Manufacturer; Country	National Institute of Preventive Medicine; Taiwan	Premium; India	VINS; India	Queen Saovabha Memorial Institute; Thailand	
Snake species / Antivenom	Antivenom *B. multicinctus/N.n.naja* (Neurobivalent antivenom)	Snake venom antiserum I.P.	Snake Venom Antiserum I.P. (Asia)	Cobra Antivenin	Haemato-polyvalent snake antivenom
B. caeruleus			Pakistan (49)		
B. sindanus			Pakistan (40)		
N. naja	Pakistan (50)		Pakistan (50)	Pakistan (50)	
D. russelii		Pakistan (39)	Pakistan (39, 47)		
E. carinatus					Pakistan (64)

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.

PHILIPPINES

Manufacturer; Country	Research Institute for Tropical Medicine (Biologicals Manufacturing Division); Philippines
Snake species / Antivenom	Monovalent (*Naja philippinensis*) Cobra Antivenin
N. philippinensis	#, Philippines (27)
N. samarensis	Philippines (27)

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.

SRI LANKA

Manufacturer; Country	Bharat; India		Premium; India	VINS; India	National Institute of Health; Pakistan	Queen Saovabha Memorial Institute; Thailand		
Snake species / Antivenom	Snake Venom Antiserum (Polyvalent)		Snake venom antiserum I.P.	Snake Venom Antiserum I.P. (Asia)	Polyvalent Antisnake Venom Serum	Haemato-polyvalent snake antivenom	Malayan pit viper antivenin	Neuro-polyvalent snake antivenom
B. caeruleus	Sri Lanka (54)			Sri Lanka (49)	Sri Lanka (54)			
N. naja	Sri Lanka (54)	Sri Lanka (62)		Sri Lanka (24, 51, 62)	Sri Lanka (54)			Sri Lanka (63)
D. russelii	Sri Lanka (54)		Sri Lanka (39)	Sri Lanka (25, 39, 51)	Sri Lanka (54)	Sri Lanka (64)		
E. carinatus	Sri Lanka (54)			Sri Lanka (51)	Sri Lanka (54)			
H. hypnale				Sri Lanka (51)		Sri Lanka (64)	Sri Lanka (64)	

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.

TAIWAN

Manufacturer; Country	Shanghai Serum Bio-technology; China		National Institute of Preventive Medicine; Taiwan			Queen Saovabha Memorial Institute; Thailand	Institute of Vaccines and Biological Substances; Vietnam
Snake species / Antivenom	*Agkistrodon acutus* antivenin	*Bungarus multicinctus* antivenin	Antivenom *B. multicinctus/N.n. naja* (Neurobivalent antivenom)	*Doboia siamensis* monovalent antivenom	Monovalent Antivenin Snorkel Viper	Neuro-polyvalent snake antivenom	Refined earth tiger snake antivenom
B. multicinctus		Taiwan (28)	#, Taiwan (28)				
N. atra			#, Taiwan (46)	Taiwan (46)		Taiwan (46)	Taiwan (46)
D. acutus	Taiwan (22)				#, Taiwan (22)		

Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.

Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.

Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country.

Manufacturer; Country	Shanghai Serum Bio-technology; China		National Institute of Preventive Medicine; Taiwan			Queen Saovabha Memorial Institute; Thailand	Institute of Vaccines and Biological Substances; Vietnam
Snake species / Antivenom	*Agkistrodon acutus* antivenin	*Bungarus multicinctus* antivenin	Antivenom *B. multicinctus/N.n. naja* (Neurobivalent antivenom)	*Doboia siamensis* monovalent antivenom	Monovalent Antivenin Snorkel Viper	Neuro-polyvalent snake antivenom	Refined earth tiger snake antivenom
For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table** 1 Study characteristics.							

THAILAND

Manufacturer; Country	Bharat; India	VINS; India	Persero; Indonesia	Queen Saovabha Memorial Institute; Thailand					
Snake species / Antivenom	Snake Venom Antiserum (Polyvalent)	Snake Venom Antiserum I.P. (Asia)	Serum Anti Bisa Ular Polivalen (SABU)	Banded krait antivenin	Cobra Antivenin	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Neuro-polyvalent snake antivenom	Russell's viper antivenin
B. candidus				Thailand (67)				#	
N. kaouthia	Thailand (62)	Thailand (62)			#, Thailand (52, 56, 63, 66, 68, 69)			#, Thailand (56, 58)	
N. siamensis					Thailand (68)				
T. albolabris						#, Thailand (34, 65)	#		
D. siamensis			Thailand (41)				#, Thailand (59)		#, Thailand (41, 44, 61)
Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country.									

Manufacturer; Country	Bharat; India	VINS; India	Persero; Indonesia	Queen Saovabha Memorial Institute; Thailand					
Snake species / Antivenom	Snake Venom Antiserum (Polyvalent)	Snake Venom Antiserum I.P. (Asia)	Serum Anti Bisa Ular Polivalen (SABU)	Banded krait antivenin	Cobra Antivenin	Green Pit Viper Antivenin	Haemato-polyvalent snake antivenom	Neuro-polyvalent snake antivenom	Russell's viper antivenin
Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country. Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country. For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.									

VIETNAM

Manufacturer; Country	Queen Saovabha Memorial Institute; Thailand		Institute of Vaccines and Biological Substances; Vietnam
Snake species / Antivenom	Cobra Antivenin	Neuro-polyvalent snake antivenom	Refined earth tiger snake antivenom
N. kaouthia	Vietnam (56)	Vietnam (56)	#
Hashtag (#) shows that those snake venoms were included in the immunizing mixture in the development of antivenom in each country. Green color shows antivenom with cross-neutralizing and/or neutralizing ability against lethality of medically important venomous snakes inhabited in the addressed country.			

Manufacturer; Country	Queen Saovabha Memorial Institute; Thailand		Institute of Vaccines and Biological Substances; Vietnam
Snake species / Antivenom	Cobra Antivenin	Neuro-polyvalent snake antivenom	Refined earth tiger snake antivenom
Red color shows antivenom that **cannot** cross-neutralize and/or neutralize against lethality of medically important venomous snakes inhabited in the addressed country. For more details of cross-neutralizing and/or neutralizing ability of available Asia antivenoms, such as, ED50 and potency, please see **Table 1** Study characteristics.			

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