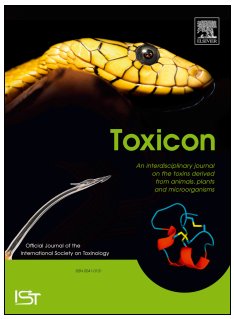
Journal Pre-proof



Exotic (non-native) snakebite envenomation in Japan: A review of the literature between 2000 and 2022

Yoshihiro Aoki, Ken Yoshimura, Atsushi Sakai, Atsuko Tachikawa, Yutaka Tsukamoto, Kensuke Takahashi, Shuhei Yamano, Chris Smith, Koichi Hayakawa, Osamu Tasaki, Koya Ariyoshi, David A. Warrell

PII: S0041-0101(23)00212-X

DOI: https://doi.org/10.1016/j.toxicon.2023.107226

Reference: TOXCON 107226

To appear in: *Toxicon*

Received Date: 28 April 2023

Revised Date: 25 June 2023

Accepted Date: 11 July 2023

Please cite this article as: Aoki, Y., Yoshimura, K., Sakai, A., Tachikawa, A., Tsukamoto, Y., Takahashi, K., Yamano, S., Smith, C., Hayakawa, K., Tasaki, O., Ariyoshi, K., Warrell, D.A., Exotic (non-native) snakebite envenomation in Japan: A review of the literature between 2000 and 2022, *Toxicon* (2023), doi: https://doi.org/10.1016/j.toxicon.2023.107226.

CRediT author statement

Yoshihiro Aoki: Conceptualization, Methodology, Investigation, Writing - Original Draft
Ken Yoshimura: Conceptualization, Methodology, Investigation, Writing - Review & Editing
Atsushi Sakai: Conceptualization, Methodology, Validation, Writing - Review & Editing
Atsuko Tachikawa: Conceptualization, Methodology, Writing - Review & Editing
Yutaka Tsukamoto: Conceptualization, Methodology, Writing - Review & Editing
Kensuke Takahashi: Conceptualization, Methodology, Writing - Review & Editing
Shuhei Yamano: Conceptualization, Methodology, Writing - Review & Editing
Chris Smith: Supervision, Writing - Review & Editing
Koichi Hayakawa: Supervision, Writing - Review & Editing
Osamu Tasaki: Supervision, Writing - Review & Editing
Koya Ariyoshi: Supervision, Writing - Review & Editing
David A. Warrell: Conceptualization, Supervision, Writing - Review & Editing

Each author listed in the manuscript has seen and approved the submission of the report and takes full responsibility for its content.

Exotic (non-native) snakebite envenomation in Japan: A review of the literature between 2000 and 2022

Main findings of the study (N = 11)

- **Family of the snakes**: Viperidae, 4; Colubridae, 4; Elapidae, 3
- **Age**: From 16 to 63 years
- **Sex**: Male, 10; Female, 1
- **Body parts bitten**: Hand injury: 11
- **Signs of envenomation**: Cytotoxic, 10; Neurotoxic, 3
  -"Compartment syndrome", 3
  -Respiratory failure requiring mechanical ventilation, 3
- **Management**: Antivenom, 2; Surgical procedure, 6
- **Complications**: Acute kidney injury, Rhabdomyolysis, Coagulopathy, Finger dysfunction, etc.

Case 1. *Gloydius brevicaudus*

Case 2. *Bungarus candidus*

Case 5. *Dendroaspis angusticeps*

Research article

Exotic (non-native) snakebite envenomation in Japan: A review of the literature between 2000 and 2022

Yoshihiro Aoki,[a,b] Ken Yoshimura,[c] Atsushi Sakai,[c] Atsuko Tachikawa,[d] Yutaka Tsukamoto,[d] Kensuke Takahashi,[a,b,e] Shuhei Yamano,[a] Chris Smith,[b,f] Koichi Hayakawa,[a] Osamu Tasaki,[g] Koya Ariyoshi,[b,e] David A. Warrell[h]

a. Coordination Office for Emergency Medicine and International Response, Acute and Critical Care Center, Nagasaki University Hospital, Nagasaki, Japan
b. School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
c. Japan Snake Institute, Gunma, Japan
d. Department of Emergency Medicine, Nagasaki Harbor Medical Center, Nagasaki, Japan
e. Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
f. Department of Clinical Research, London School of Hygiene and Tropical Medicine Faculty of Infectious and Tropical Diseases, London, UK
g. Acute and Critical Care Center, Nagasaki University Hospital, Nagasaki, Japan
h. Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK.

Corresponding author

Yoshihiro Aoki, MD

Coordination Office for Emergency Medicine and International Response, Acute and Critical Care Center, Nagasaki University Hospital, Nagasaki, Japan, 1-7-1 Sakamoto, Nagasaki, Nagasaki 852-8102, Japan

Tel: +81-95-819-7200; Fax: +81-95-819-7215; E-mail: yaoki-hki@umin.ac.jp[1]

[1] **Abbreviations:** ICU, intensive care unit; JSI, Japan Snake Institute; NASBR, North American Snakebite Registry; NPIS, National Poisons Information Service; PLA_2, phospholipase A2; UK, the United Kingdom; US, the United States;

Abstract

A limited number of studies have investigated the clinical characteristics of snakebite envenomation by exotic (non-native) snakes in Japan. This study reviewed the literature to determine the status and risk of bites by exotic pet snakes in Japan. We reviewed reports of snakebite due to exotic snakes in Japan published between 2000 and 2022, excluding reports of bites by snakes native to Japan, such as *Gloydius blomhoffii*, *Rhabdophis tigrinus*, and *Protobothrops flavoviridis*. During the study period, 11 exotic snakebites were recorded, involving 11 species. The majority of those bitten (10/11 cases) were male, all cases were hand injuries, and there were no fatalities. The snakes responsible belonged to the Colubridae (4/11 cases), Viperidae (4/11 cases), and Elapidae (3/11 cases) families. Cases of envenomation by *G. brevicaudus*, *Bungarus candidus,* and *Dendroaspis angusticeps* were of particular interest. Ten of the eleven patients developed local cytotoxic signs, and three developed "compartment syndrome," in which the surgeons performed decompressive incisions. Two bites from elapid snakes and one from a viperid snake resulted in respiratory failure. Antivenom was given in two cases. Complications were observed, such as acute kidney injury, rhabdomyolysis, coagulopathy, and residual dysfunction of the affected finger. Emergency rooms should be prepared to manage patients who have been bitten by exotic snakes, even though the number of reported cases is not high in Japan. Initial stabilization of patients is crucial, before a definitive diagnosis is made, as with native snakebite envenomation. Finger bites are reported in most cases, which may result in functional impairment of the fingers. In order to collect more comprehensive patient data in Japan, a reporting system for all snakebite envenomations should be considered.

Keywords:

Colubridae; Elapidae; Emergency Medicine; Envenoming; Snakebite; Viperidae

1. Introduction

The global pet boom has led to an increase in reptile breeders, suppliers, exporters, and smugglers worldwide. In 2016, Japan imported 192,000 live reptiles worth $3.93 million, ranking fourth in the world.[1] Exotic (non-native) snakes are one of the most popular reptiles, not only exhibited in zoos but also widely kept as pets. However, the number of snake keepers and manufacturers in Japan remains unknown. Since 2007, under revised provisions of the Act on Welfare and Management of Animals, animals such as venomous snakes that may cause harm to human life, body, or property have been designated as specified animals and prohibited from being kept as pets in Japan. Nevertheless, there is an apparently small, but unknown number of illegal holdings and captive breeding of these animals in Japan which creates a greater risk of bites and envenomations.[2]

In Japan, snakebites by indigenous (native) species of venomous snakes are a familiar problem.[3] "Mamushi" (*Gloydius blomhoffii*), "habu" *(Protobothrops flavoviridis)* and "yamakagashi" *(Rhabdophis tigrinus)* are the three main venomous snake species in Japan, with an estimated annual incidence of approximately 1,000 cases and 10 deaths for "mamushi," 100 cases for "habu," and 34 cases with 4 deaths over the past 40 years for "yamakagashi;" while antivenom is widely available for "mamushi" and "habu" in most tertiary hospitals in endemic areas, for "yamakagashi" is non-approved drug devised by the research group and stockpiled at only limited facilities.[4] On the other hand, a few bites by non-native species have been reported since the 1970s in Japan.[5–7] The species involved included both viperid and elapid species, such as the Korean "mamushi" (*Agkistrodon caliginosus)*,[5] southern Pacific rattlesnake (*Crotalus helleri*),[6] and Siamese cobra (*Naja kaouthia*).[7] Reported cases have demonstrated shock[6] and respiratory failure necessitating ventilator management.[7] In 2007, Sakai[2] published a domestic review article on snakebites by imported snakes in Japan. No additional reports have detailed the clinical characteristics of 'exotic snakebites' in Japan, including bites by illegally bred snakes. This study aimed to review the literature to determine the status and risk of bites by exotic pet snakes in Japan.

2. Methods

We conducted a literature review of published reports between 2000 and 2022. Patient data were identified through searches on PubMed and Scopus, using the terms "snakebite" and "Japan." In Scopus, we limited the sources to journal articles in the medical field. A Japanese literature search was conducted using the "ICHUSHI" database. The initial survey was completed by January 12, 2023. We also referred to the Japan Snake Institute (JSI)'s official journal, "*The Snake*," which was published until 2002. Conference abstracts and Japanese literature were also included in the study. Reports concerning snakes native to Japan were excluded, such as those concerning "mamushi" *(G. blomhoffii)*, "yamakagashi" *(R. tigrinus)*, "habu" (*P. flavoviridis)*, "Tsushima mamushi" *(G. tsushimaensis)*, "Sakishima habu" *(Trimeresurus elegans)*, "himehabu" *(Ovophis okinavensis)*, and "Taiwan habu" *(P. mucrosquamatus)*. However, we included a case of a bite by an illegally kept Okinawan dwarf lancehead snake, called "himehabu" (*O. okinavensis*), which, although Japanese, is not native to Honshu. Reports before 2000 were also excluded from the analysis. The literature search was validated by two researchers (YA, KY).

From each case report, the following items were extracted and descriptively summarized: year of report, age, sex, snake species, common name and family of the snake, country of origin, legality of possession, activity at the time of bite, past bite history, time from bite to visit, bite site, number of fang marks, local findings,

neurological symptoms, presence of respiratory disturbance, "compartment syndrome," (defined as a condition that, in the opinion of the surgeons, required decompressive fasciotomy), "life-threatening" (defined as the presence of systemic envenoming causing respiratory muscle paralysis, acute kidney injury, or coagulopathy during the clinical course), pre-visit treatment, antivenom treatment, surgical treatment, other treatment, presence of JSI consultation, intensive care unit (ICU) management, ventilator days, hospital days, secondary infections, complications, and outcome. If available, the information collected was partially supplemented or validated by JSI internal records.

3. Results

We found only 11 cases reported between 2000 and 2022 (Figure 1).[8-18] Information about the patients' backgrounds and the responsible snake are shown in Table 1. Out of the 11 species, eight of the snakes responsible are pictured in Figure 2. The photographs of Case 2 (*Bungarus candidus*), Case 5 (*Dendroaspis angusticeps*), and Case 6 (*D. viridis*) are of the actual snakes, which JSI took over from the owners after the incidents. *Gloydius brevicaudus* in Case 1 was imported as an ingredient in Chinese herbal medicine. In Case 4, the patient captured "himehabu" (*O. okinavensis*) in Okinawa and illegally brought the snake home to Honshu. All other snakes, were imported by pet shops from outside Japan (no detailed geographical information was available). Patients were aged between 16 and 63 years, and 10 were male. Four of the snakes (36%) belonged to the Viperidae family, three (27%) to the Elapidae family, and four (36%) to the Colubridae family. At the time of the reporting, five (45%) were being kept illegally, according to the animal welfare law. Five of the bite victims were injured during intentional contacts, such as touching or feeding. The other six did not disclose the circumstances of the bites.

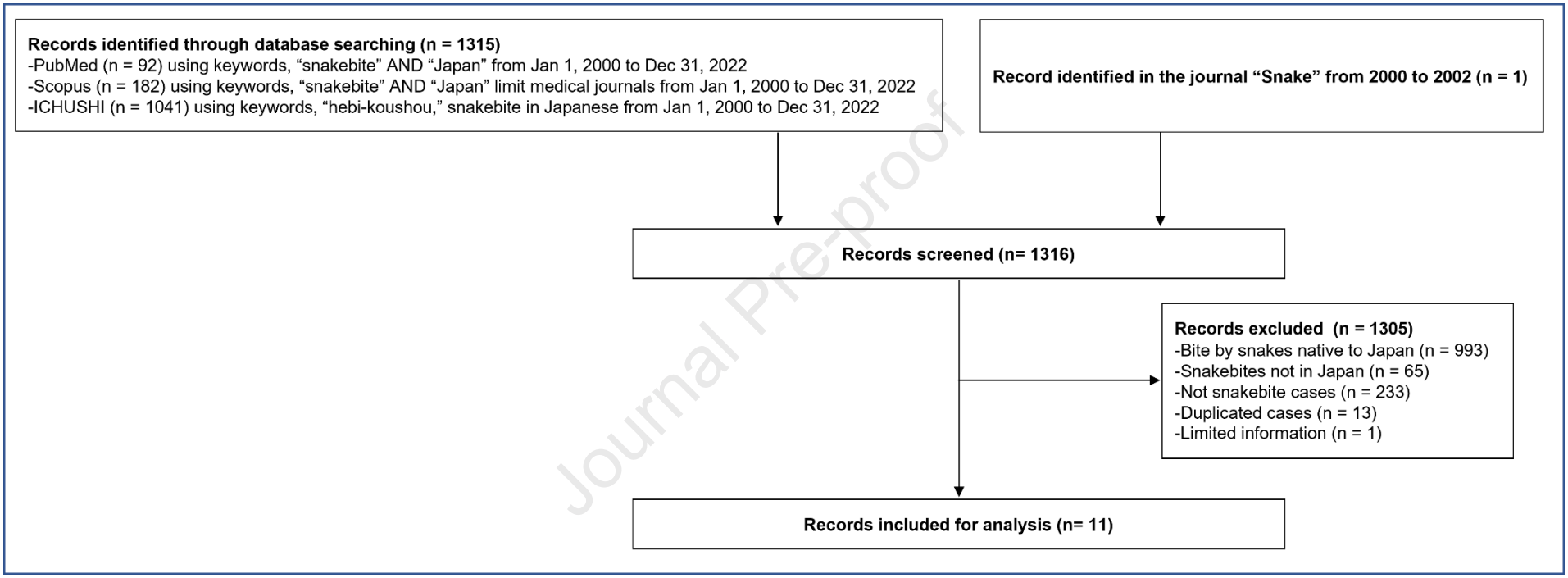


Fig. 1. Flowchart of study cases

Fig. 2. Photographs of the same snake species responsible for the bite in the literature.

A, *Gloydius brevicaudus* (Case 1); B, *Bungarus candidus* (Case 2, the actual snake); C, *Atheris ceratophora* (Case 3); D, *Ovophis okinavensis* (Case 4); E, *Dendroaspis angusticeps* (Case 5, the actual snake); F, *Dendroaspis viridis* (Case 6, the actual snake); G, *Heterodon nasicus* (Case 7); H, *Bitis arietans* (Case 9)© Japan Snake Institute

A summary of the clinical manifestations, treatment, and outcomes are shown in Tables 2 and 3. Two cases were seen within 30 minutes of the bite, while one was seen after nearly 24 hours. All bites were on the hands. Ten patients (91%) had local cytotoxic signs such as swelling and redness, and three (27%) developed "compartment syndrome" (see above). Three patients (27%) had obvious neurotoxic findings with ptosis, diplopia, and respiratory muscle paralysis. Out of 11 cases, five (Case 1, 2, 5, 6, and 9) were considered life-threatening severe envenomations with systemic signs such as respiratory muscle paralysis, acute kidney injury, and coagulopathy (Tables 2 and 3).

Tourniquets had been applied before arrival at the hospital in three cases (27%). It was confirmed that in four cases (36%), the JSI was consulted regarding diagnosis and management plan. Antivenom was administered in two cases (18%) due to *G. brevicaudus* (Case 1) and *B. candidus* (Case 2). In Case 1, the antivenom for *G. blomhoffii* was administered to the patient with a *G. brevicaudus* bite because it was the only available antivenom, but it was reported to be ineffective. In Case 2, the *B. multicinctus* antivenom refined from horse serum by the Shanghai Institute of Biological Products in China, which was kept in the JSI, was transported to the hospital with the cooperation of police. One vial (8000 units) of the antivenom combined with neostigmine was effective in treating the patient with neurotoxic signs, as paralysis in the extremities improved in the following day and spontaneous breathing under the mechanical ventilator reappeared on day 3 of admission. No adverse reactions related to the antivenom in both cases were reported. Surgical procedures were performed in six patients

(55%), including debridement, incision, fasciotomy (decompressive incisions), and skin-grafting. Three patients (27%), envenomed by *G. brevicaudus* (Case 1), *B. candidus* (Case 2), and *D. viridis* (Case 6), required assisted ventilation, and one (9%) due to *G. brevicaudus* (Case 1) had acute kidney injury requiring hemodiafiltration. There were various other complications, such as coagulopathy due to *D. angusticeps* (Case 5) and *Bitis arietans* (Case 9), rhabdomyolysis due to *G. brevicaudus* (Case 1), possible psychological effects of chronic fatigue due to *B. candidus* (Case 2), dermonecrosis with ulceration due to *Atheris ceratophora* (Case 3） and *D. angusticeps* (Case 5), chronic dermatitis of possible allergic reaction at the bite site due to *Heterodon nasicus* (Case 7), and finger dysfunction due to *D. angusticeps* (Case 5) and *B. arietans* (Case 9). Hospital stays ranged from a few days to more than 50 days. In Case 1, the patient was reported to have been discharged on day 54 after prolonged mechanical ventilation support. There were no fatalities.

4. Discussion

Eleven cases of snakebite envenomation by exotic (non-native) pet snakes in Japan have been reported in scientific journals since 2000, which is relatively fewer than the number of cases reported from other countries.[19-22] Antivenom was administered in a few cases, and more than half of the cases were thought by their clinicians to require surgical intervention. All the patients eventually recovered but in Case 1, bitten by a short-tailed “mamushi” (*G. brevicaudus*), Case 2 bitten by a Malayan krait (*B. candidus*), and Case 6 bitten by a western green mamba (*D. viridis*), they required multidisciplinary treatment with assisted ventilation for respiratory muscle paralysis. In addition, Case 5 (*D. angusticeps*) and Case 9 (*B. arietans*) were also considered life-threatening severe cases since they developed coagulopathy. Particularly in Case 1, the patient required hemodiafiltration and long-term mechanical ventilation with more than 50 days including continuous positive airway pressure mode after administration of antivenom for *G. blomhoffii*. This fact may suggest that patient care could be challenging in the absence of species-specific antivenom in exotic snakebite cases. However, even when a specific antivenom is not available, assisted ventilation can be life-saving.[23,24] In addition, as was observed in Case 2 with *B. candidus*, supportive care with anticholinesterase inhibitors may be helpful for treating neurotoxic snakebite envenomation. Neostigmine has been suggested as an initial or additional treatment for envenomation caused by species whose venoms primarily exhibit post-synaptic neurotoxicity, such as cobras.[25,26] However, response to anti-cholinesterase has also be documented in victims of envenomation by species whose venoms contain both pre- and post- synaptic neurotoxins.[27] Of note, antivenom cannot reverse paralysis caused by destruction of nerve terminals by pre-synaptic neurotoxins such as β-bungarotoxin in *B. candidus* venom or the phospholipase A2 (PLA_2) neurotoxin in *G. brevicaudus* venom. More prolonged ventilatory support will be required than for paralysis caused by postsynaptic neurotoxins, to allow development of new synapses.[28]

As in the management of snakebite worldwide, in Japan, the diagnosis of the snake responsible is

usually made clinically, based on history and clinical symptoms and signs.[4] The main venomous snakes native to Japan are the Japanese pit viper or "mamushi" (*G. blomhoffii*), of Hokkaido, Honshu, Shikoku, and Kyushu areas; the "yamakagashi" (*R. tigrinus*) of Honshu, Shikoku, and Kyushu areas; and the "habu" (*P. flavoviridis*) of Okinawa and the Amami Islands.[4] *G. blomhoffii* and *P. flavoviridis* are members of the Viperidae family whose bites most commonly cause local tissue damage, indicated by raised serum creatine kinase levels, and, in the case of *G. blomhoffii*, very rarely thrombocytopenia, coagulopathy, acute kidney injury and mild neurotoxicity.[4] Some patients might develop binocular diplopia due to paralysis in the external ocular muscles following a *G. blomhoffii* bite.[29] The Tsushima pit viper, or "Tsushima-mamushi" (*G. tsushimaensis*), while technically a separate species from *G. blomhoffii*, also causes symptoms such as local swelling, diplopia, acute kidney injury, and disseminated intravascular coagulation,[30] even though no fatalities have been reported from this species thus far. Currently, there are five species of "habu" in Japan, including the "Taiwan-habu" (*P. mucrosquamatus*), which was imported but eventually naturalized in Japan. The bites from these species have increasingly become a concern. In contrast, *R. tigrinus*, of the Colubridae family, has the characteristic of causing severe coagulopathy, although there are few cases of bites.[31] Few patients bring photographs of the causative snakes, or the snakes themselves, and care must be taken to avoid incorrect identification if the diagnosis is based on the person's memory and description. Notably, in the case of exotic pet snakes, species diagnosis is relatively easy because the owner is often familiar with the snake species, and medical staff can consult an expert to identify the snake itself or the photograph. However, further bites must be carefully avoided when photographing or approaching the snakes. Moreover, we should remember that pet owners may be reluctant to declare the snake responsible because of its illegality.[32] Neurotoxic envenomation should be suspected in cases of unexplained paralysis, respiratory failure or unconsciousness if the circumstances or evidence of a bite site suggest the possibility of a snakebite, even though native snakes in Japan usually do not result in severe neurological signs.

Recently, observational studies on the characteristics of exotic snakebites were reported from the United Kingdom (UK)[21] and the United States (US).[22] Although the majority of snakes responsible in a descriptive review of 19 snakebites involving envenomation by non-native species reported to the North American Snakebite Registry (NASBR) in the US from 2013 to March 2022 was from the Viperidae family, more than half of those in the UK study during 2009-2020 (n = 321) were from the Colubiridae family. However, in the UK study, although most patients were asymptomatic or mildly symptomatic (87%), there were 15 cases of severe envenomation, all of which were caused by viperid or elapid snakes, with one fatality. In our current study from Japan, Colubridae species were also reported in four out of 11 cases, but all life-threatening cases were caused by viperid or elapid snakes, as in the UK study. Therefore, even among exotic snakebites, the Colubridae family rarely causes severe envenomation. Regarding the patient's gender and part of the body bitten, all studies from the UK, the US, and Japan were consistent in that most victims were males bitten on the hands. Most pediatric

exotic snakebites were caused by colubrid snakes in the UK[21] and boa constrictors in the US.[33] There were no pediatric cases younger than 16 years old in the current review in Japan. The predominance of hand bites in the UK, the US, and Japan emphasizes the risk of intentional touching by pet keepers. This contrasts with bites provoked by inadvertent contact from occupations such as farming, which more often involve lower extremities.[28] Fingers are crucial adjuncts to everyday life; therefore special precautions should be taken to protect them from bites and avoid debilitating sequelae. Cytotoxic signs were reported as the primary symptom in the UK, US, and Japan studies, but five patients in the UK study required mechanical ventilation due to bites from a monocled cobra (*N. kaouthia*), an Indian cobra (*N. naja*), an eastern green mamba (*D. austiceps*), an eastern sand viper (*Vipera ammodytes meridionalis*), and a forest cobra (*N. melanoleuca*). Similarly, two patients in the US study bitten by monocled cobras (*N. kaouthia*), and three in the Japan study bitten by a short-tailed mamushi (*G. brevicaudus*), a Malayan krait (*B. candidus*), and a western green mamba (*D. viridis*) required mechanical ventilation. Most snakes responsible for respiratory muscle paralysis are in Elapidae family, but viperid snakes can also cause severe neurological manifestations. Remarkably, in Case 5 bitten by an eastern green mamba (*D. augusticeps*), significant cytotoxic signs were noted, whereas expected neurotoxicity was absent, indicating a highly atypical clinical course of envenomation by this species. The potentially fatal risk of venom-induced anaphylaxis has been described in the UK; however, no recognized cases of anaphylaxis were present in the current review, even though previous bites were described in Cases 1, 3, 6, and 11.

Of the 11 cases, six patients underwent some form of surgical intervention. Surgical management in snakebites is generally associated with a number of incorrect interventions, and it should be noted that the conditions in which interventions were performed and the indications for the procedures were not consistent from case to case when reviewing previous reports. In this study, "compartment syndrome" was defined as a case in which a surgeon judged that decompressive incisions were necessary. However, inappropriate fasciotomies are not uncommon, due to misdiagnosis of compartment syndrome.[28] Only in Case 1 (*G. brevicaudus*), was the diagnosis of compartment syndrome based on an intra-compartmental pressure consistently >40 mmHg. On the other hand, in Case 5 (*D. angusticeps*), there was an increase in compartment pressure >40 mmHg, but due to severe coagulopathy, no decompressive incision was performed, and the case was not included as a "compartment syndrome" in our review. Some snakebite cases show marked swelling, so careful follow-up is necessary to check for signs of distal ischemia. However, the invasive procedure of decompressive incisions should be based firmly on elevated intra-compartmental pressure. Debridement of necrotic tissue is also important to prevent infection, but may later require skin grafting as in Case 6 (*D. viridis*); therefore, collaboration with an experienced surgeon is crucial.

The Japanese review conducted by Sakai in 2007 specifically concentrated on exotic snakebite cases in which JSI was consulted.[2] Among those cases, three overlapped with the cases included in the present review.[8-10]

Sakai's review encompassed an additional 23 snakebite cases involving imported snakes from 1967 to 2006. The cases included various snake species, such as a *B. multicinctus* (1967) resulting in dysphagia and generalized skeletal muscle paralysis, three cases of a *N. kaouthia* (1969, 1985, 1992) leading to respiratory arrest and necrosis, three cases of an *Agkistrodon caliginosus* (1971, 1972, 1975) resulting in swelling, diplopia, and blister formation, and a *Crotalus helleri* (1972) causing swelling, hypotension, reduced consciousness. Additionally, the review included one case of a *Boiga dendrophila* (1975) with symptoms of redness and swelling, five cases of *O. okinavensis* (1982, 1991, 2003, 2005, 2006) presenting with pain, swelling, and bleeding, three cases of *Sistrurus miliarius* (two in 1991, one in 2005) causing swelling, pain, tachycardia, one case of *T. elegans* (1992) involving an injury while keeping a snake captured in Okinawa at home, one case of *N. atra* (1994) where an airport worker was bitten by a snake mixed with imported flowers, and one case of *T. albolabris* (1999) where a staff member bitten by a snake that was mixed in with a container from China. Furthermore, the review also included two cases of *G. brevicaudus* (both in 2000) characterized by swelling, as well as one case of a *Tropidolaemus wagleri* (2001) presenting with swelling. After 2000, there were eight reported cases; however, none of these cases were found in the literature, and the available information was too limited to be included in our review. Bites caused by imported snakes have been documented over several decades, and while there may not be a noticeable increase in their numbers, it has been suggested that these cases could be significantly underreported.

As far as we have discovered, there has been only one death related to the exotic snake *(Malayopython reticulatus*) in Japan so far (Japanese news article online). In this case, a 66-year-old male, the father of a pet shop owner, was found dead with multiple lacerations on his head and upper extremities. A 6.5-meter-long python was outside the cage, and it was assumed that the python had attacked him. According to the police, the door of the wooden cage (1.7 meters high, 1 meter wide, and 1.85 meters deep) that contained the snake was open, and he was lying near it. We should keep in mind that large pythons are dangerous even though they are non-venomous.

This study is the first international report summarizing the clinical characteristics of bites by exotic snakes in Japan. The strength of the review is the inclusion of reports from *The Snake* which is not widely known, unpublished data from JSI consultations for partial supplementation of the reported cases, and papers in the Japanese language. However, the study has several limitations; for example, there is no case registry system for snakebites in Japan, making it unclear how many cases have gone unreported in scientific journals. One reason for the low number of reported cases might be that bites by colubrid snakes, which are not designated as specified animals by the animal welfare law except for the snakes from the four genera, *Dispholidus* sp., *Rabdophis* sp., *Tachymenis* sp., and *Thelotornis* sp., do not require permission to be kept as pets, and are rarely reported because they do not usually cause severe signs of envenomation. In Japan, as in other countries such as the UK, it seems highly likely that people bitten by venomous snakes they are keeping illegally will be reluctant to seek medical help, resulting in their exclusion from published case reports or poison center surveys.[32] A lower number of

reported cases might also result from reporting bias, as only severe or complex cases were reported. During the study period, JSI was consulted about exotic snakebites by hospitals across Japan, involving various species, such as *Tropidolaemus wagleri*, *Clelia clelia*, *Calliophis intestinalis thepassi*, and *Trimeresurus insularis* (unpublished data and patient details are not currently available). Our review includes cases in which JSI was not involved. We recommend that all hospitals and clinics in Japan be encouraged to consult the JSI to confirm appropriate initial management in exotic snakebites.

5. Conclusion

We reviewed publications on exotic snakebites in Japan, including those arising from illegally kept snakes. Although the number of cases is small, the risk of severe envenomation is clearly illustrated. It is crucial for emergency rooms to be prepared to manage patients bitten by exotic snake species. In particular, since neurotoxic symptoms can lead to respiratory paralysis, it is essential to stabilize the patient's condition in the early stages, including ensuring a patent airway. Many cases of finger bites have been reported, which may result in functional impairment of the fingers. In the future, it would be desirable to establish a reporting system for all snakebite envenomations, in order to collect more comprehensive patient data in Japan.

Acknowledgments: Not applicable.

Sources of funding: This work was not supported by any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability Statement:

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1. Wakao K, Janssen J, Chng S. [Reptile pet market in Japan.] Annu Rep Pro Nat Found Japan 2018;27:1–12. (in Japanese)
2. Sakai A. [Envenomations by the Imported Venomous Snakes.] Jpn J Toxicol 2007;10:245–52. (in Japanese)
3. Chiba T, Koga H, Kimura N, Murata M, Jinnai S, Suenaga A, et al. Clinical condition and management of 114 mamushi (*Gloydius blomhoffii*) bites in a general hospital in Japan. Intern Med 2018;57:1075–80. https://doi.org/10.2169/internalmedicine.9409-17
4. Hifumi T, Sakai A, Kondo Y, Yamamoto A, Morine N, Ato M, et al. Venomous snake bites: clinical diagnosis and treatment. J Intensive Care 2015;3:16. https://doi.org/10.1186/S40560-015-0081-8
5. Sawai Y. Snakebites by Korean mamushi in Japan. The Snake 1975;7:40–1.
6. Masuda K, Sawai Y. A case of rattlesnake bite in Japan. The Snake 1975;7:101–2.
7. Sawai Y. A severe bite by Siamese cobra in Japan. The Snake 1987;19:99–100.
8. Kawamura S, Kiyota K, Inagawa H, Terada T, Nishida M, Suzuki S, et al. A Severe envenomation from the bite of *Agkistrodon blomhoffii brevicaudus* imported from China. The Snake 2002;29:1–6.
9. Inoue T, Minagawa K, Matsuda T, Yamaguchi Y, Murata A, Shimazaki S. [A case of respiratory arrest following a snake bite (Envenomation) by *Bungarus candidus*.] Nihon Kyukyu Igakukai Zasshi 2003;14:72–6. (in Japanese) https://doi.org/10.3893/jjaam.14.72
10. Sugimoto T, Nemoto M, Aoyagi K, Kuroyanagi M, Yamada N, Uchinuma E. [Two cases of skin ulcer caused by poisonous snakebite injury.] Keiseigeka 2008;51:469–73. (in Japanese)
11. Tanizaki R, Yamada N, Doi T, Yoshida S, Shirai K, Toyota I, et al. [Case report of a dwarf lancehead snake bite in Gifu.] Chudoku Kenkyu 2011;24:241–2. (in Japanese)
12. Shirokawa M, Seki K, Nakajima Y, Koyama S, Mitsusada M. Patient without neurotoxic symptom after being bitten by an eastern green Mamba (*Dendroaspis angusticeps*). Nihon Kyukyu Igakukai Zasshi 2011;22:777–81. (in Japanese) https://doi.org/10.3893/JJAAM.22.777
13. Inoue T, Yoshitake T, Kamijo Y. [A case of compartment syndrome from a western green mamba bite.] Chudoku Kenkyu 2015;28:185. (in Japanese)
14. Kato K, Kato H, Morita A. A case of Western hognose snake bite. J Cutan Immunol Allergy 2019;2:37–8. https://doi.org/10.1002/CIA2.12041
15. Amano Y, Shimura H, Tomizawa S, Nakatsuru E. [A case of slightly poisonous snakebite requiring finger relaxation incision.] J East Jpn Orthop Traumatol 2019;31:348. (in Japanese)
16. Wakasugi M, Kawagishi T, Hatano T, Shibuya T, Kuwano H, Matsui K. Case Report: Treatment of a severe Puff Adder snakebite without sntivenom administration. Am J Trop Med Hyg 2021;105:525–7.

https://doi.org/10.4269/AJTMH.21-0291

17. Terashige S, Nishiyama T, Takeshima S, Hatanaka K, Sugiura T, Sasa R, et al. Snakebite and local envenomation by *Boiruna maculata* treated without antivenom. Acute Med Surg 2021;8:e674. https://doi.org/10.1002/AMS2.674

18. Ohno H, Funakoshi H, Sugiura S, Sakai A, Shimura H. [A case of conservative treatment for *Philodryas baroni* (Baron's Green Racer) bite in a pet animal.] Nihon Rinsho Kyukyu Igakukai Zasshi 2022;25:735–9. (in Japanese)

19. Warrick BJ, Boyer LV, Seifert SA. Non-native (exotic) snake envenomations in the U.S., 2005-2011. Toxins (Basel) 2014;6:2899–911. https://doi.org/10.3390/TOXINS6102899

20. Miller SW, Osterhoudt KC, Korenoski AS, Patel K, Vaiyapuri S. Exotic Snakebites Reported to Pennsylvania Poison Control Centers: Lessons Learned on the Demographics, Clinical Effects, and Treatment of These Cases. Toxins 2020;12:755. https://doi.org/10.3390/TOXINS12120755

21. Jagpal PS, Williams HA, Eddleston M, Lalloo D, Warrell D, Sandilands EA,et al. Bites by exotic snakes reported to the UK National Poisons Information Service 2009-2020. Clin Toxicol (Phila). 2022;60:1044–50. https://doi.org/10.1080/15563650.2022.2077748

22. Basse J, Ruha AM, Baumgartner K, Mullins ME, Greene S, Wax PM, et al. Clinical Presentations, Treatments, and Outcomes of Non-native Snake Envenomations in the United States Reported in the North American Snakebite Registry. J Med Toxicol 2022 2022:1–10. https://doi.org/10.1007/S13181-022-00912-421.

23. Pochanugool C, Wilde H, Jitapunkul S, Limthongkul S. Spontaneous recovery from severe neurotoxic envenoming by a Malayan krait *Bungarus candidus* (Linnaeus) in Thailand. Wilderness Environ Med 1997;8:223–5. https://doi.org/10.1580/1080-6032(1997)008[0223:SRFSNE]2.3.CO;2

24. Hung HT, Höjer J, Du NT. Clinical features of 60 consecutive ICU-treated patients envenomed by *Bungarus multicinctus.* Southeast Asian J Trop Med Public Health 2009;40:518–24 .

25. WHO SEARO Guidelines for the Management of Snakebites 2nd ed New Delhi, WHO, 2016. https://www.who.int/docs/default-source/searo/india/health-topic-pdf/who-guidance-on-management-of-snakebites.pdf?sfvrsn=5528d0cf_2

26. Faiz MA, Ahsan MF, Ghose A, Rahman MR, Amin R, Hossain M, et al. Bites by the monocled cobra, *Naja kaouthia*, in Chittagong Division, Bangladesh: Epidemiology, clinical features of envenoming and management of 70 identified cases. Am J Trop Med Hyg 2017;96:876–84. https://doi.org/10.4269/AJTMH.16-0842

27. Warrell DA, Looareesuwan S, White NJ, Theakston RD, Warrell MJ, Kosakarn W, et al. Severe neurotoxic envenoming by the Malayan krait *Bungarus candidus* (Linnaeus): response to antivenom and

anticholinesterase. Br Med J (Clin Res Ed) 1983;286:678–80. https://doi.org/10.1136/BMJ.286.6366.678

28. Seifert SA, Armitage JO, Sanchez EE. Snake Envenomation. N Engl J Med. 2022;386:68-78. https://doi.org/10.1056/NEJMra2105228

29. Takeshita T, Yamada K, Hanada M, Oda-Ueda N. Case report: Extraocular muscle paresis caused by snakebite. Kobe J Med Sci 2003;49:11–5.

30. Yokoi H, Sakai A, Kodama T, Magome S, Itose O, Tawara M, et al. Evaluation of a treatment algorithm for Tsushima mamushi (*Gloydius tsushimaensis*) snakebites, after its introduction to Tsushima island, Nagasaki, Japan. Intern Med 2021;60:3093–9. https://doi.org/10.2169/internalmedicine.7131-21

31. Hifumi T, Sakai A, Yamamoto A, Morokuma K, Otani N, Takahashi M, et al. *Rhabdophis tigrinus* (yamakagashi) bites in Japan over the last 50 years: A retrospective survey. Front Public Heal 2022; 9:775458. https://doi.org/10.3389/fpubh.2021.775458

32. Warrell DA. Commissioned article: management of exotic snakebites. QJM An Int J Med 2009;102:593–601. https://doi.org/10.1093/QJMED/HCP075

33. Schulte J, Domanski K, Smith EA, Menendez A, Kleinschmidt KC, Roth BA. Childhood victims of snakebites: 2000-2013. Pediatrics. 2016;138:e20160491. https://doi.org/10.1542/peds.2016-0491

369 **Table 1.** Patient backgrounds and causative snake information.

Case	Year*	Age	Sex	Causative species	Common name of the snake	Family	Distribution	Purpose	Legality	Activity at time of bite	Snakebite history
1[8]	2002	63	M	*Agkistrodon blomhoffii brevicaudus* (*Gloydius brevicaudus*)	Short-tailed pit viper	Viperidae	North Korea, South Korea, China, Russia	An owner of a herbal medicine shop	Legal**	Grabbing	Twice
2[9]	2003	40	M	*Bungarus candidus*	Malayan krait or Blue krait	Elapidae	Southeast Asia	Friend's pet	Illegal	Handling	ND
3[10]	2008	16	M	*Atheris ceratophora*	Usambara bush viper	Viperidae	Tanzania	Pet	Illegal	ND	Once
4[11]	2011	20	M	*Ovophis okinavensis*	Dwarf lancehead snake, Himehabu	Viperidae	Japan (Okinawa)	Pet	Illegal	ND	ND
5[12]	2011	40	M	*Dendroaspis angusticeps*	Eastern green mamba	Elapidae	Southern and East Africa	Pet	Illegal	ND	ND
6[13]	2015	23	M	*Dendroaspis viridis*	Western green mamba	Elapidae	Western Africa	Pet	Illegal	ND	Twice
7[14]	2019	19	M	*Heterodon nasicus*	Western hognose snake	Colubridae	North America	Pet	Legal	Feeding	ND
8[15]	2019	24	M	*Hydrodynastes gigas*	False water cobra	Colubridae	South America	A pet shop keeper	Legal	ND	ND
9[16]	2021	23	M	*Bitis arietans*	Puff adder	Viperidae	Sub-Saharan Africa	Pet	Legal**	ND	ND
10[17]	2021	50	M	*Boiruna maculata*	Mussurana	Colubridae	South America	Pet	Legal	Handling	ND
11[18]	2022	23	F	*Philodryas baroni*	Baron's green racer	Colubridae	South America	Pet	Legal	Handling	Multiple

*Year of publication; **With official permission; ND: not described

370

371

372

373 **Table 2.** Clinical features of cases in the literature of the study.

374

Case	Time of visit from bite (hours)	Part of the body bitten	Local findings during the course										Neurological findings					Laboratory findings on admission
			Number of fang marks	Pain	Itchiness	Numbness	Swelling	Redness	Bleeding	Blister	Necrosis	Compartment syndrome	Disturbance of consciousness (drowsiness/coma)	Ptosis	Blurred/ double vision	Paralysis	Respiratory failure	
1[8]	A few hours	Finger	ND	ND	ND	+	+	ND	ND	ND	ND	+	-	ND	+	-	+	Elevated myoglobin and CK, myoglobinuria, respiratory and metabolic acidosis, elevated hematocrit
2[9]	1~16	Finger	ND	+	ND	+	-	-	ND	ND	ND	-	+	+	+	+	+	Elevated WBC, elevated CK, respiratory acidosis
3[10]	2	Finger	ND	+	ND	ND	+	+	+	+	+	-	−	ND	ND	ND	ND	No abnormal findings
4[11]	<24	Finger	2	ND	ND	ND	+	ND	ND	ND	ND	-	-	ND	ND	ND	ND	No abnormal findings
5[12]	0.5	Finger	1	+	ND	+	+	+	+	+	+	-	-	-	-	-	-	Decreased fibrinogen
6[13]	1	Finger	ND	ND	ND	ND	+	+	ND	ND	ND	+	-	ND	ND	ND	+	Elevated CK
7[14]	2	Hand	1	ND	+	-	+	+	ND	+	ND	-	-	-	-	-	-	Slightly elevated C-reactive protein
8[15]	5, 19	Finger	ND	+	ND	+	+	ND	ND	+	ND	+	ND	ND	ND	ND	ND	ND
9[16]	0.5	Finger	2	+	ND	-	+	+	-	-	-	-	-	-	-	-	-	No abnormal findings
10[17]	20	Finger	ND	+	ND	-	+	+	+	+	+	possible	-	ND	ND	ND	ND	slightly increased inflammatory markers
11[18]	2	Finger	ND	+	ND	+	+	ND	ND	+	ND	-	ND	ND	ND	ND	ND	No abnormal findings

ND, not described; WBC, white blood cells; CK, Creatine phosphokinase

375

376 **Table 3.** Treatment and prognosis of the cases in the literature of the study.

Case	First aid	JSI consultation	Antivenoms	Other treatments	Surgical procedure	ICU	Ventilator-Days	Hospital-Days	Secondary infections	Complications	Outcomes
1[8]	Cleaning	ND	+	Hemodiafiltration (14 days)	Fasciotomy	+	53	54	ND	Nonoliguric renal failure, Rhabdomyolysis	Survive
2[9]	Oxygen, infusion	+	+	Steroid, Histamine-2 receptor blocker, Neostigmine	-	+	8	44	ND	Chronic symptoms: Fatigue, Numbness, Dysgeusia, Dry eye	Survive
3[10]	ND	+	-	CEZ, Anti-tetanus, GM ointment, sulfadiazine silver	Incision	ND	0	ND	ND	Local skin necrosis (cured after 10 weeks)	Survive
4[11]	ND	ND	-	CTRX, Anti-tetanus, Cepharanthine	-	ND	0	5	ND	ND	Survive
5[12]	Tourniquet	+	-	CEZ, anti-tetanus, Pentazocine, Clomipramine, Carbamazepine	Debridement	+	0	44	ND	Coagulopathy, Local wound ulcer (epithelialized at 136 days after the bite), Neuropathic pain, PIP joint stiffness	Survive
6[13]	Tourniquet	+	-	ND	Fasciotomy, Flap surgery	+	1<	12	ND	-	Survive
7[14]	ND	ND	-	CCL, Topical corticosteroid	-	ND	0	ND	possible	Chronic dermatitis	Survive
8[15]	Tourniquet	ND	-	ND	Fasciotomy	ND	0	12	ND	ND	Survive
9[16]	ND	Not specifically described	-	CEZ, anti-tetanus, Fentanyl, rTM, HBO	-	ND	0	15	ND	Hypotension, Venom-induced consumption coagulopathy, Mild contractures of the middle and ring fingers	Survive
10[17]	ND	ND	-	Goreisan	Incision	ND	0	7	ND	-	Survive
11[18]	ND	ND	-	Anti-tetanus	-	ND	0	4	-	-	Survive

JSI, Japan Snake Institute; ICU, intensive care unit; ND, not described; CEZ, cefazoline; GM, gentamicin, CTRX, ceftriaxone; PIP, proximal interphalangeal; CCL, cefaclor; rTM, recombinant thrombomodulin; HBO, hyperbaric oxygen therapy

377

378

Highlights

- A literature review of exotic snakebite reports in Japan published between 2000 and 2022 was conducted.
- Out of 11 cases reported, ten were male, and all suffered from hand injuries.
- Two from elapid snakes and one from a viperid snake developed respiratory paralysis requiring mechanical ventilation.
- Various complications were observed, such as acute kidney injury, rhabdomyolysis, coagulopathy, and finger dysfunction.
- Emergency rooms should be prepared to manage patients bitten by exotic snake species.

Ethical statements

This research was conducted ethically in accordance with the Declaration of Helsinki. Ethics approval was not required because this is a literature review research.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: