



## Twelve month prospective study of snakebite in a major teaching hospital in Mandalay, Myanmar; Myanmar Snakebite Project (MSP)



Julian White<sup>a,c,\*</sup>, Sam Alfred<sup>b,c</sup>, David Bates<sup>a,c</sup>, Mohammad Afzal Mahmood<sup>c</sup>, David Warrell<sup>d</sup>, Robert Cumming<sup>e</sup>, Khin Thida Thwin<sup>f</sup>, Myat Myat Thein<sup>g</sup>, Myo Thant<sup>g</sup>, Zaw Myo Naung<sup>g</sup>, Ye Htet Naing<sup>g</sup>, Su Sint Sint San<sup>g</sup>, Myat Thet Nwe<sup>g</sup>, Chen Au Peh<sup>c,h</sup>

<sup>a</sup> Toxinology Dept., Women's & Children's Hospital, North Adelaide, SA, 5006, Australia

<sup>b</sup> Emergency Department, Royal Adelaide Hospital, Adelaide, SA, 5000, Australia

<sup>c</sup> University of Adelaide, Adelaide, SA, 5000, Australia

<sup>d</sup> Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK

<sup>e</sup> University of Sydney, Australia

<sup>f</sup> Ministry of Health and Sport, Government of Myanmar, Myanmar

<sup>g</sup> Myanmar Snakebite Project Mandalay Office, Myanmar

<sup>h</sup> Department of Renal Medicine, Royal Adelaide Hospital, Adelaide, SA, 5000, Australia

### ARTICLE INFO

#### Keywords:

Snakebite  
Antivenom  
Russell's viper  
AKI  
Coagulopathy  
Prospective observational study  
Myanmar

### ABSTRACT

The Myanmar Snakebite Project is an Australian government (Department of Foreign Affairs and Trade) supported foreign aid project in collaboration with the Myanmar government with the aim of improving outcomes for snakebite patients in Myanmar. As part of the project a case record database was established to document prospective cases of snakebite presenting to Mandalay General Hospital, in Upper Myanmar. The study period was 12 months (1-2-2016 to 31-1-2017). Snake identity was based on a mixture of identified dead snakes brought with patients, doctor's clinical opinion and patient identification. 965 patients were enrolled during the 12 month period, of whom 948 were included for analysis. The male: female ratio was 1.58:1. Most cases involved bites to the lower limbs (82.5%) and adults involved in farm work, confirming snakebite as an occupational disease in this community. Motorised transport was by far the most common form of transport to health care and most patients sought care from the health system (87.7%), not traditional healers (11.5%) as their first point of contact. The officially promoted application of a pressure pad, bandage and immobilisation as first aid for snakebite was almost never used, while most patients used some form of tourniquet (92.0%). 85.4% of cases where a snake ID was listed were bitten by Russell's vipers. Russell's viper bites were responsible for all fatalities (9.8% of cases) and all cases of Acute Kidney Injury (AKI). For all cases, clinical features included local swelling (76.5%), local pain (62.6%), AKI (59.8%), incoagulable blood (57.9%), regional lymphadenopathy (39.8%), nausea/vomiting (40.4%), thrombocytopenia (53.6%), abdominal pain (28.8%), shock (11.8%), secondary infection (8.6%), panhypopituitarism (2.1%). AKI required renal replacement therapy (RRT) in 23.9% of cases, all ascribed to Russell's viper bite. Green pit viper bites were the next most common cause of bites (7.6%) and were associated with incoagulable blood (29%) and occasionally shock (5%) and local necrosis (3%), and in one case AKI not requiring RRT. In contrast to Russell's viper bites, green pit viper bite was most likely to occur in the home (49%). Some green pit viper patients were treated with Russell's viper antivenom (15%), presumably because they had incoagulable blood, although this antivenom is not effective against green pit viper envenoming. For the entire patient group, antivenom was given in 80.5% of cases. The most common indications were presence of coagulopathy/non-clotting blood (59.8%), local swelling (47.4%), oliguria/anuria (19.8%), heavy proteinuria (19.4%). A febrile reaction to antivenom was reported in 47.9% of cases, while anaphylaxis, occurred in 7.9% of cases.

\* Corresponding author. Toxinology Dept., Women's & Children's Hospital, North Adelaide, SA, 5006, Australia.

E-mail address: [julian.white@adelaide.edu.au](mailto:julian.white@adelaide.edu.au) (J. White).

<https://doi.org/10.1016/j.toxcx.2018.100002>

Received 14 March 2018; Received in revised form 21 November 2018; Accepted 26 November 2018

Available online 7 December 2018

2590-1710/Crown Copyright © 2018 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Snakebite is arguably the most neglected of all Neglected Tropical Diseases, affecting at least 2.5 million people annually, and probably causing more than 100,000 fatal cases every year (White et al., 2018; WHO, 2007, 2017). The Asian region has long been known as the most important region for snakebite globally, with India alone suffering at least 45,000 snakebite-related deaths each year (Mohapatra et al., 2011). Past reports have indicated that Myanmar (Burma) also had a serious snakebite problem (Swaroop and Grab, 1954). The Myanmar Snakebite Project (MSP) is a collaborative joint venture between the governments and people of Australia and Myanmar to improve outcomes for snakebite patients (White et al., 2018). As part of that project the MSP team is collecting prospective case data. This paper reports the first 12 months of data from the major teaching hospital in Mandalay, Myanmar.

The object of this study was to provide clinical audit data from the major hospital serving a key region known to have a high snakebite burden, to allow health authorities in Myanmar to better understand the profile of snakebite, which may contribute to development of new or revised health system responses to snakebite, thereby improving outcomes for snakebite patients.

## 2. Methods

Following ethics approval from the Myanmar Ministry of Health and University of Adelaide, a data collection program, based on a custom built relational database (FileMakerPro) was developed by the MSP clinical team, in collaboration with other senior medical colleagues at Mandalay General Hospital (MGH). Data collection forms generated by the database were used to collect data manually on each patient presenting with suspected snakebite, primarily as an audit system better to understand the impact of snakebite on the health system. Senior MSP clinical team members engaged and trained local Myanmar doctors who were the sole case data collectors and subsequently entered data into the database. These local doctors were employed by the MSP, not by the hospital, and were not responsible for treatment of patients in the study. During the reported study period, a total of 6 local doctors were employed, though not all simultaneously, with rostering to ensure availability to see patients and collect data. These doctors liaised with colleagues in the MGH emergency department, medical acute wards and the renal unit, to ensure all patients presenting with snakebite were accessed for the study. Patients enrolled were asked to give informed consent to participate. Virtually all patients, or their families if the patient was unable to give consent, agreed to participate in the study. Patients who refused to participate in the study did not have a case data record created and therefore we have no data on these patients, or how many patients refused consent. The study period reported on in this paper was February 1st, 2016 to January 31st, 2017, but case data collection is ongoing within the Project and has extended to other hospitals, with a view to becoming a long term management tool for the Myanmar health system.

Information categories for data collection are listed in Table 1. Wherever possible, for each question or data field a value list system (list of approved answers) was used to ensure consistency and the ability readily to analyse results.

Inclusion criteria were a history consistent with the patient's having been bitten by a snake, including sufficient information to confirm this diagnosis. Exclusion criteria was inability to collect sufficient data to allow analysis. Prevailing attitudes within the health system prevented collection and identification of dead snakes brought in by the patient within the current study period. This is being addressed and dead snakes are now being retained and identified in at least some hospitals. Since this study was primarily developed as an audit, we did not collect blood samples for later in-vitro identification of the snakes responsible.

Coagulopathy was defined as a positive 20 min whole blood clotting test (20WBCT) which is the national standard for assessing snakebite

coagulopathy in Myanmar. Formal laboratory clotting tests were, in most cases, unavailable, but where such tests were performed, most commonly just an INR, this was used as confirmation of coagulopathy when outside the established normal range.

Thrombocytopenia was defined as a platelet count below the established normal range for the laboratory conducting the test.

Acute kidney injury (AKI) was defined as either a requirement for renal replacement therapy (RRT), or, in the absence of this requirement, a peak serum creatinine measured > 120 µmol/L for males and >100 µmol/L for females, coupled with a substantial rise and subsequent fall consistent with an acute event.

**Table 1**

Main information categories covered in the database and acquisition forms used by specifically trained medical officers to acquire data from the patient and hospital records.

Main category	Subcategory	Questions
Details about the snakebite	Basic	Date & time of bite
		Geographic location (township)
	Circumstances of bite	Age range
		Activity when bitten
		Was snake seen
		Was snake kept
		Snake ID & method
		Part of body bitten
		How many times bitten
		Point of first contact for care
Timing	First aid & who applied	
	Date & time of arrival at first health care facility	
	Date & time of arrival at last health care facility	
	Was patient transferred to a renal unit or ICU	
Relevant past medical history	Past medical history	
	Allergies	
	Medications	
Medical assessment on arrival at last health care facility	General symptoms	
	Local bite effects	
	Extent of local swelling	
	Evidence of capillary leak	
	Evidence of neurotoxic paralysis	
	Evidence of coagulopathy	
	Details of coagulation testing including type of test(s), when first abnormal and when first resolved	
	Medical management of case	Antivenom use
Was first dose optimal (defined)		
Total amount of antivenom given, by antivenom type		
Acute kidney injury Respiratory problems		Adverse reactions to antivenom
		Was dialysis given and type used
		Was intubation or ventilation used and when commenced and ceased
	Outcome of intubation and ventilation	
	Was non-invasive ventilation used and indications and outcome	
Summary information	Summary of treatments used	Value list of available treatments
		Complications ascribed to bite
	Final outcome	Type of outcome
		Date and time
Serial clinical and laboratory data	Events or tests recorded	Date and time for each record
		20WBCT, INR, aPTT, FDP/D-dimer, creatinine, platelet count, haemoglobin, antivenom use, other comments/events/interventions

Capillary leak syndrome was defined as present based on established clinical criteria, including the presence of conjunctival oedema or haemorrhage, periorbital oedema, generalized oedema, or pulmonary oedema.

Shock was defined on standard clinical criteria, including cardiovascular manifestations such as marked hypotension. For bite site infection it was not possible to confirm infection using microbiologic testing as this resource was not available for this purpose in snakebite patients.

Resource limitations prevented assessment for rhabdomyolysis, such as routine measurement of creatine kinase levels, or assaying for myoglobinuria.

Where percentages were calculated in addition to absolute numbers the percentage was determined based on the subset of cases in the particular category where data were available, which may be less than the total number listed in that category.

### 3. Results

In the 12 month period 1-2-2016 to 31-1-2017 there were 965 patient presentations to MGH recorded with a diagnosis of snakebite and captured within the database. After 17 cases were excluded because of one or more major inconsistencies in data, 948 cases were available for analysis. There were 580 male patients and 368 female patients (ratio 1.58:1 M:F). The MGH is an adult hospital, so the large majority of patients were within the adult age range, the largest group being the 30–50 year old group (see Fig. 1). For cases where the snake type was listed (803), Russell's viper (*Daboia siamensis*) was, by far, the most common snake type recorded (686 cases; 85.4%), with only 17 cobra bite cases (*Naja* spp.), 4 krait bite cases (*Bungarus* spp.), 61 green pit viper bite cases (*Trimeresurus* spp.), with 4 cases of bites by “other venomous” snakes and 31 cases of bites by “non-venomous” snakes. The snake identity was not stated in 145 cases (15.3%). However, for all cases, the snake was identified by a doctor in only 37.8% (358 cases), while it was based on the doctor's clinical opinion in a further 18.0% (171 cases). In 74.8% (709 cases). The initial snake identification was also based on the patient's description/opinion.

In this population, snakebite was predominantly an occupational disease affecting farm workers. 53.3% (505 cases) were recorded as being bitten while engaged in “farm duties” and a further 19.5% (185 cases) while walking outside, which included farm-related activities. In only 12.0% (114 cases) the bite occurred inside the home and in 0.8% (8 cases), while asleep. In contrast to studies of snakebite in western nations, in this study there were only 2 cases reported where the bite occurred while interfering with the snake. Consistent with this, the body part bitten was the lower limb in 82.5% (782 cases) and the upper limb, including the hand in only 16.6% (157 cases).

Where the point of first contact for patients was recorded (886; 93.5%), in 734 cases (82.8%) it was listed as “hospital” and in 43 cases

(4.9%), “rural health center”, while in only 102 cases (11.5%) was it listed as “traditional healer”. Similarly, the person who applied first aid, among 720 cases where this information was recorded, were traditional healers in only 88 reported cases (12.2%), patients themselves in 171 cases (23.8%), and family or friends in 435 cases (60.4%). Health staff applied first aid in only 19 cases (2.6%). A pressure pad plus bandage and immobilisation was rarely used (6 cases; 0.7%) as first aid, despite this method being the officially approved snakebite first aid within Myanmar, with research support (Pe et al., 2000; Tun-Pe et al., 1995), and shown in public education posters and leaflets and taught in public education sessions. In contrast, in cases where some form of first aid was used, tourniquets were most commonly used (674 cases; 92.0%) and other contraindicated methods were uncommon (tattooing, 63 cases, 8.6% - Fig. 2; cuts at the bite site, 45 cases, 6.1%).

As might be expected, many different symptoms were recorded. Local effects at the bite site were common. In 76.5% (721 cases) local swelling was recorded; 74.8% (705 cases) had visible bite marks, 62.6% (590 cases) reported pain, and 39.8% (375 cases) had regional lymphadenopathy. Local bleeding 7.2% (68 cases) and blistering 6.9% (65 cases) were far less common, but only 5.6% (53 cases) reported no local effects from the bite. Among systemic symptoms, the most common were nausea/vomiting 40.4% (378 cases), abdominal pain 28.8% (269 cases), renal angle pain 19.9% (186 cases) and headache 15.7% (147 cases).

Overall complications recorded are listed in Fig. 3. Acute Kidney Injury (AKI) was the most common complication (557 cases; 59.8%), followed by coagulopathy (540 cases; 57.9%); and thrombocytopenia (500 cases; 53.6%). Panhypopituitarism, a previously reported complication of Russell's viper bite (Tun-Pe et al., 1987) secondary to anterior pituitary haemorrhage or infarction, was recorded in 20 cases (2.1%). Other medically important complications that affect treatment included shock (114 cases; 12.2%); based on clinical opinion of the treating doctor as recorded in case notes and/or observed by the doctor recording case data), local bite site necrosis (51 cases; 5.5%) and bite site secondary infection (82 cases; 8.8%; based on clinical impression/features, not by microbiological testing which was not generally available).

Minor evidence of neurotoxicity (ptosis, 7 cases; ophthalmoplegia, 3 cases; dysphagia, 1 case; dysarthria, 3 cases) occurred in a small group of patients, but only 3 cases developed limb weakness and no cases required intubation and ventilation for neurotoxic respiratory paralysis/compromise. Of the 7 cases showing some evidence of neurotoxicity, the snake was identified as Russell's viper by the patient in 2 case and in one of these was supported by the doctor's identification of the dead snake. In both of these 2 cases the patients developed coagulopathy and AKI,



Fig. 2. Tattooing of bitten limb adjacent to bite site as a form of traditional first aid; this method is not recommended and may result in secondary medical problems. [Original photo copyright © Julian White, used with permission].

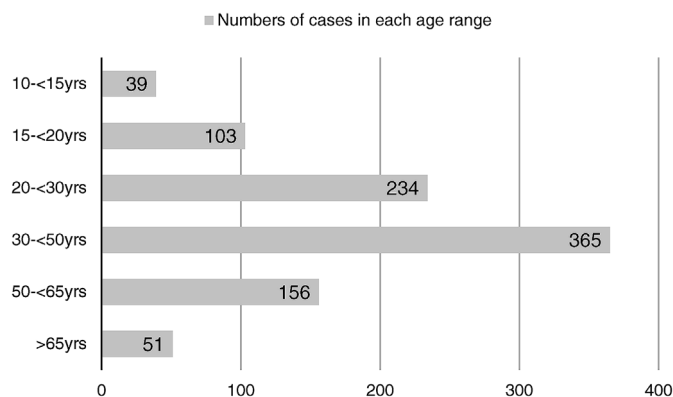


Fig. 1. Age range of enrolled patients.

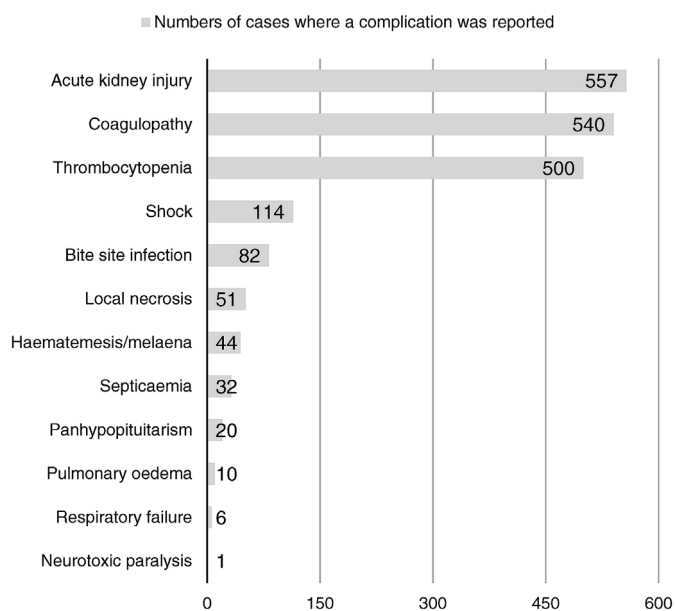


Fig. 3. List of complications recorded across entire patient group. Cases with inadequate or uncertain information have been excluded.

consistent with Russell's viper envenoming and inconsistent with a cobra or krait bite. The snake was unidentified in the remaining 5 cases. Respiratory failure (not paralysis) was recorded in a further 6 cases, 5 fatal, all due to bites by Russell's viper. Pulmonary oedema occurred in 10 cases, 8 fatal, following bites by Russell's viper; in none of these cases was neurotoxicity recorded.

Where coagulopathy was recorded (540 cases), this was mostly based on results of an abnormal clotting test, the 20WBCT. Frank haematuria occurred in 122 cases, gastrointestinal bleeding in 98 cases, mucosal bleeding in 32 cases, bite site bleeding in 40 cases and cannula site bleeding in 5 cases.

RRT for AKI was required in 227 cases (23.9% of all cases; 40.8% of cases with AKI). No patients required intubation.

For bites by Russell's viper, coagulopathy occurred in 68.9% (467), thrombocytopenia in 68.2%, AKI in 72.2%, of whom 213 required dialysis (31.3% of all bites by this species; 43.6% of those with AKI), and there were 84 fatalities (12.2%). There was a strong association between bites by Russell's viper and farm related activities ("farm duties", 65.9%; "walking outside", 18.4%; total 84.3%), compared to inside the home (6.0%). This was also reflected in the body region bitten; 86.5% in the lower limb.

There were 17 bites by cobras with one case of local necrosis and no deaths. Neurotoxic paralysis was recorded in only 2 of these cases, neither requiring intubation or ventilation. In one case the snake was caught and subsequently identified by the treating doctor, while in the other case it was based on the doctor's clinical opinion and the patient's opinion. In this latter case the initial 20 min Whole Blood Clotting Test (20WBCT) was recorded as positive (non-clotting), but a repeat test 1 h later and all subsequent tests were normal (clotting). It is likely this initial test was in error. There were 4 bites by kraits (patient identification only), with no documented evidence of neurotoxicity and no deaths. We cannot be certain if these cases were actually krait bites and no conclusions can be drawn from this in regard to clinical presentation of krait bites in this part of Myanmar. However, this data does indicate that krait bites are a rare cause of snakebite presenting to the health system in this area.

Green pit viper bites (*Trimeresurus* spp.) were the most common species of snake involved (61 cases; 7.6%), after Russell's viper. The snake identity was based on the treating doctor's ID of the dead snake in nearly half of cases (29 cases; 48%) as well as the patient's opinion (59

cases; 97%); these snakes are distinctive, quite different from Russell's viper in colour. In contrast to overall data, most bites occurred in the home (23 cases; 49%), followed by walking outside (16 cases; 34%), in only 3 cases associated with "farm duties". There is no antivenom in Myanmar to treat envenoming by these snakes (several different species may be involved). None of the cases in our study was fatal, at least during hospital stay, but 3 patients were discharged "on request" which can be an indication that death is expected and the family wished this to occur at home. It has not been possible to determine the final outcome in these 3 cases. In 17 cases (29%) a coagulopathy was present and there were 3 cases with shock (5%), 2 with gastro-intestinal-tract (GIT) bleeding, 2 with local necrosis (3%) and 1 reported with AKI. For this last patient, the local effects were limited to pain and local swelling, but there was a persistent coagulopathy, despite antivenom, and there was shock, but no oliguria/anuria and only a small rise in serum creatinine (peak 150 μmol/L), so RRT was not required. Local swelling was present in the majority of patients (38 cases; 66%), mostly restricted to the bite site (20 cases; 34%), but in 4 cases it involved more than 2/3 of the bitten limb. Local necrosis occurred in 2 cases, both with coagulopathy. Russell's viper antivenom was given in 9 cases (15%), despite being inappropriate.

A wide variety of treatments were used (Fig. 4). Antibiotics were given in almost every case (936 cases; 98.8%), even though local bite site infection was far less commonly reported.

Antivenom was used in most cases (762; 80.5%). Antivenoms available in Myanmar at this time were "Viper" antivenom (specific against Myanmar Russell's viper) and "Cobra" antivenom (specific against monocled cobra), both made by Burma Pharmaceutical Industries (a government owned producer), and Indian-sourced polyvalent antivenoms. The latter were used in only a minority of cases, because insufficient BPI antivenom was locally available. The snakebite management guidelines list a number of criteria as indications for antivenom (Table 2) and this diversity was reflected in the indications recorded, with non-clotting blood (392 cases; 59.8%), local swelling (311 cases; 47.4%), oliguria/anuria (130 cases; 19.8%), heavy proteinuria (127

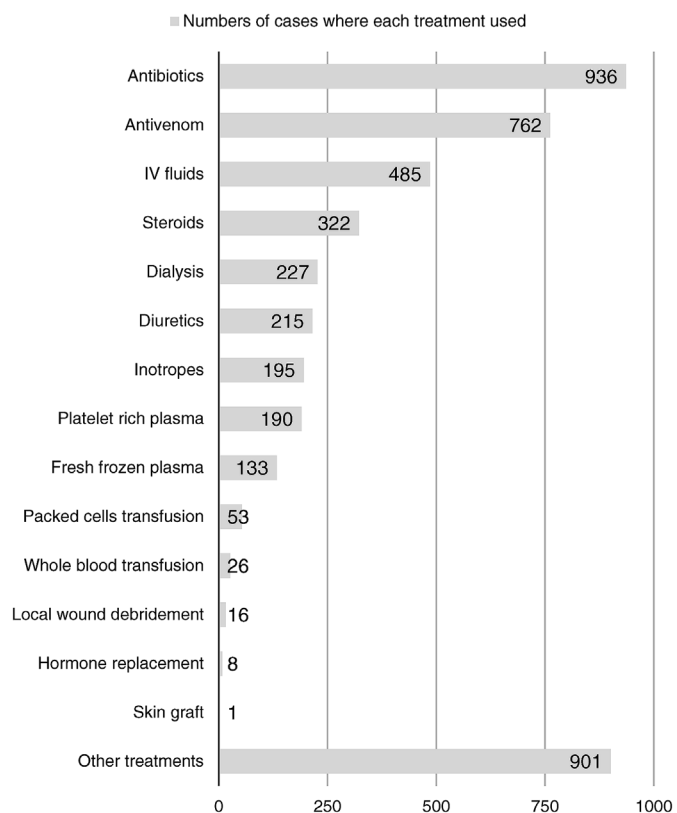


Fig. 4. Treatments used in treating snakebite during this study period.

**Table 2**

Indications for administering antivenom in Myanmar, based on nationally developed guidelines.

Indication
Severe local swelling
Rapid extension of swelling
Tender regional lymphadenopathy
Non clotting blood
Spontaneous bleeding
Renal angle tenderness
Heavy proteinuria
Oliguria/anuria
Neurotoxicity

cases; 19.4%) and tender lymphadenopathy (86 cases; 13.1%) being the most common (multiple indicators could be present in a single patient). Where sufficient information was recorded, febrile and related non-anaphylactic adverse reactions to antivenom occurred in 47.9% of patients receiving antivenom (365 cases) and severe early adverse reactions, including anaphylaxis occurred in 7.9% of patients (60 cases).

Recording accurate outcome for snakebite patients proved difficult because of traditional community views about place of death and autopsy, the latter being an official requirement for deaths in hospital. After adjusting for the local idiosyncrasies, 796 patients left hospital alive with the expectation they would survive (84.0%), 54 absconded, outcome unknown, 6 were discharged at their request (most likely to die at home) and 92 either died in hospital or were listed in such a way that their death was certain (9.7%).

#### 4. Discussion

This paper documents a large prospective observational study of snakebite from a single large hospital in central Myanmar. This hospital (MGH) is one of few in the country to have a full renal medicine department and RRT facilities, therefore attracts an arguably skewed cohort of patients with more severe envenoming, particularly patients bitten by Russell's viper. MGH is located in a region with one of the highest incidences of snakebite in Myanmar, and the presence of its renal unit attracts additional snakebite patients from 2 other high incidence regions nearby that lack RRT capability. This potential bias is reflected in the overwhelming dominance of Russell's viper bite cases in this study.

The initial findings from this ongoing study, reported here, indicate the importance of Russell's viper bite as a cause of both snakebite and AKI in Myanmar. The clinical findings of effects of envenoming caused by Russell's viper confirm earlier studies. There is local tissue injury at the bite site, coagulopathy and a high incidence of AKI that requires RRT in a substantial proportion of cases (Myint-Lwin et al., 1985; Thein-Tham et al., 1991; Tin-Nu-Swe et al., 1993; Warrell, 1989). Previously reported sporadic cases of panhypopituitarism are confirmed by this study (Antonypillai et al., 2011; Than-Tham et al., 1989; Tun-Pe et al., 1987). A new finding is the possible association between Myanmar Russell's viper (*Daboia siamensis*) bite and evidence of mild neurotoxicity, particularly ptosis, although recorded in only a few cases so far and not confirmed by rigorous neurological examination or photographic evidence. Although its venom contains a pre-synaptic PLA<sub>2</sub> neurotoxin (Wang et al., 1992), neurotoxicity has never reported in human victims of Eastern Russell's viper (*Daboia siamensis*) anywhere in the world. However, such neurotoxicity, associated with myotoxicity, is a familiar feature of envenoming by the Western Russell's viper (*Daboia russelii*), especially in Sri Lanka and southern India (Kularatne, 2003; Phillips et al., 1988; Warrell, 1989). If this current project can be extended to other parts of Myanmar, the geographical distribution of putative *D. siamensis* neurotoxicity may be defined. As the presence of neurotoxicity is currently used to differentiate viper and elapid envenoming, and hence the choice of antivenom, this new information may have direct clinical relevance to patient management.

This study shows an apparently low incidence of elapid snakebites in the Mandalay region, at least among patients presenting to MGH. No cases of severe neurotoxicity requiring assisted ventilation were recorded. If this finding is confirmed by wider case acquisition across the Mandalay health division, there are clear implications for both production and stocking of antivenoms. Two species of cobra have been described in Myanmar, the monocled cobra (*Naja kaouthia*) and the Mandalay spitting cobra (*Naja mandalayensis*) (Das, 2010). While the former is well characterised clinically (Warrell, 1995), there is little clinical or toxicological information available for the latter species. If the clinical effects of envenoming by Mandalay spitting cobras resemble those of some other spitting cobras (e.g. *N. siamensis* in Thailand; Warrell, 1995) local tissue injury with little or no neurotoxicity may be expected. If this were to be the case, it would explain why neurotoxic cobra bites were uncommon in the Mandalay area. No cases with venom spit ophthalmia were recorded.

Our data on green pit viper bites suggest that these snakes' medical importance may have been under-appreciated in Myanmar, as potential causes of coagulopathy, local tissue injury, shock and AKI. If further study confirms this profile, there may be a case for providing a specific antivenom to treat these cases, at least those with systemic envenoming.

In designing this study we had anticipated that traditional healers would be commonly used by rural villagers bitten by snakes, potentially delaying assessment and treatment within the health system. However, the data show that most patients preferred the health system. This may reflect a bias in our data towards patients who believed that they had been bitten by a dangerous snake, particularly Russell's viper. It is possible that for bites by other snakes, traditional healers are more frequently used and since these cases are less likely to develop serious medical problems, they are unlikely to be represented in admission data from a tertiary hospital. A recent study has provided support for the view that in this region of Myanmar, traditional healers are not a cause of significant snakebite deaths, unrecorded in the official health system (Schioldann et al., 2018).

Limitations of this study include the uncertainty over correct identification of the snake, even when the dead snake was brought and identified by the doctor. Reluctance among some health staff to keep and preserve dead snakes has limited the ability of the health system to collect more reliable data to link expertly-identified snake species with a particular clinical profile. We are actively encouraging a change in attitude and policy, to favour routine preservation of snakes brought with snakebite patients. We will also encourage taking photos of dead snakes, but a photo cannot replace the value of a dead preserved snake as a taxonomic specimen, if and when the taxonomy of these snakes changes. Coagulopathy was mostly determined by the 20WBCT, a test that is widely used but is susceptible to false positivity if vessels other than glass are used. Its sensitivity has been questioned (Franca et al., 2003; Isbister et al., 2013; Ratnayake et al., 2017; Sano-Martins et al., 1994). The ability to follow up patients after discharge is limited in Myanmar. This lack of good follow up data limits the assessment of longer term effects of both envenoming (such as panhypopituitarism) and adverse reactions to antivenom (serum sickness). Because many patients were referred to MGH from other hospitals or health centers, obtaining information on symptoms, signs and treatment prior to arrival was, to some extent, retrospective. For many variable measured and listed in this paper the total subset of patients for a given variable might be diminished by incomplete or missing data.

As a measure of the extent of the snakebite problem in the Mandalay region, this clinical database provides many indications about clinical severity and social-economic burden of this problem. However, patients who were admitted to Mandalay General Hospital were undoubtedly among the sickest. Thus, for every patient admitted to MGH, we estimate, based on discussions with medical colleagues and public health officials in Myanmar that there were probably approximately 10 more who were managed in township hospitals but did not require admission to the MGH. To obtain a more accurate picture of the overall situation, we are

setting up similar clinical databases for these township hospitals.

The methodology, specifically the case record database and data acquisition forms, developed through this project are potentially applicable to study snakebite in other hospital settings. The MSP is already enrolling patients into versions of this database from other Mandalay hospitals, from several township hospitals which drain to Mandalay and patients from a few hospitals elsewhere in Myanmar. With Ministry of Health and Sports support it should be possible to enroll patients widely across the whole country, with a view to using this database as a tool to help guide health policy and response to snakebite nationally.

### Conflict of interest

The authors declare no conflicts of interest in relation to this work.

### Ethical statement

This paper has no ethical issues. There are no financial conflicts for authors. No patient information is provided which might allow identification of a patient. No clinical trial studies are herein reported. No animal research studies are involved. Ethics approval for all Myanmar Snakebite Project work has been granted by both the University of Adelaide and the Department of Medical Research, Myanmar.

### 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.

### Acknowledgements

The authors thank other Project team members and contributors for their valued input that has ensured the success delivered so far. The authors particularly thank their many colleagues in Myanmar in the Ministry of Health and Sports and Ministry of Industry and local staff members employed as a result of the Project; without their hard work and commitment the Project could not have delivered the success achieved to date. The authors, on behalf of all Project team members, Myanmar colleagues and staff and especially the people of Myanmar suffering under the burden of snakebite, thank those organisations, institutions and governments who have, through funding or in-kind support, made this Project possible; the Government of Australia, Department of Foreign Affairs and Trade (the major funder), the Government of Myanmar, Seqirus Ltd and its parent company, CSL Ltd (Australia), the University of Adelaide (Australia), the University of Sydney (Australia), CSIRO Australian Animal Health Laboratories, Venom Supplies (Australia), the Women's & Children's Hospital (Australia), the Royal Adelaide Hospital (Australia), the Nuffield Department of Clinical Medicine, University of Oxford (UK), the Senkenberg Museum, Frankfurt (Germany).

### Transparency document

Transparency document related to this article can be found online at <https://doi.org/10.1016/j.toxcx.2018.100002>.

### References

Antonypillai, C.N., Wass, J.A., Warrell, D.A., Rajaratnam, H.N., 2011. Hypopituitarism following envenoming by Russell's vipers (*Daboia siamensis* and *D. russelii*) resembling Sheehan's syndrome: first case report from Sri Lanka, a review of the literature and recommendations for endocrine management. *QJM* 104 (2), 97–108.

- Das, I., 2010. A Field Guide to the Reptiles of South East Asia. Bloomsbury Natural History, London.
- França, F.O., Barbaro, K.C., Fan, H.W., Cardoso, J.L., Sano-Martins, I.S., Tomy, S.C., Lopes, M.H., Warrell, D.A., Theakston, R.D., Butantan Institute Antivenom Study Group, 2003. Envenoming by *Bothrops jararaca* in Brazil: association between venom antigenaemia and severity at admission to hospital. *Trans. R. Soc. Trop. Med. Hyg.* 97 (3), 312–317.
- Isbister, G.K., Maduwage, K., Shahmy, S., Mohamed, F., Abeysinghe, C., Karunathilake, H., Ariaratnam, C.A., Buckley, N.A., 2013. Diagnostic 20-min whole blood clotting test in Russell's viper envenoming delays antivenom administration. *QJM* 106 (10), 925–932.
- Kularatne, S.A., 2003. Epidemiology and clinical picture of the Russell's viper (*Daboia russelii russelii*) bite in Anuradhapura, Sri Lanka: a prospective study of 336 patients. *Southeast Asian J. Trop. Med. Publ. Health* 34 (4), 855–862.
- Mohapatra, B., Warrell, D.A., Suraweera, W., Bhatia, P., Dhingra, N., Jotkar, R.M., Rodriguez, P.S., Mishra, K., Whitaker, R., Jha, P., 2011. Snakebite mortality in India: a nationally representative mortality survey. *PLoS Neglected Trop. Dis.* 5 (4) e1018.
- Myint-Lwin, Warrell, D.A., Phillips, R.E., Tin-Nu-Swe, Tun-Pe, Maung-Maung-Lay, 1985. Bites by Russell's viper (*Vipera russelli siamensis*) in Burma: haemostatic, vascular, and renal disturbances and response to treatment. *Lancet* 2 (8467), 1259–1264.
- Pe, T., Mya, S., Myint, A.A., Aung, N.N., Kyu, K.A., Oo, T., 2000. Field trial of efficacy of local compression immobilization first-aid technique in Russell's viper (*Daboia russelii siamensis*) bite patients. *Southeast Asian J. Trop. Med. Publ. Health* 31 (2), 346–348.
- Phillips, R.E., Theakston, R.D., Warrell, D.A., Galigedara, Y., Abeyskera, D.T., Dissanayaka, P., Hutton, R.A., Aloysius, D.J., 1988. Paralysis, rhabdomyolysis and haemolysis caused by bites of Russell's viper (*Vipera russelli pulchella*) in Sri Lanka: failure of Indian (Haffkine) antivenom. *Q. J. Med.* 68 (257), 691–715.
- Ratnayake, I., Shihana, F., Dissanayake, D.M., Buckley, N.A., Maduwage, K., Isbister, G.K., 2017. Performance of the 20-minute whole blood clotting test in detecting venom induced consumption coagulopathy from Russell's viper (*Daboia russelii*) bites. *Thromb. Haemostasis* 117 (3), 500–507.
- Sano-Martins, I.S., Fan, H.W., Castro, S.C., Tomy, S.C., Franca, F.O., Jorge, M.T., Kamiguti, A.S., Warrell, D.A., Theakston, R.D., 1994. Reliability of the simple 20 minute whole blood clotting test (WBCT20) as an indicator of low plasma fibrinogen concentration in patients envenomed by Bothrops snakes. Butantan Institute Antivenom Study Group. *Toxicon* 32 (9), 1045–1050.
- Schioldann, E., Mahmood, M.A., Kyaw, M.M., Halliday, D., Thwin, K.T., Chit, N.N., Cumming, R., Bacon, D., Alfred, S., White, J., Warrell, D.A., Peh, C.A., 2018. Why snakebite patients in Myanmar seek traditional healers despite availability of biomedical care at hospitals? Community perspectives on reasons. *PLoS Neglected Trop. Dis.* 12 (2), e0006299.
- Swaroop, S., Grab, B., 1954. Snakebite mortality in the world. *Bull. World Health Organ.* 10 (1), 35–76.
- Than-Than, Francis, N., Tin-Nu-Swe, Myint-Lwin, Tun-Pe, Soe-Soe, Maung-Maung-Oo, Phillips, R.E., Warrell, D.A., 1989. Contribution of focal haemorrhage and microvascular fibrin deposition to fatal envenoming by Russell's viper (*Vipera russelli siamensis*) in Burma. *Acta Trop.* 46 (1), 23–38.
- Thein-Than, Tin-Tun, Hla-Pe, Phillips, R.E., Myint-Lwin, Tin-Nu-Swe, Warrell, D.A., 1991. Development of renal function abnormalities following bites by Russell's vipers (*Daboia russelii siamensis*) in Myanmar. *Trans. R. Soc. Trop. Med. Hyg.* 85 (3), 404–409.
- Tin-Nu-Swe, Tin-Tun, Myint-Lwin, Thein-Than, Tun-Pe, Robertson, J.I., Leckie, B.J., Phillips, R.E., Warrell, D.A., 1993. Renal ischaemia, transient glomerular leak and acute renal tubular damage in patients envenomed by Russell's vipers (*Daboia russelii siamensis*) in Myanmar. *Trans. R. Soc. Trop. Med. Hyg.* 87 (6), 678–681.
- Tun-Pe, Phillips, R.E., Warrell, D.A., Moore, R.A., Tin-Nu-Swe, Myint-Lwin, Burke, C.W., 1987. Acute and chronic pituitary failure resembling Sheehan's syndrome following bites by Russell's viper in Burma. *Lancet* 2 (8562), 763–767.
- Tun-Pe, Aye-Aye-Myint, Khin-Ei-Han, Thi-Ha, Tin-Nu-Swe, 1995. Local compression pads as a first-aid measure for victims of bites by Russell's viper (*Daboia russelii siamensis*) in Myanmar. *Trans. R. Soc. Trop. Med. Hyg.* 89 (3), 293–295.
- Wang, Y.M., Lu, P.J., Ho, C.L., Tsai, I.H., 1992. Characterization and molecular cloning of neurotoxic phospholipase A2 from Taiwan viper (*Vipera russelli formosensis*). *Eur. J. Biochem.* 209, 635–641.
- Warrell, D.A., 1989. Snake venoms in science and clinical medicine. 1. Russell's viper: biology, venom and treatment of bites. *Trans. R. Soc. Trop. Med. Hyg.* 83 (6), 732–740.
- Warrell, D.A., 1995. Clinical toxicology of snakebite in Asia. In: Meier, J., White, J. (Eds.), *Handbook of Clinical Toxicology of Animal Venoms and Poisons*. CRC Press, Boca Raton, pp. 493–594.
- White, J., Alfred, S., Mahmood, A., Warrell, D.A., Cumming, R., Bates, D., Thida Thwin, Khin, Aung, Zaw, Moody, J., Eagles, D., Ragas, K., Dunstan, N., Peh, C.A., 2018. An approach to managing a neglected, neglected tropical disease; the Myanmar snakebite project. *Toxicon XXX*. *Toxicon* (in press).
- World Health Organisation, 2007. Rabies and Envenomings: a Neglected Public Health Issue. World Health Organisation, Geneva.
- WHO, 2017. Snakebite Envenoming: what Is Snakebite Envenoming. <http://www.who.int/snakebites/disease/en/>.