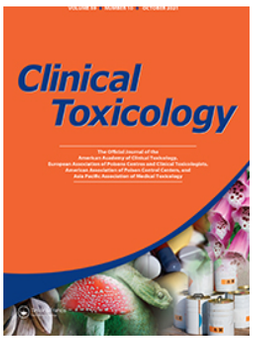

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REVIEW

The clinical course and treatment of black mamba (*Dendroaspis polylepis*) envenomations: a narrative review

Mark Aalten[a]*, Carsten F. J. Bakhuis[a]*, Ilias Asaggau[a]*, Maaike Wulfse[a], Maurits F. van Binsbergen[a], Eran R. A. N. Arntz[a], Max F. Troenokarso[a], Jashvin L. R. Oediet Doebe[a], Ubah Mahamuud[a], Leila Belbachir[a], Myrthe Meurs[a], Nastya A. Kovalenko[a] and Marcel A. G. van der Heyden[b]

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ABSTRACT

Context: The black mamba (*Dendroaspis polylepis)* is, due to its extremely toxic venom, one of the most dangerous snake species in Sub-Saharan Africa. A *D. polylepis* bite is a medical emergency and requires adequate action to prevent severe complications. However, there are no comprehensive reviews available based on clinical cases, and no readily accessible guidelines for standardized treatment. Therefore, we aim to provide an overview regarding the currently available clinical literature on *D. polylepis* envenomations; in order to promote knowledge on symptomatology and treatment options.

Methods: We searched for cases reporting humans bitten by *D. polylepis* in PubMed, Embase, Scopus, and Sabinet. We searched the reference lists of all eligible articles for additional articles. After quality assessment, 29 cases were included in this review. We used descriptive analysis to create an overview of the collected parameters.

Discussion: Among the included case reports and case series, *D. polylepis* envenomations most frequently resulted in decreased respiratory function, sweating and paralysis. The onset of symptoms usually occurred within 60 minutes. Neurological symptoms occurred more often than symptoms of autonomic dysfunction. In the reported cases most patients (26/29) received antivenom and most survived (25/29). We recommend the reporting of additional structured case reports to improve future analyses on the clinical course of envenomations, in order to improve public health response to *D. polylepis* envenomations.

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Introduction

The World Health Organization (WHO) has designated snakebites to be a Neglected Tropical Disease (NTD) [1]. This makes it the only NTD that is not an infectious disease [2]. Most of this burden falls on Africa. In Africa, the Black Mamba (*Dendroaspis polylepis)* is one of the most hazardous snakes, due to its length, speed, and the toxicity of its venom [3]. Therefore, the WHO categorized *D. polylepis* as a species of "highest medical importance" [4]. Bites occur mainly in endemic areas of Sub-Saharan Africa (especially from Kenya to South Africa), but also occasionally in non-endemic areas (especially Europe and North America) due to trafficking by private collectors [3,5,6]. Thus, due to its dangerousness and its prevalence in endemic and non-endemic regions, knowledge of envenomations and the biological characteristics of *D. polylepis* is critical to reduce casualties.

D. polylepis is a member of the Elapidae snake family [5]. It is a non-endangered widespread species in Sub-Saharan Africa [5,7]. Its taxonomical name can be translated to "tree reptile with many scales", whilst its popular name "black mamba" originates from the black-blue color inside its mouth [7,8]. However, the external skin color is most frequently dark-, yellow-, or olive brown. Green-gray variants occur in juvenile black mamba's [6,9]. The length of an adult specimen varies from approximately 2 to 4 meters and it can move up to 20 km/h [3,6,8–10]. *D. polylepis* primarily lives in forested savanna or in riverine forest, predominantly in areas with rocky hills. It moves both on the ground and in trees [5].

Accurate numbers of envenomations are difficult to estimate for two main reasons. Victims might have difficulties to identify the snake species [11,12], and snakebite incidence shows seasonal variability [3]. Therefore, the true frequency remains unclear.

Polyvalent antivenoms are used in the treatment of bites from various snake species. Currently, for *D. polylepis* venom,

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Supplemental data for this article can be accessed here.

eight effective polyvalent antivenoms are available in Sub-Saharan Africa. Of these, the South African Institute for Medical Research (S.A.I.M.R.) Polyvalent Snake Antivenom manufactured in South Africa proved to be the most efficient against *D. polylepis venom* [13]. Neil at al. described in 1998 that the S.A.I.M.R. polyvalent antivenom is the most used snake antivenom in Africa since 1971 [14]. Besides polyvalent antivenom, monovalent and trivalent (neutralizing the venom of all three mamba species in Africa) antivenoms were developed and tested during the 1950's and 1960's. Since 1971, the trivalent mamba antivenom is incorporated into S.A.I.M.R Polyvalent Snake Antivenom [15].

D. polylepis envenomation should be considered a medical emergency and needs to be met with rapid medical treatment [16]. In 2019, the WHO announced that the neglection of snake envenomation is a public health issue [1]. However, there are currently no scientific reviews providing an overview of the clinical course of *D. polylepis* envenomations. Moreover, there are no readily accessible guidelines for standardized treatment. This results in a knowledge gap on the clinical effects of and treatment possibilities for an envenomation. This narrative review aims to offer a summary of the existing case reports on human *D. polylepis* envenomation and to provide a general overview on the current state of the clinical course and treatment of a *D. polylepis* envenomation.

Methods

We conducted this review according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [17].

Search strategy

The aim of this search was to find all case reports describing patients bitten by *D. polylepis*. We predefined the search strategy and PICO at the start, and constructed strategies for parameter extraction and risk of bias assessments. No review protocol was released to the public. We executed the search in four databases: PubMed (Medline), Embase, Scopus and Sabinet on July 20, 2020. We used the following search in PubMed:

- #1: (black mamba*[Title/Abstract] OR mamba, black[Title/Abstract] OR dendroaspis polylepis[Title/Abstract] OR "dendroaspis"[Mesh])
- #2: (bite*, snake[Title/Abstract] OR bite[Title/Abstract] OR snakebite*[Title/Abstract] OR snake envenomation*[Title/Abstract] OR envenomation*, snake[Title/Abstract] OR "Snake Bites"[Mesh])
- #3: #1 AND #2

The searches for Embase, Scopus, and Sabinet were optimized to the specific search databases (Supplementary methods).

Assessment of study eligibility

Following duplicate removal, we screened articles for title/abstract relevance. The screening of articles was independently performed by two reviewers (MA and CFJB). When there was a conflict of judgement between the two reviewers, the full text of the article was read. We assessed the full text of the selected articles for eligibility, using the predefined in- and exclusion criteria. Inclusion criteria were: (1) human individual(s), (2) envenomed by a bite of the *D. polylepis* described in (3) case report or case series. Exclusion criteria were: (1) publication type other than case report/series, (2) envenomation by other snake species than *D. polylepis,* and (3) no full text available. No language or publication year restrictions were applied. We resolved conflicts of judgement by consensus. The reference lists of the included articles were searched for additional articles. Finally, we performed a quality assessment for selected articles. We used Rayyan software (QCRI, Doha, Qatar) for all stages of result screening [18].

Quality assessment

The quality of all individual case reports was independently assessed by three reviewers (MA, MFB and CFJB) based on the Joanna Briggs Institute Checklist for Case Reports [19]. We assessed each case report based on eight domains (Table 1). Case reports with a maximum of two mentions of "no" and/or "unknown" were included. Articles with three times "no" and/or "unknown" were discussed by the reviewers. Articles with a minimum of four times "no" and/or "unknown" were excluded. A unanimous decision amongst the three reviewers for inclusion or exclusion was required.

Recorded parameters

We recorded, when available, the following parameters from all included case reports: (1) patient characteristics (sex, age, country of case origin, continent, ethnicity, survival), (2) snake and bite description (snake length, snake captivity, location of bite on body, amount of punctures, and wound characteristics), (3) clinical symptoms, (4) type and dosing of antivenom, (5) supportive treatment (circulatory support, respiratory support, cardiopulmonary resuscitation (CPR), and other treatments), and (6) vital signs (blood pressure, heart rate, respiratory rate, temperature, consciousness, saturation, heart rhythm). Symptoms, vital signs, treatments and antivenom were reported per timestamp noted in the case report. The reported timestamps were either mentioned explicitly in the case reports/case series or were estimated by using the provided descriptions in the text. All parameters were gathered utilizing Castor EDC [38].

Symptoms were either described using the established medical term or were interpreted to fit in one of the symptoms. For example, dyspnea and ventilation/oxygen dependence were all considered as "decreased respiratory function". Slurred speech or inability to speak was interpreted as "dysarthria", whilst a throat constriction and a swollen tongue were regarded as "dysphagia". "Paresthesia" was used in this

Table 1. Risk of bias assessment following the Joanna Briggs Institute appraisal checklist for case reports.

	Score base on appropriate JBI appraisal checklist for case reports†								
Author	1	2	3	4	5	6	7	8	Overall appraisal
Quarch [24]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Erulu [20]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Zavada [10]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Blumenthal [9]	Y	N	Y	Y	Y	Y	Y	U	Inclusion
Schutzbach [21]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Hilligan 1* [22]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Hilligan 2* [22]	Y	N	Y	Y	Y	Y	NA	Y	Inclusion
Naidoo [23]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Harvey [24]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Shah [25]	U	N	Y	Y	Y	Y	Y	Y	Inclusion
Strover [26]	U	N	Y	Y	Y	Y	Y	Y	Inclusion
Krengel [27]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Saunders [28]	U	Y	Y	Y	Y	Y	Y	Y	Inclusion
Louw 1* [29]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Louw 2* [29]	Y	N	Y	U	Y	Y	Y	Y	Inclusion
Hodgson [3]	Y	Y	Y	Y	N	U	Y	Y	Inclusion
Durrant [30]	Y	Y	Y	Y	Y	U	Y	Y	Inclusion
Branch [31]	Y	Y	Y	Y	Y	Y	Y	Y	Inclusion
Haagner [32]	Y	Y	Y	Y	Y	Y	Y	Y	Inclusion
Devlin [33]	Y	Y	Y	U	Y	U	Y	Y	Inclusion
Visser 1* [34]	N	N	Y	U	Y	U	Y	Y	Exclusion
Visser 2* [34]	Y	N	Y	U	Y	Y	U	Y	Exclusion
Visser 3* [34]	Y	N	Y	U	Y	Y	Y	Y	Inclusion
Visser 4* [34]	Y	N	Y	Y	Y	Y	Y	Y	Inclusion
Visser 5* [34]	Y	N	Y	U	Y	Y	Y	Y	Inclusion
Blake [35]	N	N	Y	NA	U	U	Y	N	Exclusion
Read [36]	N	N	Y	NA	Y	Y	Y	N	Exclusion
Blaylock 1* [37]	Y	N	Y	Y	Y	Y	NA	N	Inclusion
Blaylock 2* [37]	Y	N	Y	U	Y	Y	Y	N	Inclusion
Blaylock 3* [37]	Y	N	Y	U	Y	Y	NA	N	Inclusion
Blaylock 4* [37]	Y	N	Y	Y	Y	Y	Y	N	Inclusion
Blaylock 5* [37]	Y	N	Y	Y	Y	Y	Y	N	Inclusion
Blaylock 6* [37]	Y	N	Y	U	Y	Y	NA	N	Inclusion

Y: yes; N: no; U: unknown; NA: not applicable.
†The JBI appraisal checklist scores case reports on a clear description of eight domains: (1) demographic characteristics, (2) relevant medical history, (3) current clinical condition, (4) diagnostic test/methods and results, (5) intervention(s) or treatment, (6) post-interventions clinical condition, (7) adverse or unanticipated events and (8) takeaway lessons.
*The author has more than one case report publicized in the same article. The numbers are set in the order they appear in the article.

review to describe a sensation of "pins and needles". A subjective feeling of a low body temperature by the patient (e.g., shivering) was regarded as "cold fits", whilst an objective feeling of low temperature of the extremities was considered as cold extremities. Fullness in the head is used once as a term in a case report, and once described as a feeling of a "thick head". The term "drowsy" embodies all perceptions of abnormal sleepiness or lethargy in the patient, either by the patient him/herself or the health care professional.

Descriptive analysis

The collected parameters were described in baseline tables using frequency tables. The case characteristics were described for patient bitten in the endemic area (Africa) and the non-endemic areas (e.g., Europe). For all parameters, we report median and interquartile range (IQR) since the number of included cases is insufficient to utilize mean ± SD. Concerning discrete variables, frequency and percentage of the total number of cases reporting this variable are noted. Cases with missing parameters were excluded per variable. Descriptive statistics were performed using IBM SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Results

Search results

The systematic search resulted in 172 potentially relevant articles after duplicate removal, combining the different databases up to July 20, 2020. We assessed 37 articles for eligibility after title/abstract screening, whereafter 16 were included in this review. The reference list search resulted in an additional six articles. Therefore, we included 22 articles in the quality assessment, mentioning 33 cases (Figure 1).

Quality of reporting

Of Blaylock (1982) the first six of the seven elapid bite case reports were used [37]. The seventh case was fully reported by Saunders (1980) [28]. Of Hogdson et al. (1996) only the third case report was used, the other cases were more extendedly reported in other included articles [23,28,29]. The third case was originally reported by Markwalder et al. (1987) [39], of which the full text was not accessible. Therefore, the description by Hodgson et al. (1996) was used [3]. After quality assessment, we included 29 of 33 cases (Table 1).

Case characteristics

Most of the patients were male (86%). The median reported age was 28 (IQR = 22–34; range 1–50) years. Most cases

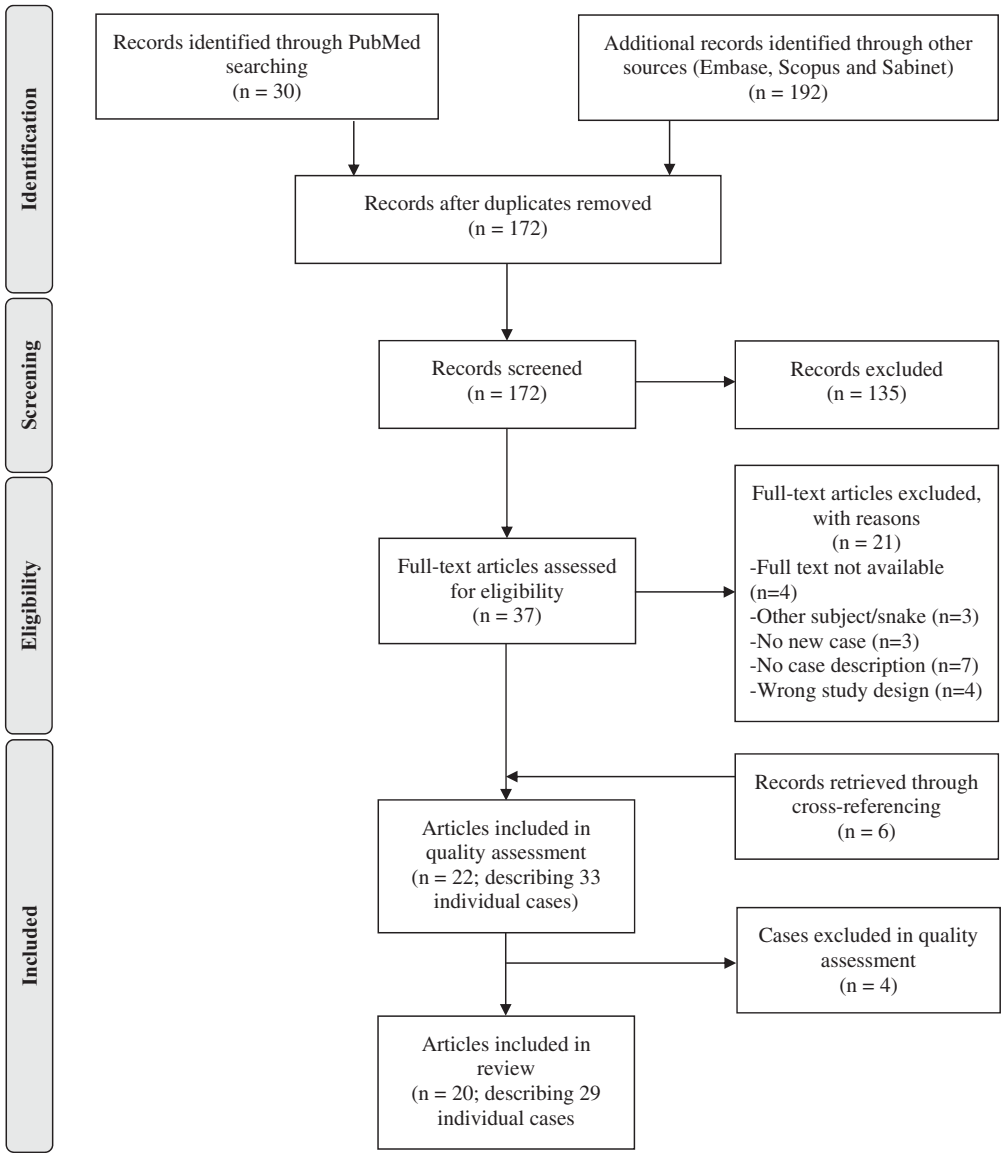

Figure 1. Flowchart of the record-selection process.

(69%) were from an African country. Twenty-five patients (86%) survived the envenomation. Antivenom was administrated to 26 patients (90%). The median time upon hospital arrival was 70 minutes (IQR = 30–135; range 6–420) in the endemic countries and 30 minutes (IQR = 25–45; range 10-60) in the non-endemic countries.

Snake length was reported in 15 cases with a median of 205 cm (range 45–400 cm), which was often an estimation. In endemic countries the snake was mostly wild (79%), whilst the snake was held captive in all the non-endemic case reports. The most often recurring bite locations were the leg (14 incidents, 48%), the hand (ten incidents, 35%), and the forearm (four incidents, 14%). Common immediate characteristics of the bite wound included swelling in 11 cases (48%) and pain in nine cases (39%) (Table 2).

Symptoms

Thirty-three different symptoms that patients presented with were reported. Out of the 33 cases, decreased respiratory function was the most common symptom (Table 3). Decreased respiratory function, sweating, paralysis and skin swelling were reported in more than 50% of the cases. The median time of presentation was 35, 60, 60, and 120 minutes respectively for sweating, decreased respiratory function, skin swelling, and paralysis.

Of the top ten most frequent symptoms, six are neurologic symptoms (paralysis, dysarthria, dysphagia, paresthesia's, ptosis, and hypersalivation). These neurologic symptoms often had their onset within 120 minutes. Paresthesia's, dizziness, pain and hemorrhage had their onset mostly within 30 minutes after the bite. Rhabdomyolysis was reported once with a creatinine kinase of 16.049 U/L [40].

Antivenom

Twenty-six (90%) patients received antivenom therapy following a *D. polylepis* envenomation. Of antivenom recipients, in 19 (73%) cases S.A.I.M.R. polyvalent (mamba) antivenom was administered with a median of two vials per case and a

Table 2. General case characteristics for the 29 case reports on human *D. polylepis* envenomation.

Case characteristic	Total ($N = 29$) Count (%)	Endemic bite ($N = 23$) Count (%)	Non-endemic bite ($N = 6$) Count (%)
Sex	24 Male (83) 5 Female (17)	18 Male (78) 5 Female (22)	6 Male (100)
Median age in years (IQR); range	28 (22–34); 1–50 2 Undescribed	28 (16–36); 1–50 2 Undescribed	31 (24–34); 22–35
Country of case origin* ($N = 26$)	9 South Africa (35) 8 Zimbabwe (31) 2 Swaziland (8) 2 Switzerland (8) 1 Czech Republic (4) 1 Germany (4) 1 Kenya (4) 1 Pakistan (4) 1 United States (4) 3 Undescribed	9 South Africa (39) 8 Zimbabwe (35) 2 Swaziland (9) 1 Kenya (4) 3 Undescribed**	2 Switzerland (33) 1 Czech Republic (17) 1 Germany (17) 1 Pakistan (17) 1 United States (17)
Survival	25 Yes (86) 4 No (14)	19 Yes (83) 4 No (17)	6 Yes (100)
Antivenom received	26 Yes (90) 3 No (10)	21 Yes (91) 2 No (9)	5 Yes (83) 1 No (17)
Median time upon hospital arrival in minutes (IQR); range	60 (30–98); 6–420	70 (30–135); 6–420	30 (25–45); 10–60
Median snake length in centimeters (IQR); range	205 (120–275); 45–400 14 Undescribed	198.5 (117.5–237.5); 45–306 9 Undescribed	400 5 Undescribed
Wild/captive snake* ($N = 24$)	15 Wild (63) 9 Captive (38) 5 Undescribed	15 Wild (79) 4 Captive (21) 4 Undescribed	0 Wild (0) 5 Captive (100) 1 Undescribed
Location bite on body	10 Hand (34) 9 Lower leg (31) 4 Forearm (14) 4 Leg undefined (14) 1 Back (3) 1 Upper leg (3)	7 Hand (30) 7 Lower leg (30) 3 Forearm (13) 2 Leg undefined (9) 1 Back (4) 1 Upper leg (4)	3 Hand (50) 1 Lower leg (33) 2 Forearm (33)
Acute wound characteristics* ($N = 23$)	11 Swelling (48) 9 Dolor (39) 6 Rubor (26) 4 Hemorrhage (17) 1 Calor (4) 6 None (26) 6 Undescribed	7 Swelling (39) 8 Dolor (44) 5 Rubor (28) 4 Hemorrhage (22) 0 Calor (0) 5 None (28) 5 Undescribed	4 Swelling (80) 1 Dolor (20) 1 Rubor (20) 0 Hemorrhage (0) 1 Calor (20) 1 None (20) 1 Undescribed

*Percentage taken from total cases reporting the case characteristic, excluding cases without description.
**Specific country not mentioned, but they were all on the African continent.

median total dose of 70mL. Sixteen (84%) patients who received this antivenom survived the envenomation. Unspecified polyvalent antivenom was applied to three (12%) patients with a range of 1–7 vials per case and a total dose range of 10–79 mL. Of these, two (67%) patients survived the envenomation. Four (15%) patients were treated with the trivalent mamba antivenom with a range of 2–4 vials per case and a total dose range of 40–150 mL. All patients who received the trivalent mamba antivenom survived the envenomation. Two (8%) patients who received the polyvalent antivenom as first dose, later received additional doses of the trivalent mamba antivenom [26,33]. Another two (8%) cases reported the application of unspecified antivenom, both receiving four vials, one with a total dose of 40mL and one 150mL. Both patients survived. (Table 4). All antivenoms were applied intravenously or intramuscularly. All instances of intramuscular administered antivenom were reported in cases from the 1960's and 1970's [27,29,34,37].

Supportive treatment

Each patient received supportive treatment. In total, 18 (62%) patients received circulatory support, mostly consisting of fluid administration. Furthermore, 20 (69%) patients received respiratory support, most often intubation/ventilation. Other treatments included corticosteroids, antibiotics, a tourniquet, dextrose, a tetanus prophylaxis and antihistamine therapy. Moreover, five (17%) patients required cardiopulmonary resuscitation (CPR) (Table 5).

Cardiovascular findings

Twenty-six case reports included vital signs. Hypertension and hypotension were unusual among the reports. Median heart rates declined from 100 bpm to 83 bpm after antivenom administration with little apparent change in blood pressures. Of the 17 cases commenting on state of consciousness of the patient, seven (41%) patients were unconscious for an unspecified time period. Twenty-six cases reported on pulse. Of these, 13 (50%) cases reported at least one measurement of tachycardia (>100 bpm), whilst three (12%) reported at least one measurement of bradycardia (<60 bpm). In two cases bradycardia was seen after tachycardia [23,26].

Of eight case reports describing an electrocardiogram (ECG) [9,10,21–23,26, 28,40] seven had at least one ECG-abnormality [6,10,21,23,26,28,40]. Tachycardia seen on an

ECG is also considered an ECG-abnormality. Cardiac arrest occurred in three patients [9,23,24], in one patient twice [9]. ECG findings before cardiac arrest included ventricular fibrillation with tachycardia in one and ST elevation with bradycardia in another patient. Both of these patients died [9,23]. Despite receiving antivenom, six case reports noted cardiac abnormalities post-antivenom [9,10,23,26,28,40].

Discussion

Survival after envenomation was 86%, which differs from overall survival-numbers described in literature. Generally, many patients are bitten far away from health care institutions, resulting in a higher mortality rate than the cases reviewed here. The most recent mortality rate mentioned in literature is 28%, by Christensen in 1981 [12]. Without any treatment, envenomation by *D. polylepis* is met with a near 100% mortality rate [10].

Generally speaking, there are three categories of symptoms that present with black mamba envenomation: neurological, autonomic dysfunction and local symptoms [41]. These symptoms vary per case probably related to the specific composition and amount of snake venom injected. These parameters may vary amongst all individual black mamba's, relying on age, snake length and season of the year [42].

Overall, the top-three most common symptoms consisted of decreased respiratory function, sweating and paralysis. Neurological symptoms occurred more often than symptoms of autonomic dysfunction. Furthermore, these neurological symptoms usually presented soon after the envenomation and frequently arose simultaneously. Finally, envenomations by *D. polylepis* associate with a range of cardiac arrythmias, although varying in severity.

Table 3. Frequency and median time of onset of symptoms reported in the cases.

Symptom	Frequency (%)	Median time in minutes (IQR)
Decreased respiratory function	24 (82.8)	90 (28–218)
Sweating	19 (65.5)	35 (10–180)
Skin swelling	19 (65.5)	60 (31–490)
Paralysis	17 (58.6)	120 (25–345)
Dysarthria	14 (48.3)	94 (20–210)
Pain	14 (48.3)	21 (5–54)
Dysphagia	13 (44.8)	65 (19–125
Vomiting	12 (41.4)	48 (19–125)
Paresthesia's	11 (37.9)	15 (2–60)
Ptosis	10 (34.5)	105 (20–210)
Hypersalivation	10 (34.5)	87 (26–135)
Redness	10 (34.5)	189 (30–214)
Fasciculations	9 (31.0)	270 (78–485)
Restlessness	7 (24.1)	135(120–510)
Altered state of conscious	6 (20.7)	60 (13–160)
Nausea	6 (20.7)	38 (8–119)
Dizziness	5 (17.2)	5 (3–23)
Hemorrhage	5 (17.2)	0 (0–2633)
Cold fits	5 (17.2)	83 (68–275)
Visual problems	4 (13.8)	
Pupil unresponsive to light	4 (13.8)	
Pruritus	4 (13.8)	
Numbness	4 (13.8)	
Drowsy	3 (10.3)	
Paleness	2 (6.9)	
Cold extremities	2 (6.9)	
Fullness in head	2 (6.9)	
Convulsions	2 (6.9)	
Spasms	2 (6.9)	
Cough	1 (3.4)	
Shock	1 (3.4)	
Rhabdomyolysis	1 (3.4)	
Diarrhea	1 (3.4)	
Total	249	60 (15–188)

Table 5. Received supportive treatment following D. polylepis envenomation.

Support	*N* (%)*
Received support	29 (100)
Resuscitated	5 (17.2)
Circulatory support	18 (62.1)
Fluid	16 (55.2)
Anticholinergic	4 (13.8)
Diuretics	2 (6.9)
Sympathicomimetics	2 (6.9)
Cardiopulmonary bypass	1 (3.4)
Vitamin K	1 (3.4)
Inotropics	1 (3.4)
Respiratory support	20 (69.0)
Intubation/ventilation	11 (37.9)
Oxygen	8 (27.6)
Benzodiazepine agonist	6 (20.7)
Sedation	5 (17.2)
Tracheotomy	4 (13.8)
Ambubagging	1 (3.4)
Extra support	28 (96.6)
Corticosteroids	25 (86.2)
Antibiotics	11 (37.9)
Tourniquet	10 (34.5)
Dextrose	8 (27.6)
Tetanus prophylaxes	7 (24.1)
Antihistamines	6 (20.7)
Noradrenalin	5 (17.2)
Neostigmine	4 (13.8)
Anti-emetics	2 (6.9)
Hemodialysis	1 (3.4)

*Percentage taken from total cases reporting the treatment, excluding cases without description.

Table 4. Received antivenom following D. polylepis envenomation.

Antivenom	Number of cases applying specific antivenom	Median number of doses per case	Median total dose amount per case	Patient survival
No antivenom	3	–	–	–
SAIMR polyvalent (mamba) antivenom	19	2	70	16
Polyvalent antivenom (unspecified)	3*	1–7**	10–79**	2
Trivalent mamba antivenom	4*	2–4**	40–150**	4
Unspecified (anti-snakebite) antivenom	2	4**	190–400**	2

*In two cases (Louw 1 [26] & Visser 3 [33]) one dose of polyvalent antivenom was followed by two doses of trivalent mamba antivenom.
**Not enough counts for the median, instead range is reported.

Neurological symptoms usually manifested within 120 minutes in the disease course and are typically related to the neurotoxic effects of the black mamba venom. These symptoms generally resolve after antivenom administration, but patients often require additional medical therapy to decrease morbidity and mortality. Symptoms of autonomic dysfunction (e.g., vomiting, nausea, dizziness, and sweating) usually occur within 60 minutes and can be effectively managed with supportive care. Local symptoms in relation to the bite site are normally self-limiting and resolve without any additional medical intervention. The neurological and symptoms of autonomic dysfunction mostly occur simultaneously, showing the clinical picture of an envenomation "syndrome". Therefore, this only provides insight into the disease course, with statistical evidence currently lacking to show a relation between the onset of certain symptoms and the time of the bite.

Dendroaspis polylepis venom contains five different types of toxins: neurotoxins, myotoxins, coagulotoxins, nephrotoxins, and necrotoxins [42]. *D. polylepis* venom is known to be especially neurotoxic. A recent study by Laustsen et al., investigating the immunoprofile of *D. polylepis* toxins, revealed alfa-neurotoxins to be the most lethal component in acute toxicity [43]. These neurotoxins are antagonists for the nicotinic acetylcholine receptors (nAChRs) in skeletal muscles. As alfa-neurotoxins inhibit binding to the nAChRs, administration of *D. polylepis* venom will result in impeded muscle contractions and a higher concentration of ACh in the neuromuscular junction [44].

Furthermore, the *Dendroaspis* venom uniquely contains dendrotoxins which interact with the voltage-dependent potassium (Kv1) channels in skeletal muscle cells and increase the ACh release at the neuromuscular junction [43]. As this leads to hyperexcitability, convulsive symptoms may appear. Finally, this hyperexcitability may result in tetanic contractions and consequently paralysis of, for example, respiratory muscles [45].

In addition, the Kv1 channels also play a role in regulating vascular smooth muscle cell contraction and thereby influence vasoconstriction [46]. Therefore, dendrotoxins may also indirectly promote vasoconstriction and cause hypertension.

The presence of both the alfa-neurotoxins and dendrotoxins in *D. polylepis* venom contributes to the morbidity and mortality amongst its victims.

Symptoms of autonomic dysfunction of snake bites in general are due to three different effects: the snake venom itself, consequences of treatment, and the anxiety of the patient. Even when "dry" bites are delivered, patients may start sweating, feeling dizzy, or experience chest compression [47]. Therefore, symptoms of autonomic dysfunction as sweating, nausea, and vomiting might be due to a stress reaction via the sympathetic nervous system. To date, no specific components of *D. polylepis* venom have been identified to cause these specific reactions.

Van Aswegen et al. showed that the venom is also cardiotoxic by means of inducing cardiomyocyte death. The amount of cell death depends on the amount of venom injected but could reach up to 6% [48]. Furthermore, cardiac rhythm abnormalities could be caused by the effect of calciseptine, present in *D. polylepis* venom. Calciseptine can block the L-type calcium channels in the cardiac myocytes, which leads to decreased contractility [43]. Moreover, the L-type calcium channels contribute to the heart's automaticity [49] and hence their inhibition may contribute to cardiac arrhythmias.

Nevertheless, the above-mentioned pathophysiological mechanisms of the *D. polylepis* venom originates from in-vitro studies and more theoretical articles. The ECG abnormalities observed in the case reports should therefore not be considered as a primary effect of the venom only, but also as a secondary effect of severe envenomation. For example, sinus tachycardia could be linked to stress and anxiety, while cardiac arrest is seen often in cases with severe paralysis or decreased respiratory function. Moreover, ECG recordings were only reported in eight cases. Case report bias may have led to cases mentioning the ECG more often when the ECG was abnormal.

Antivenom is the principal treatment for *D. polylepsis* envenomation [41]. S.A.I.M.R. Polyvalent Antivenom was the most frequently used antivenom among the reviewed cases. This antivenom uses whole antibodies arising from horses exposed to ten venomous African snakes including *D. polylepsis*. Acute allergic reactions and delayed serum sickness may occur [16]. Acute reactions may range from urticaria, rash, and fever to severe anaphylaxis with shock [50]. Acute allergic reactions warrant temporary cessation of antivenom infusion and treatment with antihistamines, corticosteroids, and adrenaline [41]. Allergic reactions were not reported in the case reports. While allergic reactions seemed to occur, they could not be confirmed nor excluded.

Antivenom therapy alone is often insufficient for symptom management and mortality prevention. Airway access and respiratory function should be monitored cautiously to prevent early mortality. This varies depending on the level of respiratory function impairment and may range from oxygen therapy to intubation under sedation.

There is no evidence supporting the use of corticosteroids and antihistamines as premedication prior to antivenom administration [40]. However, a low dose of noradrenalin as premedication has been shown to significantly reduce adverse reactions to antivenom therapy [51].

This narrative review has several limitations. First, the amount of published literature and especially case reports is very limited. Many cases are more than 20 years old, whilst some were more than 50 years old. In the meantime, the clinical practice might have changed.

Second, the case reports included might demonstrate a certain degree of publication bias. An estimated 90,000 to 420,000 snakebites per year occur in sub-Saharan Africa [52]. Assuming that the incidence will be consistent over the years, this will lead to at least 4.7 million cases in a 52-year time period. Even if *D. polylepis* represent one percent of these reported cases (47,000), the 29 cases in this review will not represent all *D. polylepis* envenomations, Moreover, the six non-endemic case reports are probably an over-representation of cases in these countries. As a bite by a

Black Mamba is a rare event in non-endemic countries, case reports are more likely to be written there. Similarly, the 23 endemic case reports likely under-represent cases in these countries as a black mamba envenomation is a more occurring event. Publication bias could for instance have led to the high survival rate reported in this review. For example, all patients were hospitalized. As medical care and antivenom are beneficial to survival, it is likely that survival is higher among patients who receive hospital care compared to those who did not.

Third, length and amount of detail varied considerably among the case reports. This resulted in a large variance between parameters presented per case. Moreover, it was sometimes uncertain if the snakebite was definitely delivered by *D. polylepis*.

Fourth, the cause of a symptom, either the bite itself or an allergic reaction to treatment, was not always clear.

Altogether, we would recommend a more systematic reporting of the characteristics of a *D. polylepis* envenomation, using published case report format guidelines [19]. As *D. polylepis* is also held captive by snake breeders and snake holders in other parts of the world, increased awareness among health care professionals on the clinical course of black mamba envenomation is important.

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Author contributions

All authors contributed to the study conception and design. MA, CFJB, IA, MW, MFvB, ERANA, MFT, JLROD, UM, LB, MM, NAK contributed to the parameter extraction, the analysis of the results and to the writing of the first draft of the manuscript. All authors commented on previous versions of the manuscript, and read and approved the final manuscript. MAGvdH supervised the project.

Disclosure statement

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References

[1] World Health Organization. Snakebite envenoming: a strategy for prevention and control. Geneva: World Health Organization; 2019.
[2] Chippaux JP. Snakebite envenomation turns again into a neglected tropical disease! J Venom Anim Toxins Incl Trop Dis. 2017;23:38.
[3] Hodgson PS, Davidson TM. Biology and treatment of the mamba snakebite. Wilderness Environ Med. 1996;7:133–145.
[4] WHO Expert Committee on Biological Standardization. Sixty-seventh report. Geneva: World Health Organization; 2017. (WHO technical report series; no. 1004).
[5] IUCN Red List [Internet]. Dendroaspis polylepis (Black Mamba). Cambridge (UK): IUCN; 2010.
[6] Spawls S, Howell K, Hinkel H, et al. Field guide to East African Reptiles. London: Bloomsbury Publishing; 2018.
[7] National Geographic [Internet]. Black mamba, facts and photos; Washington (DC): National Geographic Partners; n.d. [cited 2020 Dec 16]. Available from: https://www.nationalgeographic.com/animals/reptiles/b/black-mamba/.
[8] Brittanica [Internet]. Black mamba. Chicago (IL): Encyclopeadia Brittanica.; 2020 [cited 2020 Dec 16]. Available from: https://www.britannica.com/animal/black-mamba
[9] Blumenthal R, Scholtz PEP, Shuttleworth JL. Black mamba death: venom versus antivenom? Am J Forensic Med Pathol. 2019;40:356–360.
[10] Závada J, Valenta J, Kopecký O, et al. Black mamba dendroaspis polylepis bite: a case report. Prague Med Rep. 2011;112:298–304.
[11] Blaylock R. Epidemiology of snakebite in Eshowe, KwaZulu-Natal, South Africa. Toxicon. 2004;43:159–166.
[12] Christensen PA. Snakebite and the use of antivenom in southern Africa. S Afr Med J. 1981;59:934–938.
[13] Ainsworth S, Menzies SK, Casewell NR et al. An analysis of preclinical efficacy testing of antivenoms for sub-Saharan Africa: inadequate independent scrutiny and poor-quality reporting are barriers to improving snakebite treatment and management. PLOS Negl Trop Dis. 2020;14(8):e0008579.
[14] Moran NF, Newman WJ, Theakston DG et al. High incidence of early anaphylactoid reaction to SAIMR polyvalent snake antivenom. Trans R Soc Trop Med Hyg. 1998;92(1):69–70.
[15] Pantanowitz L, Scott L, Southem J, Schrire L. Development of antivenoms in South Africa. S Afr J Sci. 1998;94:464–469
[16] African Snakebite Institute [Internet]. Snakebite in southern Africa. Pretoria: African Snakebite Institute; n.d. [cited 2020 Dec 16]. Available from: https://www.africansnakebiteinstitute.com/snakebite/
[17] Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62:1006–1012.
[18] Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5:210.
[19] Moola S, Munn Z, Tufanaru C, et al. Chapter 7: systematic reviews of etiology and risk. In: Aromataris E, Munn Z, editors. JBI manual for evidence synthesis. Adelaide, Australia: JBI; 2020.
[20] Erulu VE, Okumu MO, Ochola FO, et al. Revered but poorly understood: a case report of *Dendroaspis polylepis* (Black Mamba) envenomation in Watamu, Malindi Kenya, and a review of the literature. Trop Med Infect Dis. 2018;3:104.
[21] Schutzbach M, Vonderhagen S, Jäger M. Antiserumtherapie bei Schlangenbiss durch Schwarze Mamba [Antivenom therapy after a black mamba snakebite]. Unfallchirurg. 2016;119:1053–1056.
[22] Hilligan R. Black mamba bites. A report of 2 cases. S Afr Med J. 1987;72:220–221.
[23] Naidoo DP, Lockhat HS, Naiker IP. Myocardial infarction after probable black mamba envenomation. A case report. S Afr Med J. 1987;71:388–389.
[24] Harvey WR. Black mamba envenomation. S Afr Med J. 1985;67:960.
[25] Shah SARA, Naqvi SS, Abbas MA. Use of neostigmine in black mamba snake bite: a case report. Anaesth Pain Intensive Care. 2016;20:77–79.
[26] Strover HM. Report on a death from black mamba bite (*Dendroaspis polylepis*). Cent Afr J Med. 1967;13:185–186.
[27] Krengel B, Walton J. A case of mamba bite. S Afr Med J. 1967;41:1150–1151.
[28] Saunders CR. Report on a Black Mamba bite of a medical colleague. Cent Afr J Med. 1980;26:121–122.
[29] Louw JX. Specific mamba antivenom-report of survival of 2 patients with black mamba bites treated with this serum. S Afr Med J. 1967;41:1175.
[30] Durrant S, Haagner GV. Venoms and snakebite. J Herp Assoc Afr. 1992;41:46.
[31] Branch WR, Haagner GV, Morgan DR, et al. Venoms and snakebite. J Herpetol Assoc Africa. 1991;39:28–29.

[32] Haagner GV. Venoms and snakebite. J Herpetol Assoc Africa. 1990;37:58–60.
[33] Devlin J, Wood A, Kunisake T, et al. Black mamba envenomation treated with neostigmine. Clin Toxicol. 2012;50:649.
[34] Visser J, Chapman D. Snake and snakebite. Illustrative cases: front fanged species. Cape Town: Purnell; 1978; p. 115–122.
[35] Blake DK. Case history of a brown mamba bite. J Herpetol Assoc Rhod. 1960;9(10):17–18.
[36] Read PH, Foster DI, Broadley DG. Case history of a brown mamba bite in northern Rhodesia. J Herpetol Assoc Rhod. 1959;8:6–7.
[37] Blaylock RS. Snake bites at Triangle Hospital January 1975 to June 1981. Cent Afr J Med. 1982;28:1–10.
[38] CastorEDC.com [Internet]. Hoboken (NJ): Castor EDC; 2019. Available from: https://castoredc.com.
[39] Markwalder K, Koller M. Zwei Fallberichte und Uberlegungen zur Therapie von neurotoxischen Giftschlangenbissen [Mamba bites. 2 case reports and observations on the therapy of neurotoxic poisonous snake bites]. Schweiz Rundsch Med Prax. 1987;76:1281–1284.
[40] Quarch V, Brander L, Cioccari L. An unexpected case of black mamba (*Dendroaspis polylepis*) Bite in Switzerland. Case Reports Crit Care. 2017;2017:1–3.
[41] UC San Diego [Internet]. Immediate first aid for bites by black mamba (*Dendroaspis polylepis*). San Diego (CA): University of California San Diego.; n.d. [cited 2020 Dec 16]. Available from: http://toxicology.ucsd.edu/Snakebite%20Protocols/Dendroa3.htm
[42] White J. Bites and stings from venomous animals: a global overview. Ther Drug Monit. 2000;22:65–68.
[43] Laustsen AH, Lomonte B, Lohse B, et al. Unveiling the nature of black mamba (*Dendroaspis polylepis*) venom through venomics and antivenom immunoprofiling: identification of key toxin targets for antivenom development. J Proteomics. 2015;119:126–142.
[44] Barber CM, Isbister GK, Hodgson WC. Alpha neurotoxins. Toxicon. 2013;66:47–58.
[45] Kumar A, Gupta V. Neurological implications of dendrotoxin: a review. EC Pharmacol Toxicol. 2018;6:469–476.
[46] Jackson WF. KV channels and the regulation of vascular smooth muscle tone. Microcirculation. 2018;25:e12421.
[47] Weatherall DJ, Ledingham JGG, Warrell DA. Oxford textbook of medicine. Injuries, envenoming, poisoning, and allergic reactions caused by animals. 3rd ed. Oxford: Oxford University Press; 1996; p. 1126–1139.
[48] Van Aswegen G, van Rooyen JM, Fourie C, et al. Putative cardiotoxicity of the venoms of three mamba species. Wilderness Environ Med. 1996;7:115–121.
[49] Mesirca P, Torrente AG, Mangoni ME. Functional role of voltage gated Ca(2+) channels in heart automaticity. Front Physiol. 2015;6:1–13.
[50] De Silva HA, Ryan NM, de Silva HJ. Adverse reactions to snake antivenom, and their prevention and treatment. Br J Clin Pharmacol. 2016;81:446–452.
[51] Premawardhena AP, de Silva CE, Fonseka MM, et al. Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. BMJ. 1999;318:1041–1043.
[52] Kasturiratne A, Wickremasinghe AR, de Silva N et al. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. PLoS Med. 2008;5(11):e218.