

# Thrombosis and Haemostasis

## Handheld point-of-care devices for snakebite coagulopathy: a scoping review

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### Abstract:

Venom induced consumption coagulopathy (VICC) is a common complication of snakebite that is associated with hypofibrinogenaemia, bleeding, disability, and death. In remote tropical settings, where most snakebites occur, the 20-minute whole blood clotting test is used to diagnose VICC. Point-of-care (POC) coagulation devices could provide an accessible means of detecting VICC that is better standardised, quantifiable, and more accurate. In this scoping review, the mechanistic reasons that previously studied POC devices have failed in VICC are considered, and evidence-based recommendations are made to prioritise certain devices for clinical validation studies.

Four small studies have evaluated a POC international normalised ratio (INR) device in patients with Australian Elapid, *Daboia russelii* and *Echis carinatus* envenoming. All of these studies used POC INR devices that rely on a thrombin substrate endpoint, which, unlike laboratory-based INR measurement, is known to underestimate INR in patients with hypofibrinogenaemia.

Seventeen commercially available POC devices for measuring INR, activated clotting time (ACT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimer, and fibrin(ogen) degradation products (FDP) have been reviewed. POC INR devices that detect fibrin clot formation, as well as a novel POC device that quantifies fibrinogen were identified, that show promise for use in patients with VICC. These devices could support more accurate allocation of antivenom, reduce the time to antivenom administration, and provide improved clinical trial outcome measurement instruments. There is an urgent need for these promising POC coagulation devices to be validated in prospective clinical snakebite studies.

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## Handheld point-of-care devices for snakebite coagulopathy: a scoping review

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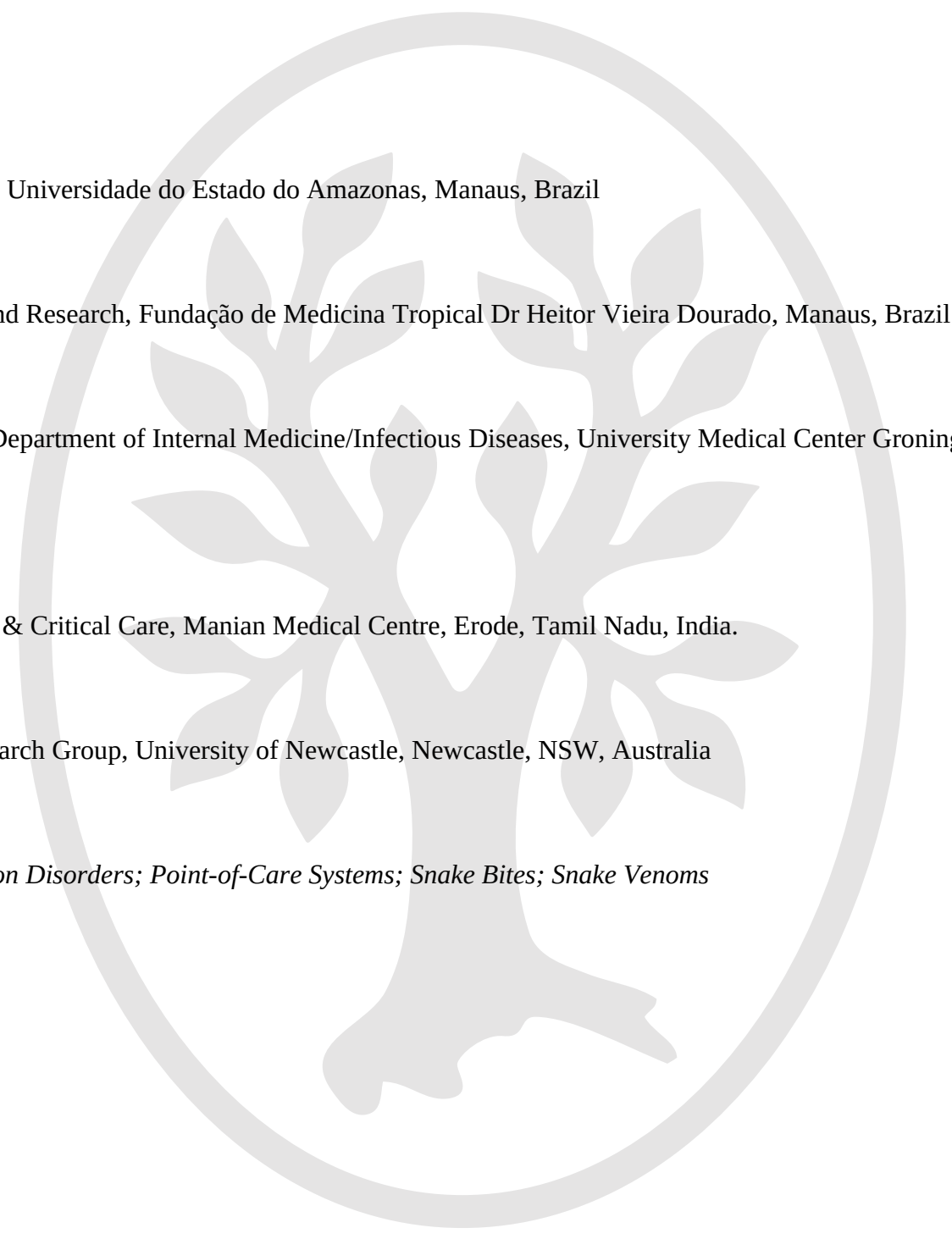
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**Abstract**

Venom induced consumption coagulopathy (VICC) is a common complication of snakebite that is associated with hypofibrinogenaemia, bleeding, disability, and death. In remote tropical settings, where most snakebites occur, the 20-minute whole blood clotting test is used to diagnose VICC. Point-of-care (POC) coagulation devices could provide an accessible means of detecting VICC that is better standardised, quantifiable, and more accurate. In this scoping review, the mechanistic reasons that previously studied POC devices have failed in VICC are considered, and evidence-based recommendations are made to prioritise certain devices for clinical validation studies.

Four small studies have evaluated a POC international normalised ratio (INR) device in patients with Australian Elapid, *Daboia russelii* and *Echis carinatus* envenoming. The devices assessed in these studies either relied on a thrombin substrate endpoint, which is known to underestimate INR in patients with hypofibrinogenaemia, have been recalled due to poor accuracy, or have since been discontinued.

Seventeen commercially available POC devices for measuring INR, activated clotting time (ACT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimer, and fibrin(ogen) degradation products (FDP) have been reviewed. POC INR devices that detect fibrin clot formation, as well as a novel POC device that quantifies fibrinogen were identified, that show promise for use in patients with VICC. These devices could support more accurate allocation of antivenom, reduce the time to antivenom administration, and provide improved clinical trial outcome measurement instruments. There is an urgent need for these promising POC coagulation devices to be validated in prospective clinical snakebite studies.

## Introduction

Snakebite causes at least 94,000 deaths each year and is a World Health Organization (WHO) listed priority neglected tropical disease [1,2]. Coagulopathy is a hallmark of systemic envenoming by diverse medically important snake species distributed across all snakebite endemic regions, including North and South American rattlesnakes and lanceheads (*Crotalus* and *Bothrops* spp.), Asian pit vipers and true vipers (e.g. the Russell's viper *Daboia russelii* and the Malayan pit viper *Calloselasma rhodostoma*), the African saw-scaled vipers and boomslang (*Echis* spp. and *Dispholidus typus*), and several Australian Elapids (e.g. the brown snake *Pseudonaja textilis* and the taipan *Oxyuranus scutellatus*).

Some snake species can cause venom induced consumption coagulopathy (VICC) through the following activities: activation of the coagulation pathway (usually at the common pathway level); fibrinogenolysis; and fibrinolysis [3,4]. VICC has been associated with a high risk of complications [5] and represents an urgent indication for antivenom [6,7]. Many of the snake species that induce VICC also disrupt small blood vessels through snake venom metalloproteinase (SVMP) toxin mediated hydrolysis of basement membrane proteins [8]. The resultant state of fibrinogen depletion and destabilised endothelial extracellular structures amplifies the risk of spontaneous bleeding, typically resulting in bite site bleeding, venepuncture site bleeding, and systemic bleeding (gingival, haematuria, conjunctival, epistaxis, etc) [9]. Serious bleeding events can also occur, including intracerebral haemorrhage, which is almost always fatal [10,11].

The WHO snakebite management guidelines for Africa [7] and Asia [6] recommend that antivenom is administered to patients with an abnormal 20-minute whole blood clotting test (20WBCT). The 20WBCT, a variation of the Lee-White Clotting Time, which was itself developed a century ago [12], entails the collection of 2 mL of whole blood into a clean glass tube and, after 20-minutes, a visual inspection for the presence or absence of a clot [13]. This test has been used in LMIC settings as it is inexpensive (only requiring a glass tube) and can be conducted in remote rural settings without the need for laboratory facilities. However, there are certain limitations to the 20WBCT. Accuracy to detect coagulopathy has been good but imperfect (84% sensitivity and 91% specificity in a recent meta-analysis [14]), which can delay antivenom administration for some patients [15]. Although the versatility of being able to use a range of glass tubes to measure the 20WBCT is an advantage, this lack of standardisation can be problematic. There have been anecdotal reports of glass tubes being unknowingly coated with substances, such as silicone, which prevent activation of the coagulation pathway by the glass surface of the tube [14].

A debate over which is the best method to detect VICC recently arose in the development of a global snakebite core outcome measurement set (COMS) [16]. Although consensus to include laboratory INR as a core outcome measure was reached, stakeholders were justifiably concerned that this could be challenging in LMIC settings and recommended that point-of-care (POC) devices be prioritised for assessment in validation studies.

Various POC coagulation devices exist, although these have largely been developed to suit the requirements of therapeutic anticoagulation services in high-income settings, and have not been validated for use in snakebite. The WHO South-East Asia snakebite guidelines state that “point-of-care devices for measuring INR and D-dimer [are] unreliable in snakebite victims,” [6] although evidence to support this statement has been limited.

This scoping review aims to (1) review the published literature on the use of POC coagulation devices in snakebite, (2) define the potential roles of POC coagulation devices in snakebite endemic settings, and (3) shortlist the most promising POC coagulation devices for evaluation in preclinical and clinical validation studies. The PRISMA extension for scoping reviews checklist was followed [17] (appendix, p1).

### **Mechanism of action of snake venom toxins on the coagulation pathway**

Several snake venom toxin families can activate and consume key components of the coagulation pathway, resulting in VICC (Figure 1a). As these toxins can vary substantially between snake species, it is important to consider their mechanism of action, as this may inform which POC coagulation devices are likely to be informative. Often, there may be several coagulant toxins present within a venom, each targeting different components of the coagulation pathway. There have been several in-depth reviews on VICC [18–22], and therefore only a focussed summary of this topic will be presented here.

### *Factor X activators*

Factor X is a major constituent of the prothrombinase complex. Snake venom toxins that specifically activate Factor X consist of either SVMPS (such as the highly characterised RVV-X from the venom of *Daboia russelli*) or snake venom serine proteases (SVSP), which have been described either in viper venoms or Elapid venoms, respectively [19,23,24]. Both these toxins activate Factor X in a similar manner to that of physiological tenases, through cleavage of an inhibitory peptide resulting in the activation of Factor X's proteolytic activity.

### *Factor V activators*

Factor V is activated to Factor Va by thrombin or factor Xa. Factor Va is the active form and is a cofactor that significantly enhances thrombin formation [25]. Venom toxin factor V activators are serine protease enzymes that act to cleave factor V, usually at a different site to thrombin, but nevertheless to an active procoagulant form. Examples include the serine protease RVV-V in Russell's viper (*D. russelii*) venom, or the thrombocytin toxin found in *Bothrops atrox* venom [25].

### *Prothrombin activators*

Prothrombin activators exist in a diverse range of venoms and have been classified into four groups (A, B, C and D) based on their toxin families and functional characteristics [26]. Group A and B prothrombin activators are SVMPS toxins which convert prothrombin into the catalytically



active thrombin intermediate, meizothrombin, which subsequently spontaneously converts to thrombin [19]. Ecarin, present in the venom of *Echis carinatus* (Indian saw scaled viper), is a well described example of a group A activator [27], while carinactivase-1, found in the venom of white-bellied carpet viper (*Echis leucogaster*), is a well characterised group B activator [28]. The primary difference between group A and B prothrombin activators is in the requirement of cofactors; group A activators act independent of the need of factor Va, Ca<sup>2+</sup> or phospholipids [29], while group B similarly do not require factor Va or phospholipids but are reliant on Ca<sup>2+</sup> [28].

Group C prothrombin activators belong to the SVSP family and are only found in the venoms of certain Australian Elapid snakes [20], such as the brown snake *Pseudonaja textilis* [30] and the taipan *Oxyuranus scutellatus* [31]. These prothrombin activators consist of both a factor Xa like and a factor Va like toxin, which form large multi-subunit enzymes, effectively mimicking the prothrombinase complex. This toxin efficiently converts prothrombin to thrombin in the presence of Ca<sup>2+</sup> and phospholipids [20], and is remarkably similar to the serine protease human clotting factors, in contrast to the SVMP prothrombin activators in viper venoms.

Group D prothrombin activators, similar to group C activators, are SVSP toxins only found in Australian Elapids [32,33], such as tiger snakes (*Notechis* spp.). This group consists of enzymes which resemble factor Xa only, and thus also require activated factor V, in addition to Ca<sup>2+</sup> and phospholipids, to effectively cleave prothrombin into thrombin [33].

### *Thrombin-like enzymes*

Numerous thrombin-like enzymes (TLEs), sometimes termed fibrin(ogen)olytic enzymes, have been identified in snake venoms, and these can be categorised as fibrinogenases, and are typically members of the SVSP or SVMP toxin families [34]. The  $\alpha$ -fibrinogenases tend to preferentially cleave the  $\alpha$ -chain of fibrin(ogen), whilst the  $\beta$ -fibrinogenases preferentially cleave the  $\beta$ -chain of fibrin(ogen) [35]. The term fibrin(ogen) highlights that these enzymes cleave both fibrinogen and fibrin clot. Unlike thrombin, these proteinases do not produce fibrinopeptides A or B and result in the formation of a soft fibrin clot that is not crosslinked .

### **Search strategy for this review**

The following terms were used to search PubMed for articles published until November 2023 that described the use of POC coagulation devices in snakebite: (snake OR venom) AND ("point of care" OR bedside) AND (coagulopathy OR coagulation OR clotting). Additional articles were sought from the reference lists of included papers, and through recommendations by the review authors. There were no language restrictions. The PubMed search identified 40 articles, of which four were included that assessed a handheld POC device to detect coagulopathy in humans with snakebite [36–40] (Table 1). No additional articles were identified from reference lists or author recommendations. One article was a short report that included limited data [36], but the corresponding author was contacted and they shared the unpublished underlying data, which have been included in this scoping review.

A list of handheld POC devices for measuring coagulation was prepared by searching the published literature, contacting commercial suppliers, and by accessing information of devices evaluated by the UK blood coagulation national external quality assessment service (NEQAS). To be eligible for inclusion, devices needed to be handheld, battery powered, fully automated, and suitable for use at the bedside. Furthermore, devices needed to be compatible with measurement in whole blood, to overcome the need for a centrifuge. Thromboelastography and thromboelastometry devices were excluded, as were devices that had been withdrawn from the market.

The following characteristics of each device were considered: parameter(s) measured, sample types accepted (blood +/- plasma), sample collection (venepuncture or capillary), sample volume, cost of device, cost of cartridge, limit of detection, whether battery operated, and the method of measurement. Devices have been presented according to the following categories, based on the aspect of the coagulation pathway that they measure: prothrombin time (or INR); activated partial thromboplastin time; activated clotting time; fibrinogen quantification; and fibrin(ogen) degradation products (FDPs), including D-dimer.

The search strategy identified 50 devices, from which 17 were eligible for inclusion in this scoping review (Table 2). The reasons for the exclusions were: not handheld (19), no longer commercially available (7), and only compatible with centrifuged plasma (1). A further 6 devices

for measuring D-dimer were excluded as they were qualitative and used a cut-off that was deemed too low for diagnosing VICC, the rationale for which has been described below.

### **Evidence for using POC devices in VICC**

Three studies that have evaluated POC coagulopathy devices in snakebite were conducted in Australia [37], although two of these only described a single case of snakebite envenoming [38,39] (Table 1). The paper by O'Rourke et al [37] was a prospective observational study that evaluated the i-STAT POC device for measuring INR in 15 participants with snakebite, which found that it consistently, and substantially, underestimated the laboratory INR, although it should be kept in mind that there can be variability in the accuracy of laboratory INR results. The sensitivity of the i-STAT device to detect an INR >1.4 was 57%, and the specificity was 88%. The other two studies, of single cases with VICC in Australia, demonstrated similar findings for the CoaguChek device, with false negative POC INR results [38,39].

The underlying data from a study conducted in India by Senthilkumaran et al [36], were made available for this scoping review (appendix, p3). This study assessed the following POC INR devices in three patients with *Echis carinatus* envenoming and 15 patients with *Daboia russelii* envenoming: Alere INRatio2, CoaguChek S, and i-STAT. All three POC devices grossly underestimated the laboratory assay, particularly when

the INR was elevated above 4. The sensitivity of the Alere INRatio2, CoaguChek S, and i-STAT devices to detect a laboratory INR  $>1.4$  were 50%, 56%, and 56%, respectively. Specificity could not be calculated as all the patients had a laboratory INR value  $>1.4$ .

The POC INR and laboratory INR values from the studies by O'Rourke and Senthilkumaran have been depicted in Figure 2. The theory as to why so many false negative results occurred has been described in the next section.

The case report by Cubitt et al is the only published report describing the use of a POC D-dimer assay to detect VICC [39]. This Cobas H232 POC device produced a borderline raised D-dimer measurement of 0.38 mg/L (upper limit of normal 0.36 mg/L), whereas the laboratory assay result was substantially higher than this.

No studies were identified on the use of a POC INR device to detect VICC in Africa, Europe, South America, or North America.

### **Prothrombin time and international normalized ratio**

The prothrombin time (PT) assay was originally defined by Arnand J Quick in 1935, as the time taken in seconds for a fibrin clot to be formed following activation of the extrinsic pathway (or tissue factor pathway) by thromboplastin [41]. This test is widely used in modern medicine

whereby the sample is collected in a blood tube containing citrate, which is subsequently centrifuged to produce platelet free plasma before adding an excess of calcium (to reverse the anticoagulant effect of the citrate) and thromboplastin (a mixture of tissue factor and phospholipid). In the laboratory environment, the PT assay is typically performed using an automated analyzer, and the endpoint is based on either optical or mechanical detection of a fibrin clot [42].

As many different forms of thromboplastin are available, which can influence the prothrombin time, the World Health Organization introduced the INR. The INR is calculated by dividing the test PT by the mean normal PT (the mean PT of the healthy adult population), using a reagent and method which has been calibrated using the recommended WHO reference thromboplastin reagent and procedure [43]. In clinical practice, the prothrombin time is typically used as a routine screen for coagulopathy in hospitalised patients, as a measure of hepatic synthetic function, and to detect disseminated intravascular coagulopathy (DIC). The INR was developed for therapeutic drug monitoring of warfarin and related drugs.

In VICC, the prothrombin time and INR tend to be severely prolonged – often to the point of being unrecordable [44]. Because the prothrombin time is based on activation of the extrinsic pathway with onward activation of the common pathway to produce a fibrin clot, it is variably affected by any change along this pathway, including low fibrinogen (common pathway) or factor II, V, VII or X deficiencies. In VICC, fibrinogen is cleaved by thrombin-like enzymes, or by endogenous thrombin that has been produced in response to venom prothrombin or factor

X activators [22]. Once circulating fibrinogen has been severely depleted, the PT and INR endpoint, at least for methods based on the detection of a fibrin clot, cannot be reached, and an unrecordable result is produced (Figure 1b).

The two studies that have clinically assessed the i-STAT device, in Australia and India, both reported multiple false negative results [36,37]. In the Australian study, of the five participants with a laboratory INR value above the upper limit of detection (INR >10), the paired i-STAT INRs were in the range of 1.2-3.2. The study in India found that amongst nine patients with a laboratory INR >10, the paired i-STAT INR values were between 1.1-1.6 (appendix, p3) [36].

The i-STAT INR cartridges contain a thrombin substrate that produces an electrochemical signal in response to the accumulation of thrombin enzyme. Thus, the false negative results most likely occurred because the patients with VICC had severely depleted fibrinogen (resulting in a prolonged lab-INR) but still had sufficient amounts of prothrombin [45], which provided the capacity to produce thrombin (resulting in a near normal POC-INR). O'Rourke et al highlighted this issue in their manuscript, and further confirmed this hypothesis by demonstrating that a similar false negative result was produced when a sample from a patient with congenital afibrinogenemia was tested [37].

The INRatio2 device tested by Senthilkumaran et al in India [36] initiates coagulation using a recombinant human thromboplastin reagent, and measures the change in electrical impedance, across the forming blood clot, between two electrodes. Theoretically, the INRatio2 device may

have maintained accuracy in patients with depleted fibrinogen, as it detects the formation of clot, rather than the production of thrombin. However, in 2016 the FDA announced a class I recall of the INRatio2 device and test strips, as it was found to produce false low INR readings that posed a ‘risk of major or fatal bleeding.’ Certain medical conditions were found to be associated with falsely low INRatio2 readings including: anaemia (haematocrit <30%), acute inflammatory conditions, bleeding, or bruising [46]; all of which frequently occur in patients with VICC.

The Coagucheck S device cartridge contain iron particles that are mixed with the sample and subject to alternating magnetic fields, which detects reduced movement of the particles as the sample clots. Thus, as this device is measuring clot formation, prolonged INR due to hypofibrinogenaemia would be detected, and the cause of the false low INR readings is uncertain. The Coagucheck S device is no longer commercially available as it has been superseded by the Coagucheck Pro II, which relies on a thrombin substrate-based endpoint, and thus would likely be inaccurate in patients with hypofibrinogenaemia.

Future studies should restrict clinical assessment of PT/INR POC devices for VICC to those devices that rely on a fibrin endpoint. As outlined in Table 2, there are three devices that fulfill this requirement: Hemochron Signature Elite, microINR and Coag-Sense.

### **Activated partial thromboplastin time**



The activated partial thromboplastin time (aPTT) is used to investigate the intrinsic pathway of the coagulation pathway. Similar to the prothrombin time, the sample is collected in a citrated blood tube, centrifuged to platelet free plasma, and the time until clot formation is reported in seconds. The difference is that the reagents include contact activators such as kaolin [47], a powdered clay mineral which activates factor XII [48], silica, or ellagic acid. The aPTT is used in clinical practice for therapeutic monitoring of unfractionated heparin infusions, and to detect deficiencies in the intrinsic pathway associated with certain bleeding disorders, such as von Willebrand disease, haemophilia A and B and acquired haemophilia [49].

As the endpoint of laboratory measured aPTT is fibrin clot formation, the aPTT, like the PT, is severely prolonged when fibrinogen is depleted (Figure 1b). In a study of Australian Elapid envenoming, the aPTT produced very similar results to the PT, and was inversely associated with fibrinogen concentration, suggesting that aPTT and PT indirectly measure coagulopathy induced by fibrinogen depletion [50].

The aPTT assay has a limited POC commercial market because therapeutic monitoring of unfractionated heparin is rarely necessary following the increasing clinical use of longer half-life fractionated heparins. Consequently, few POC-devices are available. The CoaguChek Pro II can measure aPTT, but relies on a thrombin substrate endpoint that would likely produce false negative results for VICC if compared to a laboratory based aPTT (i.e. with a fibrin clot formation-based endpoint). The Hemochron Signature Elite may be accurate, as it relies on optical detection of

the rate of flow of blood. A potential advantage of the Hemochron Signature Elite is that the same device can measure the aPTT and PT (through use of different cartridges), although these parameters are likely to provide similar results in the context of fibrinogen depletion, and the device is prohibitively expensive for snakebite (approximately \$21,400 USD for the device and \$11 USD per test strip).

### **Activated clotting time**

Similar to the aPTT, the activated clotting time (ACT) is based on the time taken for a clot to be formed following the activation of the intrinsic pathway by a factor XII activator (either celite or kaolin) (Figure 1b). The ACT was developed by Paul Hattersley in 1966 as a means to evaluate coagulopathy in whole blood, rather than in plasma [51]. As the ACT can provide rapid and reliable results at the bedside, it has become the gold standard for monitoring heparin anticoagulation during cardiopulmonary bypass surgery [52].

A high surface area powder of celite or kaolin acts as a more potent activator in ACT, rather than the glass of the tube in 20WBCT. Thus, a potential advantage of the ACT is that a result can be read earlier, with samples tending to clot within 2-minutes under normal conditions [51].

An ACT between 180 and 240 seconds has been found to correspond to a Lee-White clotting time of 35 to 45 minutes, which was a key factor in the ACT gaining favour for monitoring of heparin therapy over the Lee White method [53].

The ACT tends to be measured in theatre using desktop devices (which typically record clot formation through measuring changes in the movement of a magnet within the sample), which is not as practical as a handheld device. The i-STAT and Hemochron Signature Elite devices can measure ACT, but are unsuitable for use in VICC as the former relies on a thrombin cleavage endpoint and the latter may be too expensive. However, it should be considered that the ACT can be manually measured in a blood tube (that contains either celite or kaolin), with visual detection of clot formation – as was the original technique described by Hattersley [51]. This technique may offer a standardised, rapid, and quantifiable assay for diagnosing VICC, which could have utility for both low- and high-income settings and obviate the need for an electronic device.

In a published (although not peer reviewed) dissertation by Shenoy, adults with VICC in Vellore, India underwent measurement of 20WBCT and ACT, which were compared with a laboratory INR gold standard [54]. An ACT threshold of 4-minutes was 94% sensitive and 97% specific for predicting an INR above 1.2 at admission, whilst the 20WBCT had 81% sensitivity and 90% specificity [54]. In LMIC settings the ACT might offer an affordable, better standardised, more sensitive, and more specific alternative to the 20WBCT. In high income settings, the ACT could provide a more rapid result than laboratory-based coagulation studies, which would reduce the time to antivenom administration.

### **Fibrinogen quantification**

Although much less commonly performed than the PT and aPTT, assays to quantify circulating fibrinogen are available. The most widely used approach is the Clauss fibrinogen assay, which is based on adding a standard amount of thrombin to a diluted plasma sample and then measuring the time until clot formation [55]. Through direct cleavage of fibrinogen by thrombin, other components of the coagulation pathway are bypassed, and the concentration of fibrinogen can be estimated (Figure 1b). In clinical practice, fibrinogen is typically measured in specialist circumstances, such as the investigation of congenital fibrinogen disorders, massive trauma, disseminated intravascular coagulation (DIC), or obstetric haemorrhage [56].

Fibrinogen has theoretical value in diagnosing VICC, particularly for TLE predominant snake venoms that cleave fibrinogen without affecting other factors in the coagulation pathway [40]. Clinical data are limited, but a study in Australia that compared the time to improvement of different clotting assays found that fibrinogen was of limited additional benefit for measuring response to antivenom treatment [50], with median times of recovery for PT, aPTT and fibrinogen of 9.2-hours, 5.2-hours, and 8.8-hours, respectively [50]. A study conducted in patients with *Echis pyramidum* envenoming in Djibouti demonstrated a similar pattern with median recovery times of 25-hours, 9-hours, and 40-hours for the PT, aPTT, and fibrinogen assays, respectively [44]. However, time to recovery of these assays in response to antivenom therapy is not necessarily clinically meaningful, and further studies comparing coagulation dynamics against clinically significant outcomes, such as the risk of bleeding events [57], are urgently needed.

One eligible POC device for measuring fibrinogen was identified; the qLabs FIB system (Stago). This device was recently compared with a Clauss derived laboratory gold standard and demonstrated 93.5% sensitivity and 100% specificity to predict a fibrinogen cut-off of 2.0 g/L [58]. Furthermore, the accuracy of the qLabs FIB system was maintained at low fibrinogen levels, which are typical in VICC, to the lower limit of detection of 1.0 g/L [58].

### **Fibrinogen degradation products (FDPs), fibrin degradation products (FDPs), and crosslinked fibrin degradation products (XDPs)**

Following formation of a normal fibrin clot, plasmin acts to degrade: (1) soluble fibrinogen to fibrinogen degradation products (FDPs); (2) soluble fibrin to fibrin degradation products (also abbreviated to FDPs) and (3) crosslinked insoluble fibrin to crosslinked fibrin degradation products (XDPs). D-dimer is an XDP that has gained favour as a target for diagnostic testing because it is more specific than FDPs for the investigation of venous thromboembolism [59] and it is relatively stable (due to its resistance to further digestion by plasmin) [60].

Because D-dimer measurement is used to investigate venous thromboembolism (VTE) in emergency and ambulatory care facilities in high-income settings, many D-dimer POC devices are available. However, these devices are often qualitative, in that they provide a binary result based on a threshold optimised for VTE (typically 0.5 mg/L). This threshold is likely to have poor specificity in snakebite as D-dimer is elevated by inflammatory disorders and trauma [61], which are caused by local envenoming. In a recent study of patients with VICC in Australia, a D-

dimer threshold of 2.5 mg/L was used [62], which demonstrated 95% sensitivity and specificity to identify VICC (defined as INR > 1.4 or fibrinogen <2.0 mg/L) [62]. It should be noted that D-dimer results vary between assays and, therefore, it may be necessary develop device specific cut-off values.

There is concern that certain snake venoms do not lead to production of crosslinked fibrin, which is a necessary precursor of D-dimer. Thrombin-like enzymes (TLEs) cleave fibrinogen to produce a soft fibrin clot, that is not crosslinked [40] and will not be degraded to form D-dimer through the action of plasmin (Figure 1b). For snake venoms predominant in TLEs, it may thus be preferable to rely on a POC device that can measure FDP, such as the PL mini handheld device (PremaLabs). Few clinical studies of snakebite envenoming have included measurement of both D-dimer and FDPs [57], and the comparative accuracy of these assays to predict clinically meaningful endpoints is unknown.

### **Potential role of point-of-care devices in clinical practice**

Snakebite predominantly occurs in remote rural settings [63] where laboratory infrastructure is limited. Even in high-income settings such as Australia, healthcare centres in rural areas, where snakebites tend to occur, do not necessarily have onsite laboratory coagulation testing [37]. POC devices could offer potential benefit to patients by providing an earlier diagnosis of VICC in rural healthcare settings, and reducing the

time to antivenom treatment. In LMIC settings, where the current standard is to measure the 20WBCT or Lee White clotting time, a POC device or the manual ACT method may improve accuracy to diagnose VICC. Increased sensitivity to detect VICC would ensure that more patients with systemic envenoming receive antivenom, whilst improved specificity would reduce the number of patients that unnecessarily receive antivenom, which is costly and often associated with a high risk of allergic reaction.

It should also be considered that the current thresholds for defining coagulopathy and administering antivenom, such as the 20WBCT in LMIC settings, or the coagulation thresholds of the snakebite bite severity score (SSS) in the USA [64], have not been optimised through clinical validation studies. For example, in a study of patients with VICC in Sri Lanka, a WBCT measurement interval of 15-minutes, rather than 20-minutes, was found to improve accuracy to detect VICC [65]. POC devices provide standardised and quantifiable measures of coagulation that can be used in future clinical studies to define evidence-based thresholds for administering antivenom, which may ultimately translate into better outcomes for patients. These studies must use clinically meaningful endpoints, to ensure that antivenom is administered to those in whom the benefits outweigh the risks.

### **Potential role of point-of-care devices in clinical research**

Many of the snakebite clinical trials that have been conducted in LMIC settings have not included any outcome measures based on laboratory coagulation assays [66]. Such assays require access to a reliable electricity supply, a centrifuge, a coagulation analyser, and appropriately trained laboratory technicians. There are substantial costs associated with setting up a laboratory facility for the purposes of a clinical trial, particularly if multiple laboratories are required across several recruitment sites, whilst funding for snakebite research has historically been limited [67]. Even if such capacity strengthening were to take place, it is unlikely that the facilities for undertaking coagulation studies would be sustainable in the light of ongoing maintenance costs.

These challenges have resulted in a situation where snakebite clinical trials based in high-income settings rely on gold standard laboratory-based coagulation study endpoints [68], whilst those in LMIC settings tend to use the 20WBCT [9]. Point-of-care devices could be the key to enabling the use of formal coagulation study endpoints in clinical trials, regardless of their setting.

Before POC tests can be advocated for use in snakebite clinical trials, their accuracy urgently needs to be assessed in prospective clinical observational studies. As demonstrated by O'Rourke et al in Australia and Senthilkumaran et al in India, accuracy can be evaluated by analysing blood samples in duplicate on a POC device and a validated laboratory-based analyser [37]. Ideally a range of POC devices that measure PT, ACT, and fibrinogen should be evaluated. Furthermore, it would be important to assess POC devices in diverse geographic settings including Africa, Asia, North and South America, and Australia. Variations in snake venom toxin compositions between biting species will mean that



different POC devices might be more or less useful in different geographic locations. Furthermore, it is important for future studies to go further than simply assessing whether POC devices can predict their corresponding laboratory-based assay. Of greater importance is whether the use of a POC device can meaningfully impact upon clinical and patient-centred outcomes [69], such as time-to-treatment, antivenom use, or frequency of bleeding events.

### **Potential role of point-of-care devices for *in vivo* pre-clinical research**

Because clinical trials are costly and time-consuming to complete, preclinical murine models of envenoming have been heavily relied upon to assess the efficacy of antivenoms before they are used in humans [70]. Ideally, antivenoms with promising preclinical efficacy should subsequently be assessed in human clinical trials, but many of the antivenoms marketed in resource limited settings have only been assessed preclinically [71].

The WHO Expert Committee on Biological Standardization recommends that antivenom efficacy should be confirmed in murine median effective dose ( $ED_{50}$ ) models prior to human use [72]. This assay involves co-administering a rapidly lethal dose of venom with antivenom to mice, with the binary measure of mortality used as the outcome measure. Despite several limitations, including growing recognition that this model does not reflect clinical snakebite [73], or the pharmacokinetics of envenoming [74], for now, such assays are the gold-standard [75].

Coagulopathy-based outcome measures are rarely used in preclinical research [76]. Literature on the use of handheld POC devices in rodent preclinical models is limited, with benchtop devices and ELISAs for measuring coagulation only occasionally being employed [77–79]. These devices require large volumes of whole blood or plasma, which typically necessitate sacrificing the animal. As handheld POCs require a reduced volume, multiple blood samples could be taken from each animal. This is known as ‘*microsampling*,’ which is an animal experimentation refinement technique encouraged by the National Centre for the Replacement, Refinement and Reduction of animals in Research (NC3Rs) that reduces the numbers of animals required for a study whilst increasing the amount of data generated [80,81].

By using low sample volumes, POC devices could be used to measure improvement in VICC, rather than simply rescue from lethal effect. Quantifiable assays, such as INR or fibrinogen, that can be recorded at multiple timepoints, would provide a more sensitive outcome measure, and provide kinetic information on the time to therapeutic effect and the occurrence of recurrent coagulopathy. As well as providing important efficacy readouts that align with clinical trial outcome measures [16], these approaches could reduce the number of mice needed to power a preclinical study, and lessen suffering through administration of lower doses of venom.

### **Cost considerations**

The affordability and potential cost-benefit of POC coagulation devices will be discussed in turn for high-income, middle-income, and low-income settings.

In high-income snakebite endemic settings, such as the USA and Australia, these devices are likely to be affordable, yet their costs would need to be justified given that laboratory-based coagulation studies are likely to be available. However, the study by O'Rourke et al, which was conducted in Australia, highlighted that many of the healthcare facilities based in the rural areas where snakebites tend to occur do not have access to on-site laboratory coagulation testing [37]. A POC device could streamline care by preventing unnecessary onward referral for coagulation testing of patients with snakebite that do not have VICC.

In middle-income settings, such as Brazil and India, certain POC devices may be affordable. The cost-benefit ratio may be particularly favourable given the high incidence of snakebite in these settings [1,82]. The most affordable POC device identified in this review was the microINR system, which costs 500 USD for the device and 2 USD per test cartridge. Considering that a course of antivenom treatment typically costs over 50 USD [83,84], and that a POC device could facilitate more effective allocation of antivenom, it is possible that the cost of the device would be off-set. Formal cost-effectiveness studies would be important to understand the indirect cost savings of implementing POC tests in these settings.

Unfortunately, in low-income settings access to essential diagnostics for a range of diseases of public health importance, including HIV and tuberculosis, is severely limited [85]. Thus, it is unlikely that funding would be allocated to rolling out POC devices for snakebite envenoming in these settings. A notable exception identified in this review is the manual ACT method. The consumables for this assay include a plastic or glass tube containing a small amount of either kaolin or celite, which are simply ground up rock or diatomaceous earth, respectively. One kilogram of celite costs approximately 20 USD, which would provide enough material to produce thousands of ACT tubes. Thus, the manual ACT method could be produced at a negligible additional cost to the 20WBCT or Lee White clotting test, whilst potentially offering improved accuracy and a more rapid result [54].

A final important consideration about the feasibility of using POC devices in low-income settings is their potential role in clinical research, including clinical trials. Although funding for snakebite research has historically been limited [67], the costs of these devices are within the limits of modest clinical research budgets, and they are more affordable than establishing laboratory facilities, which require dedicated personnel and a reliable electricity supply. Furthermore, the improved accuracy of POC devices, and their provision of a continuous outcome measure, as opposed to the binary readout of the 20WBCT, is likely to allow for a reduction in the sample size of a clinical trial, which could substantially reduce costs. The need to improve outcome measure reporting in snakebite clinical trials has recently been advocated for [66], and a group of leading global snakebite experts reached consensus that INR should ideally be measured in all future snakebite clinical trials, including those based in low-income settings [16].

## Conclusions

This review has identified a range of POC devices that show promise for diagnosing VICC without the need for laboratory facilities. Various devices that rely on a thrombin substrate-based endpoint should not be considered for evaluation, as existing mechanistic and clinical data suggest they will produce false negative results. However, POC INR devices that detect fibrin clot formation by measuring the rate of flow of the blood sample, and a recently marketed POC fibrinogen device, are particularly promising. Although POC devices remain prohibitively expensive for routine use in most low-income settings, they could be used as outcome measurement instruments in clinical trials. An exception is the manual ACT method, which may offer an affordable, rapid, and accurate bedside test for diagnosing VICC. POC devices could also support microsampling in preclinical studies, which would enable the development of clinically representative models associated with less animal suffering and greater richness of data. The devices shortlisted in this review should be prioritised for formal validation studies in preclinical and clinical studies of VICC, to better understand the extent of their utility in the field of snakebite envenoming.

**Figure 1a. Overview of the site of action of procoagulant snake venom toxins on the coagulation pathway.** The red boxes detail the major groups of coagulopathic venom toxins, their enzyme classification, and a non-exhaustive list of medically important snake species that utilise the toxin group. The dashed arrows indicate the site of the coagulation pathway where the major groups of coagulopathic venom toxins act.

Ca<sup>2+</sup>: calcium; FDPs: fibrin(ogen) degradation products; PL: phospholipid; and TF: tissue factor.

Adapted from “Coagulation Cascade”, by BioRender.com (2023). Retrieved from <https://app.biorender.com/biorender-templates>

**Figure 1b. Levels of measurement of each point-of-care device on the coagulation pathway.** The green boxes detail the names and assay types of the point-of-care devices that have been included in this review. The tails of the green arrows indicate where each assay’s activator acts on the coagulation pathway. The arrow heads highlight where the endpoint read of each assay exists on the coagulation pathway.

Ca<sup>2+</sup>: calcium; FDPs: fibrin degradation products; PL: phospholipid; and TF: tissue factor.

Adapted from “Coagulation Cascade”, by BioRender.com (2023). Retrieved from <https://app.biorender.com/biorender-templates>

**Figure 2. Comparison of laboratory and POC device INR by participant from previous studies (O’Rourke et al 2013, and Senthilkumaran et al 2014).** Figure 2a demonstrates the laboratory, i-STAT, CoaguChek S, and Alere INRatio2 INR values for fifteen

participants with *Daboia russelii* envenoming: the participants are ordered according to increasing laboratory INR values. Figure 2b shows the laboratory, i-STAT, CoaguChek S, and Alere INRatio2 INR values for three participants with *Echis carinatus* envenoming. Figure 2c describes the laboratory and i-STAT INR values for fifteen participants with Australian Elapid envenoming.

**Table 1. Summary of published literature on the use of POC devices in VICC**

<b>Author (year)</b>	<b>Geographic location</b>	<b>Sample size</b>	<b>Biting genus (sample size)</b>	<b>POC device (manufacturer); assay type</b>	<b>Findings</b>
Celenza (2010)	Australia	1	<i>Pseudonaja</i>	CoaguChek XS Plus (Roche); INR	The routine use of POC INR in an emergency department, for any disease, was evaluated against a laboratory INR gold standard. Of the 293 patients studied, one had snakebite. This

					was the only occasion where the POC INR produced a false negative result. The laboratory INR was >10; the paired POC INR was 1.4.
Cubitt (2013)	Australia	1	<i>Notechis</i>	CoaguChek (Roche); INR INRatio2 (Alere); INR Cobas h232 system (Roche); D-	This case report of <i>Notechis</i> bite described initial presentation to a small rural hospital where the INRatio2 POC device result was 1.3 (this was not confirmed by a laboratory INR). After transfer to a regional



				dimer	hospital, paired samples demonstrated a laboratory INR of >12 and a POC INR (CoaguChek) of 0.9. POC D-dimer (Cobas H232) was 0.38 mg/L whereas the laboratory D-dimer was reported as 812 mg/L.
O'Rourke (2013)	Australia	15	<i>Pseudonaja, Oxyuranus, Notechis, Pseudechis, and</i>	i-STAT (Abbott); INR	This prospective study compared the i-STAT POC device with laboratory INR in 15 participants with snakebite. i-STAT POC substantially

			<i>Acantho phis</i>		underestimated the INR in all cases with VICC. Three of the seven participants with VICC had a normal POC INR, and 1 of the 7 patients without laboratory confirmed VICC had an abnormal POC INR.
Senthilkumaran (2014)	India	18	<i>Daboia russelii, and Echis carinatu s</i>	CoaguChek (Roche); INR INRatio2 (Alere); INR i-STAT	This letter to the editor provided a narrative report highlighting that POC INR devices produce false negative results in patients with snakebite envenoming. The underlying data

				(Abbott); INR	were made available for this scoping review (appendix, p3). All three POC INR devices substantially underestimated the laboratory INR in patients with <i>Daboia russelii</i> envenoming (n=15), particularly when the laboratory INR was >4. The devices were accurate in patients with <i>Echis carinatus</i> envenoming, but there were only
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					three such cases, all of whom had a laboratory INR $\leq$ 4.3.
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**Table 2. Overview of handheld point-of-care coagulopathy devices**

Device name (manufacturer)	Blood or plasma (citrate d or native)	Sample collection	Sample volume (me)	Cost device (cost per test cartridge) USD*	Limit of detection	Confirmed battery operated	Method of measurement	Promising for snakebite
<b>INR</b>								
CoaguChek Pro II (Roche)	Blood (native)	Capillary or venous	8 $\mu$ L	\$1,900 (\$4)	INR 0.8-8.0	Yes	Activator: human recombinant tissue factor Endpoint: electrochemical detection of thrombin dependent cleavage of an electrochemical substrate.	No (thrombin endpoint prone to false negative results)

Hemochron Signature Elite (Accriva Diagnostics)	Blood (citrate d or native)	Capillary or venous	15 $\mu$ L	\$21,400 (\$11)	INR 0.8-10	Yes	Activator: thromboplastin Endpoint: optical detection of the rate of flow of the blood sample.	No (prohibitively expensive)
Xprecia Stride (Siemens)	Blood (native)	Capillary or venous	6 $\mu$ L	NA	INR 0.8–8.0	Yes	Activator: thromboplastin Endpoint: electrochemical detection of thrombin dependent cleavage of an electrochemical substrate.	No (thrombin endpoint prone to false negative results)
microINR (iLine Microsystems)	Blood (native)	Capillary or venous	3 $\mu$ L	\$500 (\$2)	INR 0.8-8.0	Yes	Activator: thromboplastin Endpoint: optical detection of the rate of flow of the blood sample.	Yes
Coag-Sense (CoaguSense Inc)	Blood (native)	Capillary or venous	12 $\mu$ L	\$1,100 (\$1.5)	INR 0.8-8.0	Yes	Activator: thromboplastin Endpoint: optical detection of the rate of flow of the blood sample.	Yes
i-STAT (Abbott)	Blood (native)	Capillary or venous	20 $\mu$ L	\$3,500 (\$6)	INR 0.9-8.0	Yes	Activator: human recombinant thromboplastin Endpoint: electrochemical detection of	No (thrombin endpoint prone

							thrombin dependent cleavage of an electrochemical substrate.	to false negative results)
LumiraDx INR (LumiraDx)	Blood (native)	Capillary or venous	8 $\mu$ L	\$5,900 (\$4)	INR 0.8-7.5	Yes	Activator: recombinant thromboplastin  Endpoint: thrombin dependent cleavage of a quenched fluorescent substrate. The fluorescent signal is detected and quantified.	No  (thrombin endpoint prone to false negative results)
<b>Activated partial thromboplastin time (aPTT)</b>								
CoaguChek Pro II (Roche)	Blood (native)	Capillary or venous	8 $\mu$ L	\$1,900 (\$4)	20-130 seconds	Yes	Activator: celite and phospholipids.  Endpoint: electrochemical detection of thrombin dependent cleavage of an electrochemical substrate.	No  (thrombin endpoint prone to false negative results)
Hemochron Signature Elite (Accriva Diagnostics)	Blood (citrate d or native)	Venous	45 $\mu$ L	\$21,400 (\$11)	20-400 seconds	Yes	Activator: kaolin and phospholipids.  Endpoint: optical detection of the rate of flow of the blood sample.	No  (prohibitively expensive)
<b>Activated clotting time (ACT)</b>								

i-STAT (Abbott)	Blood (native)	Venous	40 $\mu$ L	\$3,500 (\$14)	50- 1000 seconds	Yes	Activator: celite or kaolin cartridges available. Endpoint: electrochemical detection of thrombin dependent cleavage of an electrochemical substrate.	No (thrombin endpoint prone to false negative results)
Hemochron Signature Elite (Accriva Diagnostics)	Blood (native)	Venous	200 $\mu$ L	\$21,400 (\$11)	0-1005 seconds	Yes	Activator: celite or kaolin cartridges available. Endpoint: optical detection of the rate of flow of the blood sample.	No (prohibitively expensive)
<b>Fibrinogen</b>								
qLabs FIB system (Stago)	Blood (citrate d or native) or	Venous	15 $\mu$ L	\$1,900 (\$21)	1.0-4.0 g/L	Yes	Activator: thrombin-coated channels Endpoint: detection of the rate of flow of the blood sample by an electrometer	Yes

	plasma (citrate d)							
<b>D-dimer and other fibrinogen degradation products</b>								
Cobas h232 system D-dimer (Roche)	Blood (Heparinised)	Venous	150 µL	\$2,400 (\$12)	0.1 - 4.0 µg/ mL	Yes	Test strips contain one gold labelled and one biotinylated monoclonal antibody against fibrin degradation products. In the presence of d-dimer a sandwich complex accumulates and produces a red coloured line on the strip, the intensity of which is quantified by an optical measuring system.	No (false negative result in a case report of <i>Notechis</i> envenoming [39]).
PL mini handheld D- dimer	Blood	Capillary or venous	30 µL	\$2,100 (\$8)	0.1- 10.0 µg/mL	Yes	The PL mini strips contain antibodies fluorescently labelled with chelated lanthanide, which are used to quantify	Yes (not in snake venoms)



(PremaLabs)							particular biomarkers. When UV light is shone on the test strip a fluorescent signal is produced that is converted to a digital value, which quantifies the amount of antigen-antibody complexes on the test strip.	predominant in TLEs)
PL mini handheld FDP (PremaLabs)	Blood	Capillary or venous	30 $\mu$ L	\$2,100 (\$14)	2.5-80.0 $\mu$ g/mL	Yes		Yes
LumiraDx D-Dimer	Blood or plasma (citrate d)	Capillary or venous	15 $\mu$ L	\$5,900 (\$5)	0.19-4.0 $\mu$ g/mL	Yes	Test strips contain antibodies against fibrin degradation products that are bound to magnetic particles and fluorescent latex particles. In the presence of d-dimer these form complexes that are held in place by a magnet, and the fluorescent signal is quantitatively measured.	Yes (not in snake venoms predominant in TLEs)

\* Device and cartridge costs are estimates based on quotes provided by commercial providers. True costs are likely to vary between commercial providers and by geographic location.

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## Appendix

### PRISMA preferred reporting items extension for scoping reviews checklist [17]

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED
<b>TITLE</b>			
Title	1	Identify the report as a scoping review.	Yes
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that	Yes

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED
		relate to the review questions and objectives.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Yes
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Yes
<b>METHODS</b>			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	No
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Yes
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Yes
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Yes
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Yes
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g.,	Yes

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED
		calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Yes
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Yes
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Yes
<b>RESULTS</b>			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Yes
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Yes
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Yes
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Yes
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Yes
<b>DISCUSSION</b>			



SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Yes
Limitations	20	Discuss the limitations of the scoping review process.	Yes
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Yes
<b>FUNDING</b>			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Yes

JBIG = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

\* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision.

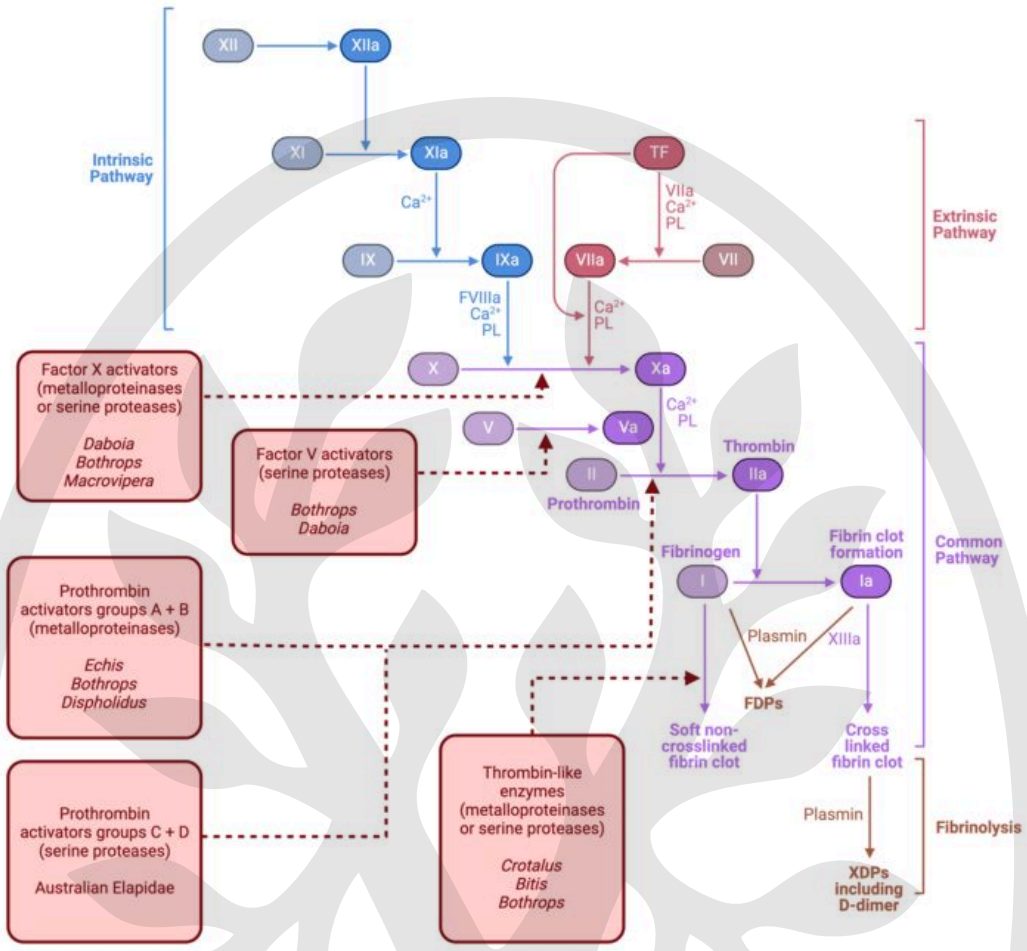
This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

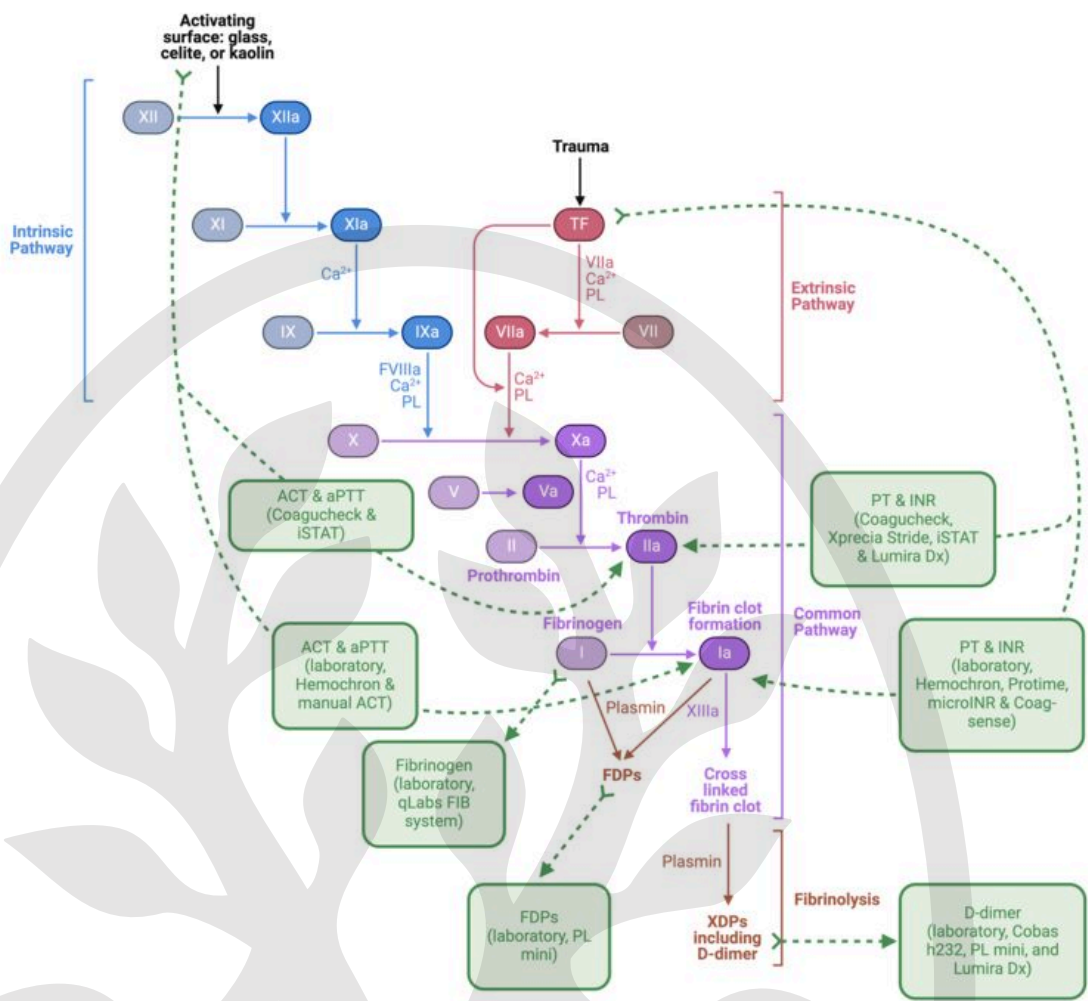
**Underlying data for the assessment of three POC INR devices against a laboratory gold standard in patients with *Daboia russelii* or *Echis carinatus* envenoming in India (Senthilkumaran et al 2014)**

Age	Gender	Snake species	Laboratory prothrombin time	Laboratory INR	Laboratory APTT	Laboratory fibrinogen	Alere INRatio2 (Alere)	CoaguChek S (Roche Diagnostics)	i-STAT (Abbott)
23	M	<i>Daboia russelii</i>	100	13.5	150	0.3	1.3	1.2	1.3
41	F	<i>Daboia russelii</i>	98	13.1	125	0.4	1.2	1.1	1.2
51	F	<i>Daboia russelii</i>	85	10.9	98	0.5	1.1	1.1	1.2
46	M	<i>Daboia russelii</i>	90	11.7	110	0.4	1.2	1.1	1.1
27	M	<i>Daboia russelii</i>	88	11.4	106	0.7	1.1	1.2	1.2
22	F	<i>Daboia russelii</i>	94	13.5	118	0.5	1.3	1.4	1.6
26	M	<i>Echis carinatus</i>	42	4.3	55	1.6	3.9	4.1	3.8
36	M	<i>Daboia russelii</i>	70	8.4	90	0.5	1.3	1.5	1.7
56	M	<i>Daboia russelii</i>	100	13.5	160	0.8	1.9	1.8	1.5
29	F	<i>Daboia russelii</i>	38	3.8	45	0.6	2.1	2.4	1.9

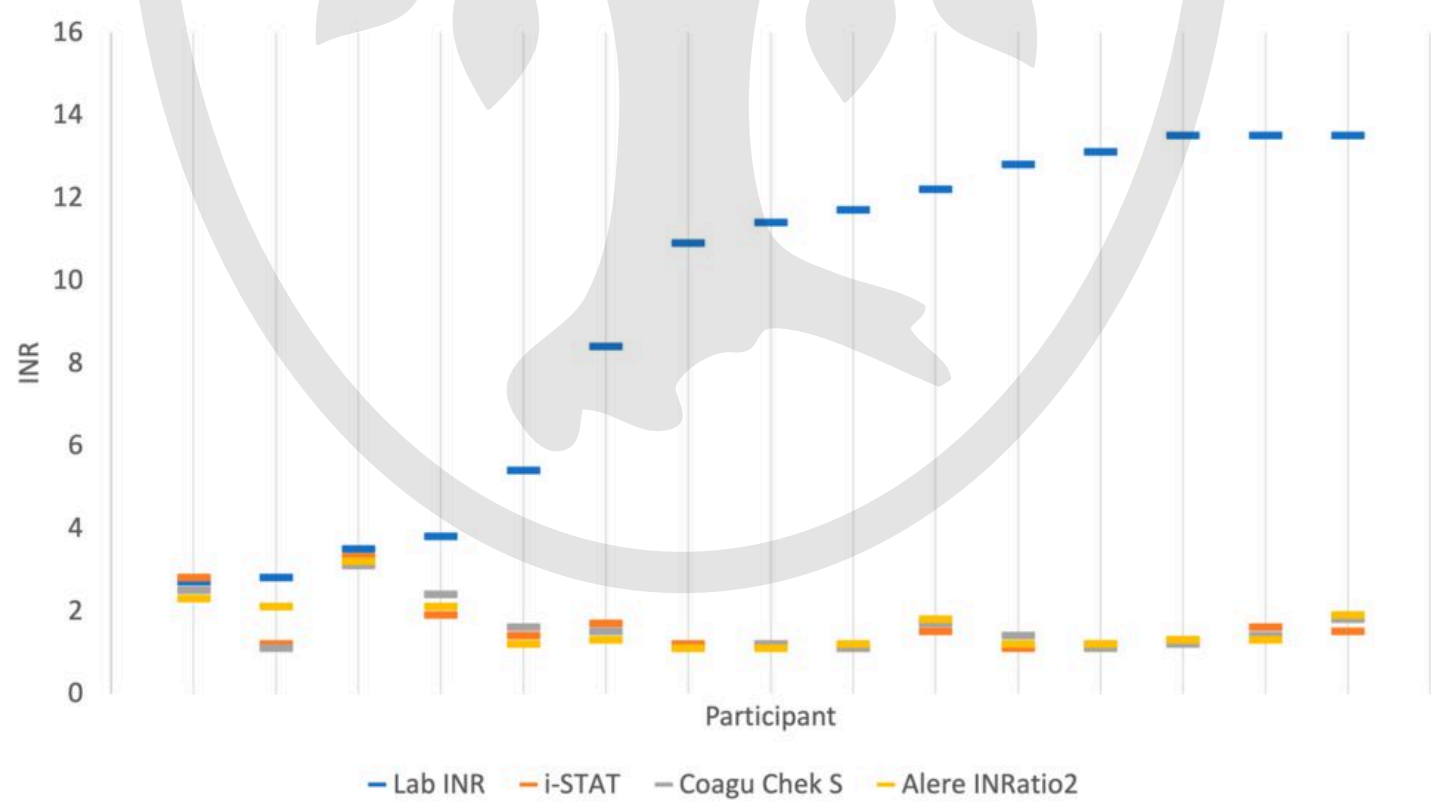
34	M	<i>Echis carinatus</i>	40	4.1	50	1.8	3.8	3.9	3.8
31	F	<i>Daboia russelii</i>	30	2.8	45	2.3	2.1	1.1	1.2
30	F	<i>Daboia russelii</i>	96	12.8	120	0.6	1.2	1.4	1.1
41	M	<i>Daboia russelii</i>	29	2.7	40	2.4	2.3	2.5	2.8
68	M	<i>Daboia russelii</i>	93	12.2	115	0.7	1.8	1.7	1.5
60	M	<i>Echis carinatus</i>	38	3.8	50	1.3	3.4	3.2	3.3
45	F	<i>Daboia russelii</i>	36	3.5	69	1.1	3.2	3.1	3.3
46	M	<i>Daboia russelii</i>	50	5.4	65	0.9	1.2	1.6	1.4

aPTT: activated partial thromboplastin time; INR: international normalized ratio



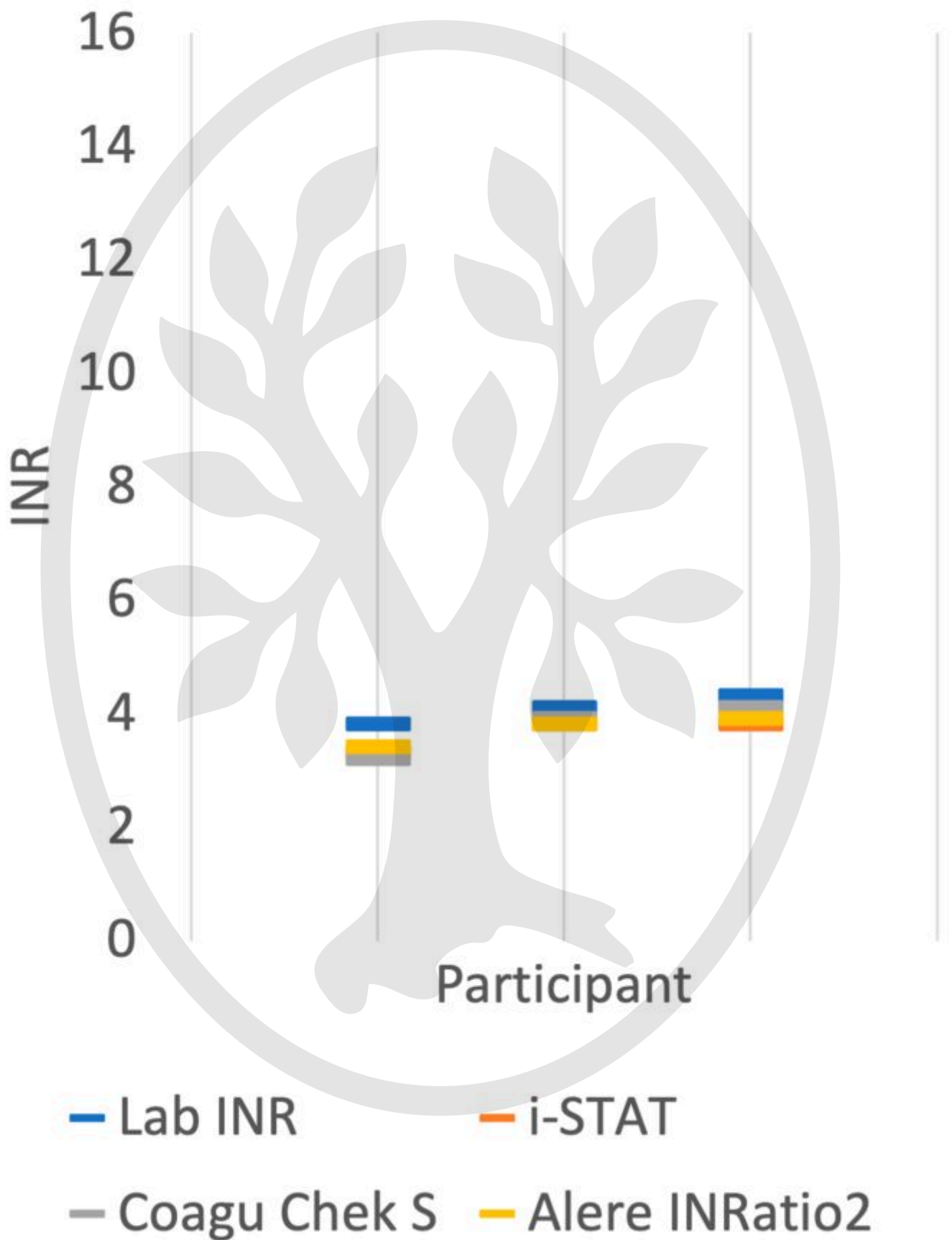


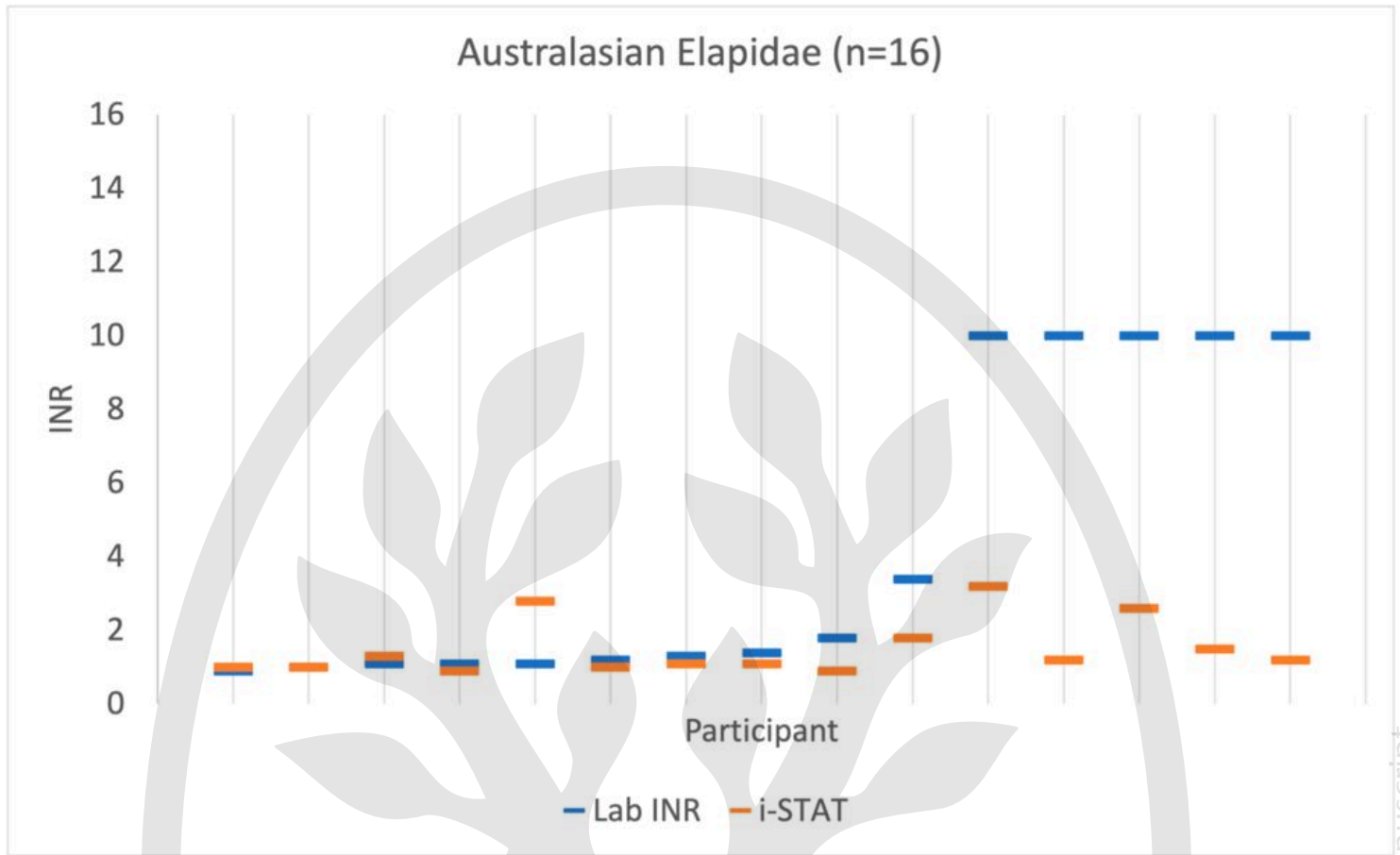
*Daboia russelii* (n=16)





# *Echis carinatus* (n=3)







# Handheld point-of-care devices for snakebite coagulopathy: a scoping review

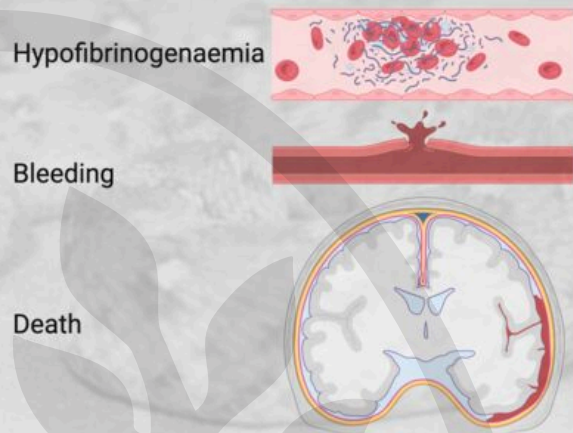
## The problem

- Snakebites cause 94,000 deaths each year.
- Most occur in remote tropical settings where laboratory facilities are unavailable.
- Improved diagnostics are needed to more accurately diagnose VICC and reduce the time to treatment.

## Aim

- To shortlist commercially available point-of-care (POC) devices to diagnose VICC.

## Snakebite associated venom induced consumption coagulopathy (VICC)



**Literature search for commercially available POC device assays**  
-16 identified

**Excluded device assays**  
-2 failed in clinical studies  
-5 inaccurate in hypofibrinogenaemia  
-3 prohibitively expensive

**Shortlisted device assays:**  
-MicroINR (INR)  
-Coag-sense (INR)  
-qLabs FIB system (fibrinogen)  
-PL mini (D-dimer)  
-LumiraDx (D-dimer)  
-PL mini (FDP)