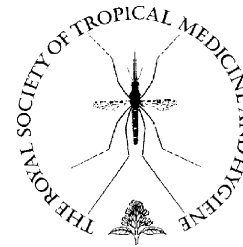




available at [www.sciencedirect.com](http://www.sciencedirect.com)



journal homepage: [www.elsevierhealth.com/journals/trst](http://www.elsevierhealth.com/journals/trst)



## LEADING ARTICLE

# Unscrupulous marketing of snake bite antivenoms in Africa and Papua New Guinea: choosing the right product—‘What’s in a name?’

David A. Warrell\*

Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

Available online 21 March 2008

### KEYWORDS

Snake bite;  
Antivenom;  
Snake taxonomy;  
*Echis ocellatus*;  
West Africa;  
*Oxyuranus scutellatus canni*;  
Papua New Guinea

**Summary** Snake bite envenoming, mainly caused by the saw-scaled or carpet viper (*Echis ocellatus*), is a neglected disease of West Africa. Specific antivenoms can save life and limb but, for various reasons, supply of these essential drugs to Africa has dwindled to less than 2% of estimated requirements. Other problems include maldistribution, inadequate conservation and inappropriate clinical use of antivenoms. In the face of this crisis, several promising new antivenoms have been developed. However, some dangerously inappropriate products of Indian origin are being marketed by unscrupulous manufacturers or distributors in Africa and Papua New Guinea, with disastrous results. A major source of confusion is labelling antivenom with ambiguous snake names that fail to distinguish the Asian species whose venoms are used in their production from the local snakes whose venoms are antigenically dissimilar.

© 2007 Royal Society of Tropical Medicine and Hygiene. Published by Elsevier Ltd. All rights reserved.

## 1. Saw-scaled viper bites in West Africa

“In January, 1959, Mons. P.H. Alexandre, a resident of that part of Togo which was then administered by France, provided me with such extraordinary information about the incidence of *Echis carinatus* [the saw-scaled or carpet viper] in Togo and the serious mortality which had resulted from its bite, that I was prompted to enquire into the incidence and effects of *Echis* bite throughout Africa.” (Charles R.S. Pitman, 1973)

Throughout most of the African mainland and on some of its offshore islands, snake bites, whilst not uncommon, are rarely fatal. In marked contrast, there are many areas

of West Africa’s Guinea savannah where snakes are such an environmental and occupational hazard that scarcely a family has escaped the lethal or maiming effects of their venoms. Africa’s most populous country, Nigeria, records 174 snake bites/100 000 population/year, where one species, the saw-scaled or carpet viper (*Echis ocellatus*), is responsible for 90% of bites and 60% of deaths (Nasidi, 2007). In fact, this species stands out as being by far the most important cause of fatal or debilitating snake bite in sub-Saharan Africa north of the Equator, especially in Burkina Faso, Ghana, Togo, Benin, Nigeria, Cameroon, Central African Republic, Sudan, northern Kenya and Somaliland. The enormous significance of this unimpressive-looking snake was suggested by French and English reports from West Africa in the 1950s (Warrell and Arnett, 1976) but was not fully comprehended until the publication of Charles Pitman’s fascinating review in 1973 (see above). *Echis* venom toxins cause potentially fatal haemorrhage or shock in human victims while their locally

\* Tel.: +44 1865 221332/220968; fax: +44 1865 220984.  
E-mail address: [david.warrell@ndm.ox.ac.uk](mailto:david.warrell@ndm.ox.ac.uk)

necrotic effects may result in permanent physical handicap (Warrell et al., 1977). Fortunately, the systemic effects are readily reversible by specific antivenom unless haemorrhagic stroke has already supervened. Following the administration of a single dose of a potent specific antivenom, such as South African Institute for Medical Research (SAIMR) *Echis* antivenom (South African Vaccine Producers, Johannesburg, South Africa) or EchiTAb™ (MicroPharm, Wales, UK), spontaneous systemic bleeding stops within 2 h and coagulopathy is corrected within 6 h in the majority of cases (Meyer et al., 1997; Warrell et al., 1974), assuming, of course, that the patient manages to reach medical care before suffering catastrophic bleeding or shock, that they are treated by properly trained medical staff and that appropriate antivenom is available.

## 2. Crisis in antivenom supply in Africa

Tragically, these criteria are rarely fulfilled in 21st century rural Africa. The crisis in antivenom supply to sub-Saharan Africa has been widely publicised (Chippaux, 2005; Gutiérrez et al., 2006; Laloo et al., 2002; Theakston and Warrell, 2000; Theakston et al., 2003). It was precipitated by the withdrawal from antivenom production of Behringwerke A.G. (Marburg, Germany) and by delayed and decreased production by the other major European producer, Sanofi-Pasteur (Lyon, France). Around that time, Africa's only indigenous producer, SAIMR, was facing problems associated with privatisation and lack of capital to replace its aging equipment. These events conspired to reduce the supply of antivenom to Africa to <20 000 ampoules/year, set against the estimated need for 1.5–2 million doses/year (Stock et al., 2007), of which Nigeria alone requires 245 000 vials (Nasidi, 2007).

To fill this gap, R.D.G. Theakston and I appealed to ten leading international antivenom producers to develop new antivenoms for the African market, targeting especially 'the big three' medically important snakes of the African savannah region, saw-scaled viper (*E. ocellatus*), puff adder (*Bitis arietans*) and black-necked spitting cobra (*Naja nigricollis*). In response, a 'Pan African' polyspecific antivenom was raised by the Instituto Nacional de Salud, Bogota, Colombia (Laing et al., 2003a, 2003b), a trispecific antivenom by the Instituto Clodomiro Picado, Costa Rica (Gutiérrez et al., 2005), a monospecific *Echis* antivenom by MicroPharm, UK, and a polyspecific African Antivipmyn® by Laboratorios Silanes, Mexico City (Chippaux et al., 2007).

## 3. Marketing of inappropriate antivenoms in Africa

While Africa awaits these promising new antivenoms, anarchy reigns! Ministries of Health, vainly trying to satisfy their countries' needs, have ordered foreign antivenoms whose trade descriptions promised efficacy but whose therapeutic effects were dire.

A case in point is reported by Visser et al. (2008) in this issue of *Transactions*. In 2003, the Ghana Ministry of Health switched from ordering Sanofi-Pasteur's FAV-Afrique™ antivenom to a 'Polyvalent Snake Antitoxin—Africa' manufactured in India, which was cheaper but was claimed to be

effective against venoms of eight species of African snakes and the West Asian saw-scaled viper, *E. carinatus multisquamatus*. At Mathias Hospital in central Ghana, this change resulted in a more than six-fold increase in case fatality to >12% in patients envenomed by *E. ocellatus*. Two batches of this antivenom tested at the WHO Collaborative Centre for the Control of Antivenoms at the Liverpool School of Tropical Medicine proved only minimally effective against *E. ocellatus* venom (G.D. Laing and R.D.G. Theakston, personal communication, 2005).

There was a very similar episode at Ginter Memorial Hospital, Bambar, northeastern Nigeria, in the early 1970s. A politically motivated change from South African (SAIMR) *Echis* antivenom to an antivenom manufactured in Iran (raised against West Asian *Echis* venom) led to an increase in case fatality from <7% to 37.5%. Failure of hospital treatment also encourages a return to dangerous and ineffective traditional remedies (Warrell and Arnett, 1976).

Inappropriate foreign antivenoms have found their way into other markets across Africa. In The Gambia, the Royal Victoria Teaching Hospital in Banjul is supplied with an antivenom from India "...prepared by hyperimmunizing horses against the venom of ... Black Mamba, Gaboon Viper, Russell's Viper and Saw-Scaled Viper". The first two of these species are African but do not occur in The Gambia but the last two are Indian species, totally irrelevant in an antivenom intended for use in Africa. Not surprisingly, this antivenom proved clinically ineffective in Banjul.

In all three cases, labelling of antivenom with the name 'Saw-Scaled Viper' was misleading because the composition and immunogenicity of the venoms of the Asian taxa, *E. carinatus* and *E. c. multisquamatus*, differ greatly from those of the West African species, *E. ocellatus* and *E. leucogaster*. Even the standard Indian polyvalent antivenoms intended for use in South Asia have been marketed blatantly in Africa. Their labels and package inserts include the words 'Cobra' and 'Saw-Scaled Viper', making them appear, to the uninitiated, suitable for the local snake bite victims in Africa. Use of English snake names alone, without the niceties of geographical and taxonomic precision (implying venom diversity), can be a prescription for therapeutic disaster.

When government supply fails, patients and their families must search for antivenom in private pharmacies. In Nigeria, this may involve long journeys to state capitals, leaving the patient bleeding to death in a district hospital. Buyers may fall foul of other creative commercial strategies such as re-labelling of misappropriated, expired government stocks and even the sale of fake products (Theakston et al., 2003).

## 4. Antivenom problems in Papua New Guinea

These irregularities are not confined to Africa. In Papua New Guinea (PNG), where snake bites are common and case fatality is high, antivenom is scarce and often unavailable (Laloo et al., 1995; McGain et al., 2004). Recently, polyvalent antivenoms manufactured by two Indian companies for bites by Indian cobra, krait, Russell's viper and saw-scaled viper have appeared in local pharmacies, costing 1200–2500 Kina (£214–447) per vial (David Williams, personal communication, December 2007). These antivenoms are not appropriate for treatment of enven-

oming by the local elapid snakes such as Papuan taipans (*Oxyuranus scutellatus canni*). In December 2007, the Health and HIV/AIDS Minister, Mr Sasa Zibe, who wished to prove allegations that unregistered antivenoms were being sold illegally without doctors' prescriptions, visited a pharmacy posing as an ordinary purchaser. He was angered to be offered Indian antivenom for 2500 Kina (£447) per vial as he had heard that a number of people had died after using this product (Papua New Guinea Post-Courier, 2007a). Another scandal in PNG is the theft from the Health Department's Area Medical Store of government stocks of expensive but highly effective antivenoms manufactured by Commonwealth Serum Laboratories (Parkville, Australia) and their resale on the open market at 2300–8300 Kina (£415–1498) per vial (Papua New Guinea Post-Courier, 2007b).

## 5. Conclusions and solutions

To improve the treatment of snake-bitten patients in Africa and PNG, many different problems must be tackled. Larger quantities of better quality, affordable antivenom are urgently needed, but equally important are their distribution to affected areas, conservation in an adequate cold chain and their correct use by properly trained staff. These aims are being strongly promoted by a new WHO initiative that offers expert advice to help national manufacturers improve their antivenoms through a process of pre-qualification (WHO, 2007a, 2007b).

The tragedies detailed in this article are a warning to antivenom manufacturers and distributors and to those responsible for purchasing antivenom for their country's use. Foreign antivenoms bearing snake names that seem relevant to national needs may prove woefully ineffective in clinical use.

**Funding:** None.

**Conflicts of interest:** None declared.

**Ethical approval:** Not required.

## References

- Chippaux, J.P., 2005. Ophidian envenomations and emergencies in sub-Saharan Africa. *Bull. Soc. Pathol. Exot.* 98, 263–268 [in French].
- Chippaux, J.P., Massougbdji, A., Stock, R.P., Alagon, A., Investigators of African Antivipmyn® in Benin, 2007. Clinical trial of an F(ab')<sub>2</sub> polyvalent equine antivenom for African snake bites in Benin. *Am. J. Trop. Med. Hyg.* 77, 538–546.
- Gutiérrez, J.M., Rojas, E., Quesada, L., León, G., Núñez, J., Laing, G.D., Sasa, M., Renjifo, J.M., Nasidi, A., Warrell, D.A., Theakston, R.D., Rojas, G., 2005. Pan-African polyspecific antivenom produced by caprylic acid purification of horse IgG: an alternative to the antivenom crisis in Africa. *Trans. R. Soc. Trop. Med. Hyg.* 99, 468–475.
- Gutiérrez, J.M., Theakston, R.D., Warrell, D.A., 2006. Confronting the neglected problem of snake bite envenoming: the need for a global partnership. *PLoS Med.* 3, e150.
- Laing, G.D., Harrison, R.A., Theakston, R.D., Renjifo, J.M., Nasidi, A., Gutierrez, J.M., Warrell, D.A., 2003a. Polyspecific snake antivenom may help in antivenom crisis. *BMJ* 326, 447.
- Laing, G.D., Renjifo, J.M., Ruiz, F., Harrison, R.A., Nasidi, A., Gutierrez, J.M., Rowley, P.D., Warrell, D.A., Theakston, R.D., 2003b. A new Pan African polyspecific antivenom developed in response to the antivenom crisis in Africa. *Toxicon* 42, 35–41.
- Laloo, D.G., Trevett, A.J., Saweri, A., Naraqi, S., Theakston, R.D., Warrell, D.A., 1995. The epidemiology of snake bite in Central Province and National Capital District, Papua New Guinea. *Trans. R. Soc. Trop. Med. Hyg.* 89, 178–182.
- Laloo, D.G., Theakston, R.D., Warrell, D.A., 2002. The African challenge. *Lancet* 359, 1527.
- McGain, F., Limbo, A., Williams, D.J., Didei, G., Winkel, K.D., 2004. Snakebite mortality at Port Moresby General Hospital, Papua New Guinea, 1992–2001. *Med. J. Aust.* 181, 687–691.
- Meyer, W.P., Habib, A.G., Onayade, A.A., Yakubu, A., Smith, D.C., Nasidi, A., Daudu, I.J., Warrell, D.A., Theakston, R.D., 1997. First clinical experiences with a new ovine Fab *Echis ocellatus* snake bite antivenom in Nigeria: randomized comparative trial with Institute Pasteur Serum (Ipser) Africa antivenom. *Am. J. Trop. Med. Hyg.* 56, 291–300.
- Nasidi, A., 2007. Snakebite as a serious public health problem for Nigeria and Africa. Presented at WHO Consultative Meeting on Rabies and Envenomings: A Neglected Public Health Issue, Geneva, Switzerland, 10 January 2007. <http://www.who.int/bloodproducts/animal.sera/A.Nasidi.pdf> [accessed 14 November 2007].
- Papua New Guinea Post-Courier, 2007a. 'Caught out!', Port Moresby, 5th December 2007. <http://www.postcourier.com.pg/20071205/news.htm> [accessed 13 December 2007].
- Papua New Guinea Post-Courier, 2007b. 'Snakebite serum stolen and peddled', Port Moresby, 25 June 2007. <http://www.postcourier.com.pg/20070625/mohome.htm> [accessed 13 December 2007].
- Pitman, C.R.S., 1973. The saw-scaled viper or carpet viper (*Echis carinatus*) in Africa and its bite. *J. Herpetol. Ass. Afr.* 9, 6–34.
- Stock, R.P., Massougbdji, A., Alagón, A., Chippaux, J.P., 2007. Bringing antivenoms to Sub-Saharan Africa. *Nat. Biotechnol.* 25, 173–177.
- Theakston, R.D., Warrell, D.A., 2000. Crisis in snake antivenom supply for Africa. *Lancet* 356, 2104.
- Theakston, R.D., Warrell, D.A., Griffiths, E., 2003. Report of a WHO workshop on the standardization and control of antivenoms. *Toxicon* 41, 541–557.
- Visser, L.E., Kyei-Faried, S., Belcher, D.W., Geelhoed, D.W., Schagen van Leeuwen, J., van Roosmalen, J., 2008. Failure of a new antivenom to treat *Echis ocellatus* snake bite in rural Ghana: the importance of quality surveillance. *Trans. R. Soc. Trop. Med. Hyg.* 102, 445–450.
- Warrell, D.A., Arnett, C., 1976. The importance of bites by the saw-scaled or carpet viper (*Echis carinatus*): epidemiological studies in Nigeria and a review of the world literature. *Acta Trop.* 33, 307–341.
- Warrell, D.A., Davidson, N.M., Ormerod, L.D., Pope, H.M., Watkins, B.J., Greenwood, B.M., Ried, H.A., 1974. Bites by the saw-scaled or carpet viper (*Echis carinatus*): trial of two specific antivenoms. *Br. Med. J.* 4, 437–440.
- Warrell, D.A., Davidson, N.McD., Greenwood, B.M., Ormerod, L.D., Pope, H.M., Watkins, B.J., Prentice, C.R., 1977. Poisoning by bites of the saw-scaled or carpet viper (*Echis carinatus*) in Nigeria. *Q. J. Med.* 46, 33–62.
- WHO, 2007a. Prequalification programme. A United Nations Programme managed by WHO. WHO, Geneva, Switzerland. <http://www.who.int/prequal/> [accessed 14 November 2007].
- WHO, 2007b. Rabies and Envenomings: A Neglected Public Health Issue —Consultative Meeting. WHO, Geneva, Switzerland. [http://www.who.int/bloodproducts/animal.sera/rabies\\_envenomings/en/index.html](http://www.who.int/bloodproducts/animal.sera/rabies_envenomings/en/index.html) [accessed 14 November 2007].