VI Reunión de la Triple Hélice en Farmacia

Vinculaciones formales y efectivas con sectores clave para la Farmacia-Industria

México, D.F. noviembre, 2017

Jorge Paniagua PhD
Consultor Senior
Suiza

AMEFFAR

Disclosure

Jorge Paniagua PhD

Consultor Senior
Laboratorios Silanes /
Instituto Bioclon

Cómo desarrollar (1) y fabricar (2) un antiveneno (3) para tratar intoxicaciones (4)?

Cómo desarrollar (1) y fabricar (2) un antiveneno (3) para tratar intoxicaciones (4)?

A través de vinculaciones efectivas

Desarrollo

- **Soporte científico sólido**.

- Epidemiological information
- Biological information
- Venom research
- Reactivity profile

- Venoms suppliers
- Immunization schedule
- Antibodies production
- Recognition profile
- Preclinical work
- Scale up production

- Regulatory strategy

Diseño de un antiveneno

Desarrollo

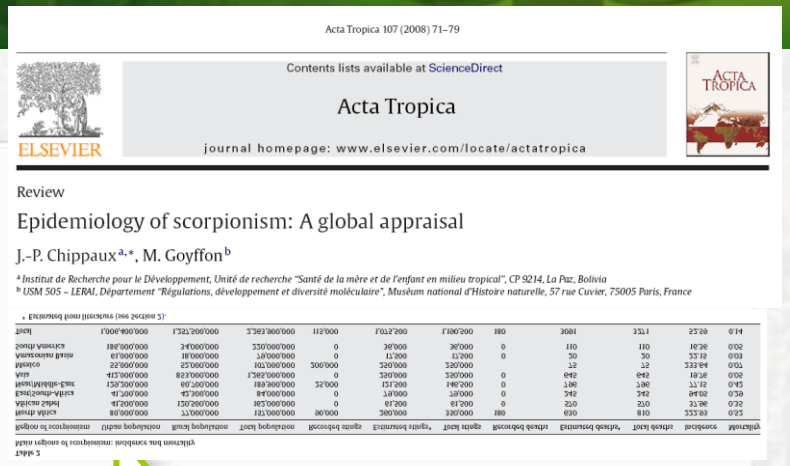
Sector salud y sector académico

- Strong scientific support.

- **Información Epidemiológica**
- Biological information
- Venom research
- Reactivity profile

- Venoms suppliers
- Immunization schedule
- Antibodies production
- Recognition profile
- Preclinical work
- Scale up production

- Regulatory strategy


Acta Tropica 107 (2008) 71–79

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Review

Epidemiology of scorpionism: A global appraisal

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[a] Institut de Recherche pour le Développement, Unité de recherche "Santé de la mère et de l'enfant en milieu tropical", CP 9214, La Paz, Bolivia
[b] USM 505 – LERAI, Département "Régulations, développement et diversité moléculaire", Muséum national d'Histoire naturelle, 57 rue Cuvier, 75005 Paris, France

Diseño de un antiveneno

Desarrollo

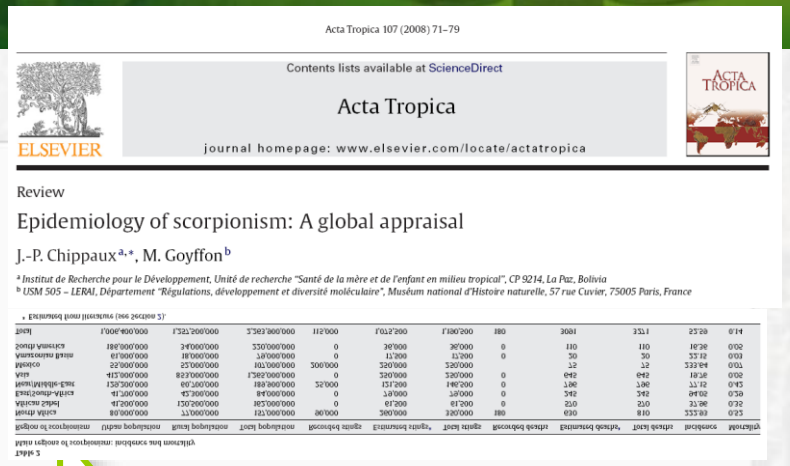
Sector salud y sector académico

- Strong scientific support.

- Epidemiological information
- **Biología de las especies**
- Venom research
- Reactivity profile

- Venoms suppliers
- Immunization schedule
- Antibodies production
- Recognition profile
- Preclinical work
- Scale up production

- Regulatory strategy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Antivenom

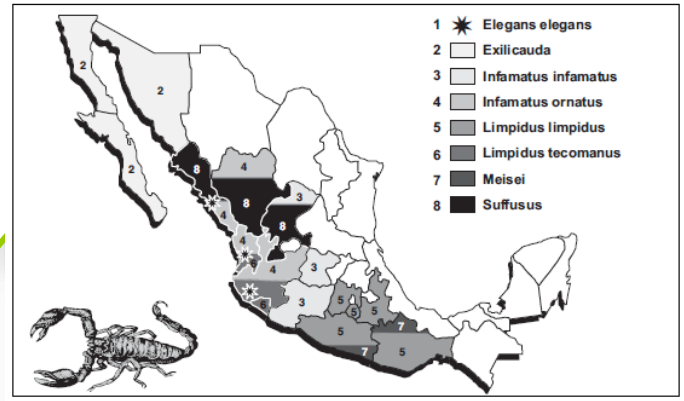


Figura 4. Distribución en México de las ocho especies más peligrosas del género Centruroide.

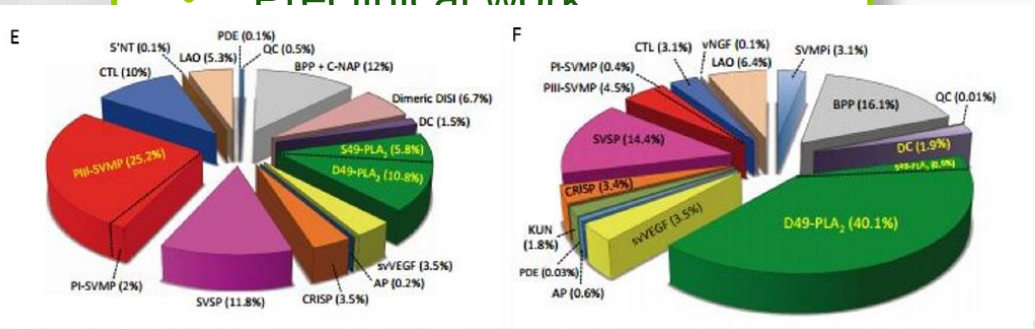
Desarrollo

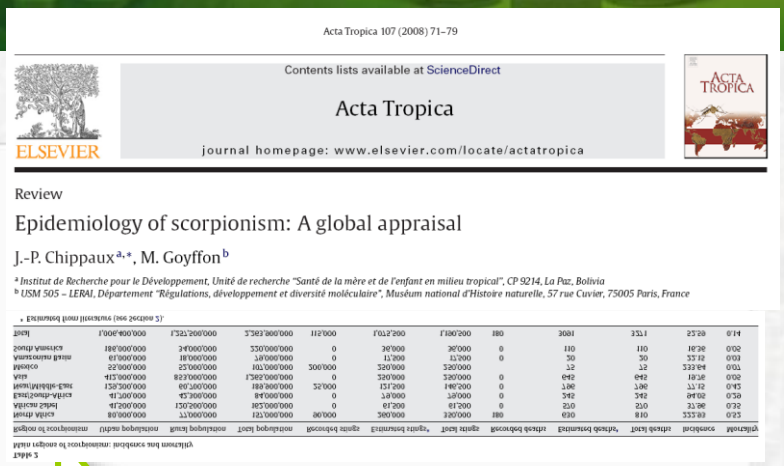
Sector salud y sector académico

- Strong scientific support.

- Epidemiological information
- Biological information
- **Componentes del veneno**
- Reactivity profile

- Venoms suppliers
- Immunization schedule
- Antibodies production
- Recognition profile
- Preclinical work

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Antivenom

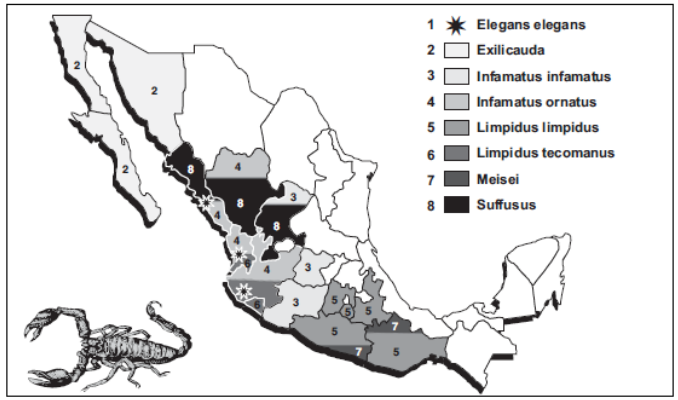


Figura 4. Distribución en México de las ocho especies más peligrosas del género Centruroide.

Desarrollo

Sector salud y sector académico

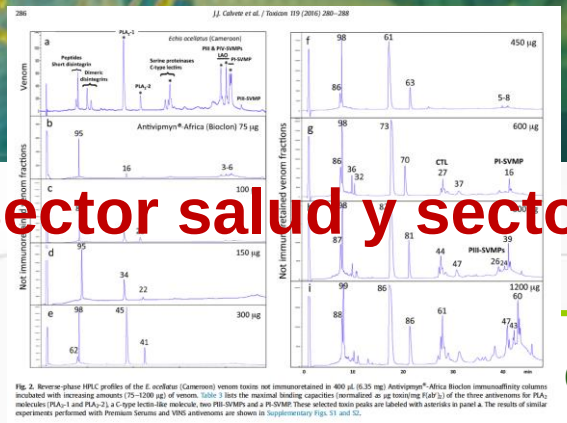
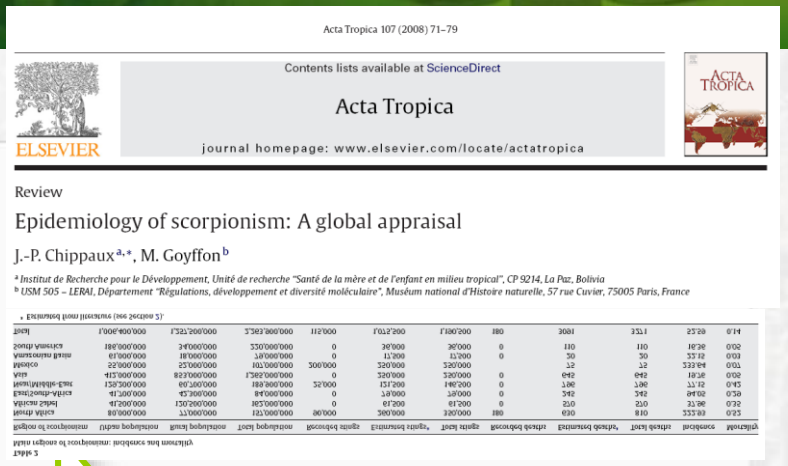


Fig. 2. Reverse-phase HPLC profiles of the *E. ocellatus* (Cameroon) venom toxins not immunoretained in 400 µL (6.35 mg) Antivipmyn®-Africa Bioclon immunoaffinity columns incubated with increasing amounts (75–1200 µg) of venom. Table 3 lists the maximal binding capacities (normalized as µg toxin/mg $F(ab')_2$) of the three antivenoms for PLA_2 molecules (PLA_2-1 and PLA_2-2), a C-type lectin-like molecule, two PIII-SVMPs and a PI-SVMP. These selected toxin peaks are labeled with asterisks in panel a. The results of similar experiments performed with Premium Serums and VINS antivenoms are shown in Supplementary Figs. S1 and S2.

c support.

- Epidemiological information
- Biological information
- Venom research
- **Perfil de reactividad**

- Venoms suppliers
- Immunization schedule
- Antibodies production
- Recognition profile
- Preclinical work



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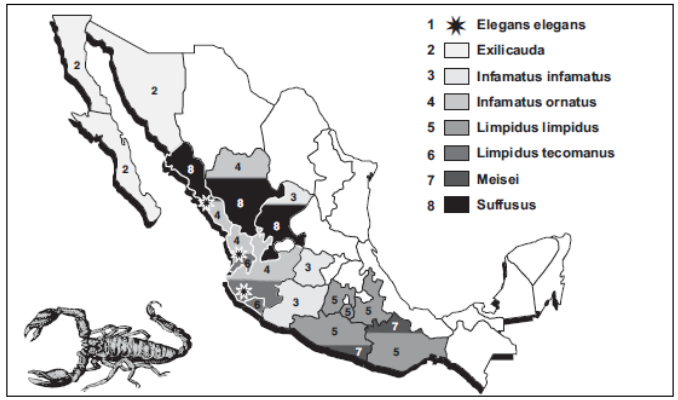
Antivenom



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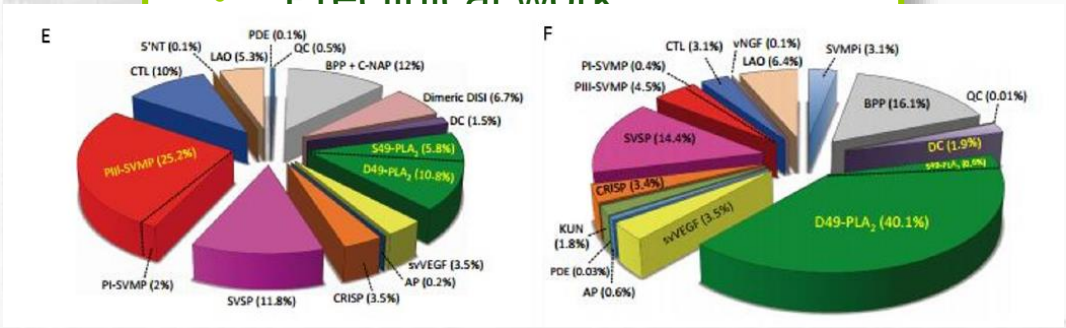


Desarrollo

Industria-Industria

- Strong scientific support.

- Epidemiological information
- Biological information
- Venom research
- Reactivity profile

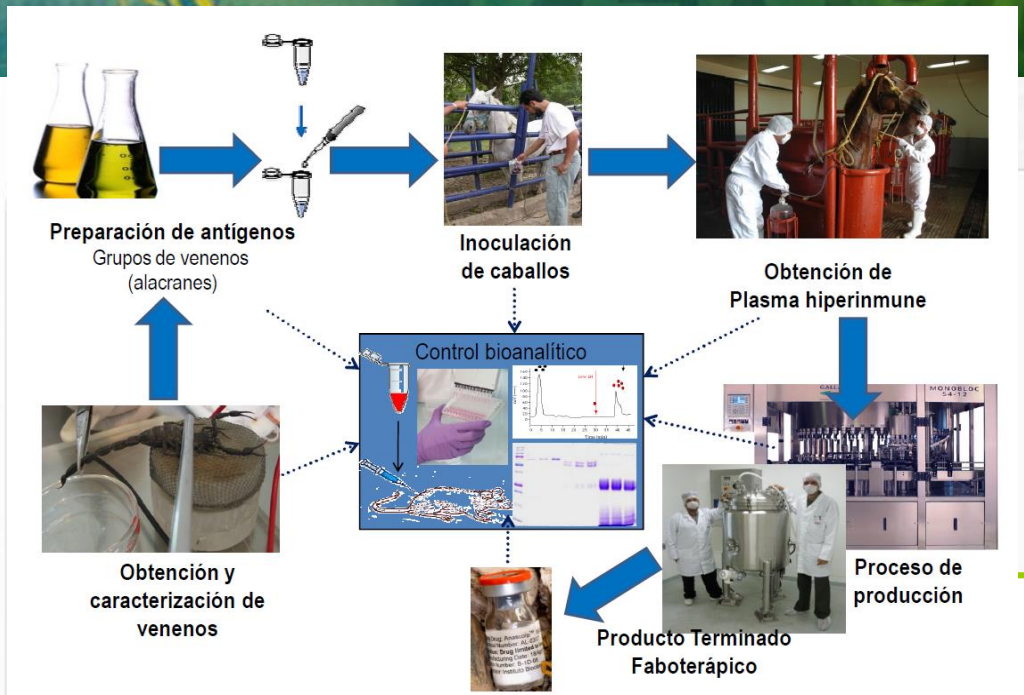
- **Proveedores de venenos**
- Immunization schedule
- Antibodies production
- Recognition profile
- Preclinical work
- Scale up production

- Regulatory strategy

Diseño de un antiveneno

Latoxan
Natural Active Ingredients

Desarrollo



- **Esquema de inmunización**
- **Producción de anticuerpos**
- Recognition profile
- Preclinical work
- Scale up production

- Regulatory strategy

Diseño de un antiveneno

Desarrollo

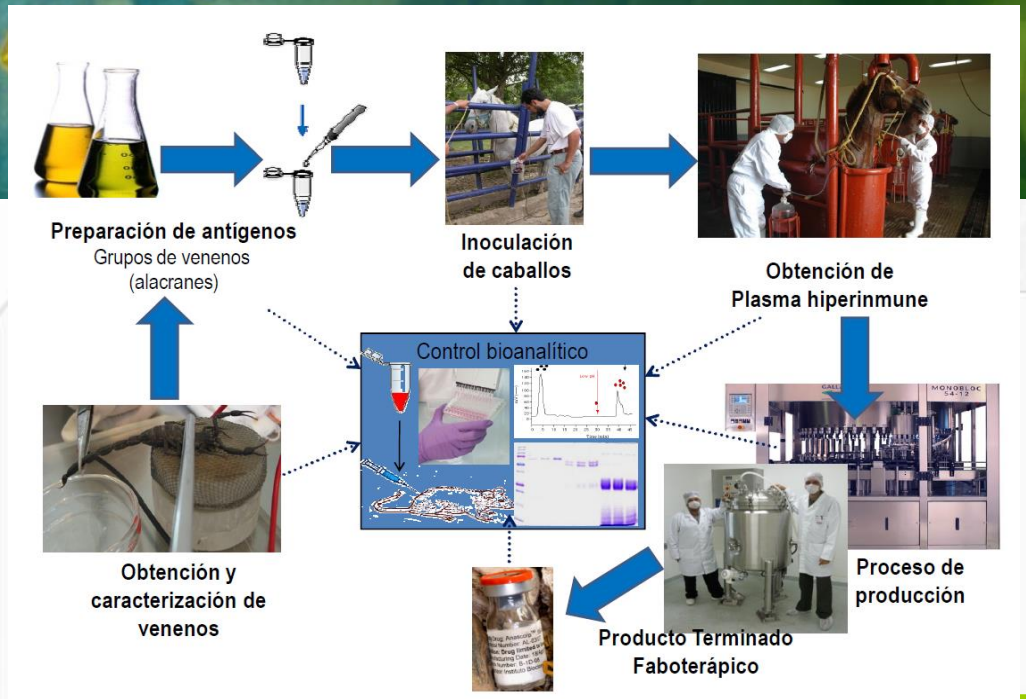


Table 4
Summary of the preclinical neutralizing ability, against the venom of *E. ocellatus* from Cameroon, of seven antivenoms distributed in sub-Saharan Africa.[a]

Neutralization (ED_{50} or ED, mg venom per mL antivenom)			
Antivenom	Lethality	Hemorrhagic effect	*In vitro* coagulant activity
Bioclon	3.73 (2.74–5.41)	5.52 ± 0.43	2.15 ± 0.01
EchiTAb G	0.98 (0.45–1.51)	4.41 ± 0.44	0.33 ± 0.01
EchiTAb-plus-ICP	3.40 (2.22–5.87)	3.04 ± 0.25	12.88 ± 0.09
FAV Afrique	2.26 (1.25–3.33)	5.35 ± 0.75	2.85 ± 0.04
Inoserp Panafricain	0.53 (0.23–0.80)	1.68 ± 0.13	0.96 ± 0.02
Premium Serums	1.44 (0.95–2.06)	5.48 ± 0.30	0.64 ± 0.02
VINS	<0.25	1.25 ± 0.04	0.10 ± 0.01

Neutralization (ED_{50} or ED, mg venom per g antivenom protein)			
Antivenom	Lethality	Hemorrhagic activity	*In vitro* coagulant activity
Bioclon	100.8 (74.0–146.2)	149.2 ± 11.6	58.1 ± 0.3
EchiTAb G	31.6 (14.5–48.7)	142.3 ± 14.2	10.6 ± 0.3
EchiTAb-plus-ICP	66.7 (43.5–115.1)	59.6 ± 4.9	252 ± 1.8
FAV Afrique	18.5 (10.2–27.3)	43.8 ± 6.1	23.4 ± 0.3
Inoserp Panafricain	26.5 (11.5–40.0)	84.0 ± 6.5	48.0 ± 1.0
Premium Serums	21.1 (14.0–30.3)	80.6 ± 4.4	9.4 ± 0.3
VINS	<10.4	52.1 ± 1.7	4.2 ± 0.4

[a] Antivenoms are listed in alphabetical order. The data of Bioclon, Premium Serums and VINS antivenoms correspond to the present study, whereas the data of EchiTAb G, EchiTAb-plus-ICP, FAV Afrique, and Inoserp antivenoms correspond to results presented in the study of Sánchez et al. (2015).

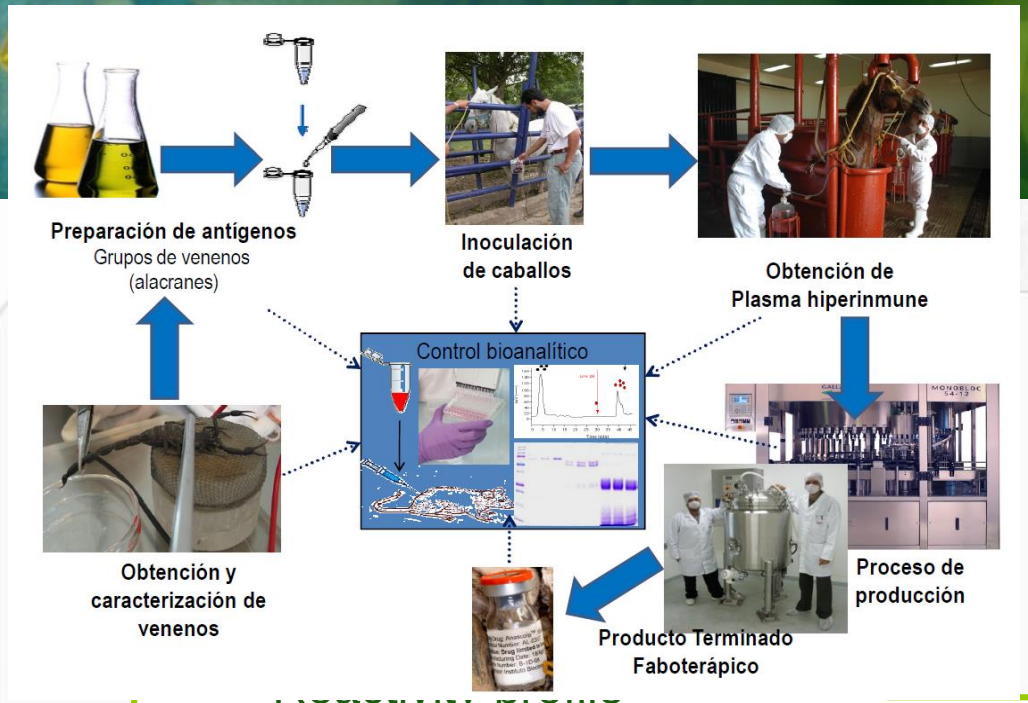
- Venoms suppliers
- Immunization schedule
- Antibodies production
- Recognition profile
- **Ensayos no-clínicos**
- Scale up production

- Regulatory strategy

design

Sector académico y/o CRO

Desarrollo



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- Venoms suppliers
- Immunization schedule
- Antibodies production
- **Perfil de reconocimiento**
- Preclinical work
- Scale up production

- Regulatory strategy

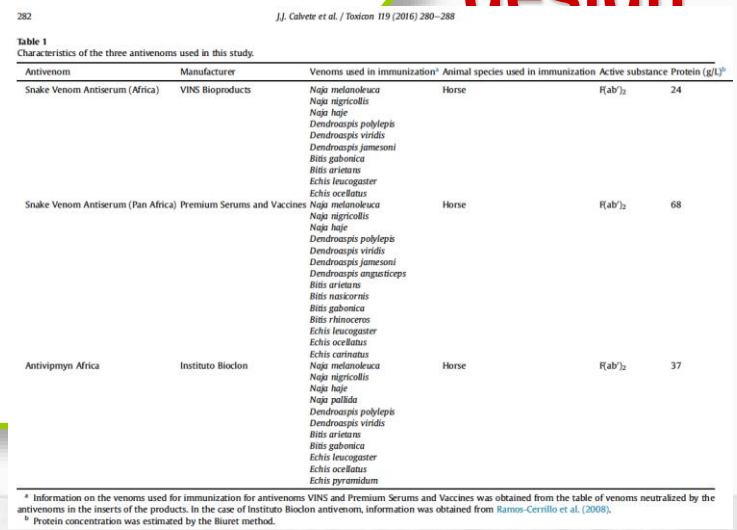

282 J.J. Calvete et al. / Toxicon 119 (2016) 280–288

Table 1
Characteristics of the three antivenoms used in this study.

Antivenom	Manufacturer	Venoms used in immunization[a]	Animal species used in immunization	Active substance	Protein (g/L)[b]
Snake Venom Antiserum (Africa)	VINS Bioproducts	*Naja melanoleuca* *Naja nigricollis* *Naja haje* *Dendroaspis polylepis* *Dendroaspis viridis* *Dendroaspis jamesoni* *Bitis gabonica* *Bitis arietans* *Echis leucogaster* *Echis ocellatus*	Horse	$F(ab')_2$	24
Snake Venom Antiserum (Pan Africa)	Premium Serums and Vaccines	*Naja melanoleuca* *Naja nigricollis* *Naja haje* *Dendroaspis polylepis* *Dendroaspis viridis* *Dendroaspis jamesoni* *Dendroaspis angusticeps* *Bitis arietans* *Bitis nasicornis* *Bitis gabonica* *Bitis rhinoceros* *Echis leucogaster* *Echis ocellatus* *Echis carinatus*	Horse	$F(ab')_2$	68
Antivipmyn Africa	Instituto Bioclon	*Naja melanoleuca* *Naja nigricollis* *Naja haje* *Naja pallida* *Dendroaspis polylepis* *Dendroaspis viridis* *Bitis arietans* *Bitis gabonica* *Echis leucogaster* *Echis ocellatus* *Echis pyramidum*	Horse	$F(ab')_2$	37

[a] Information on the venoms used for immunization for antivenoms VINS and Premium Serums and Vaccines was obtained from the table of venoms neutralized by the antivenoms in the inserts of the products. In the case of Instituto Bioclon antivenom, information was obtained from Ramos-Cerrillo et al. (2008).
[b] Protein concentration was estimated by the Biuret method.

Sector académico y/o CRO

Desarrollo

- Strong scientific support.

- Epidemiological information
- Biological information
- Venom research
- Reactivity profile

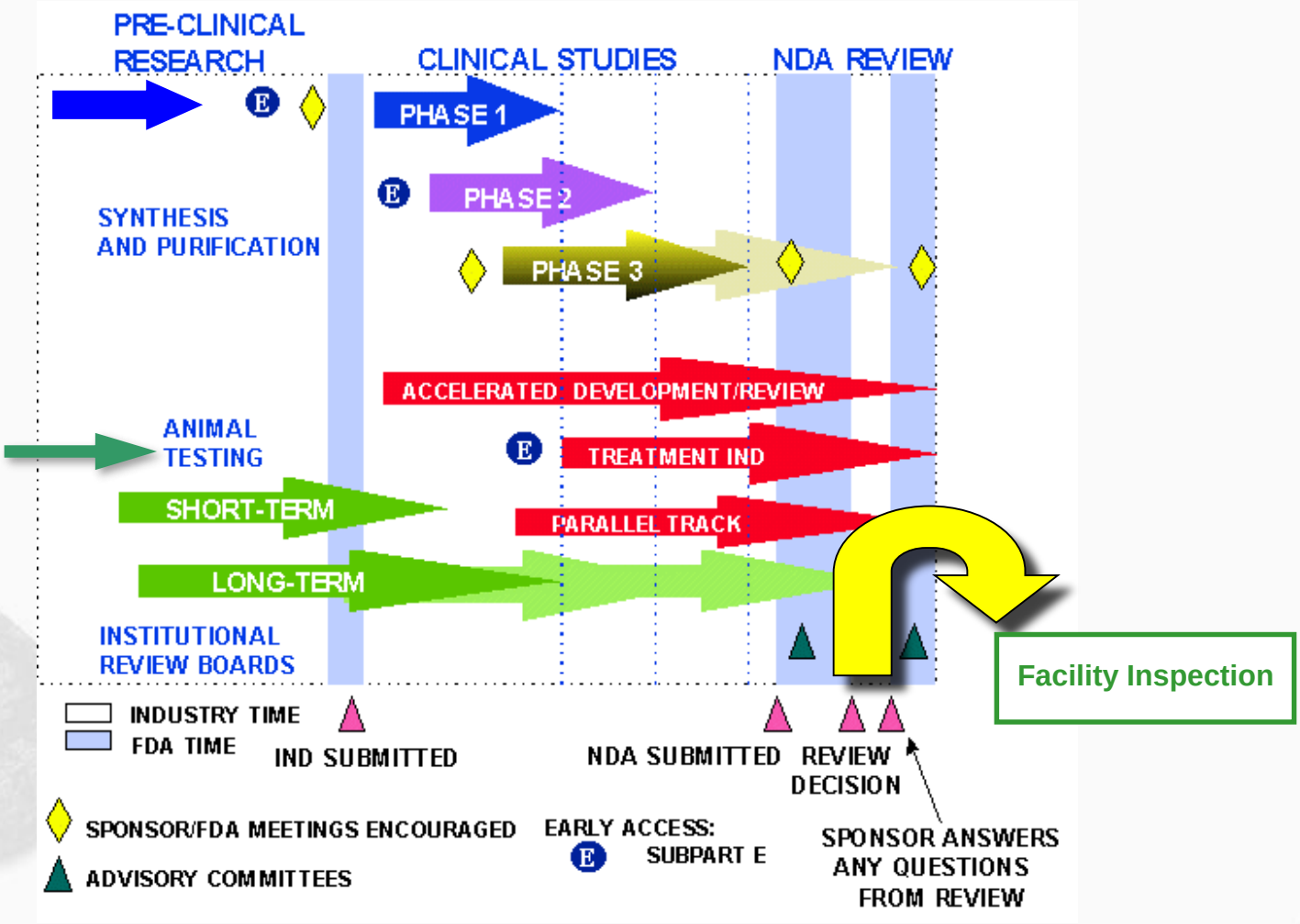
- Venoms suppliers
- Immunization schedule
- Antibodies production
- Recognition profile
- Preclinical work
- Scale up production

- **Estrategia regulatoria**

Diseño de un antiveneno

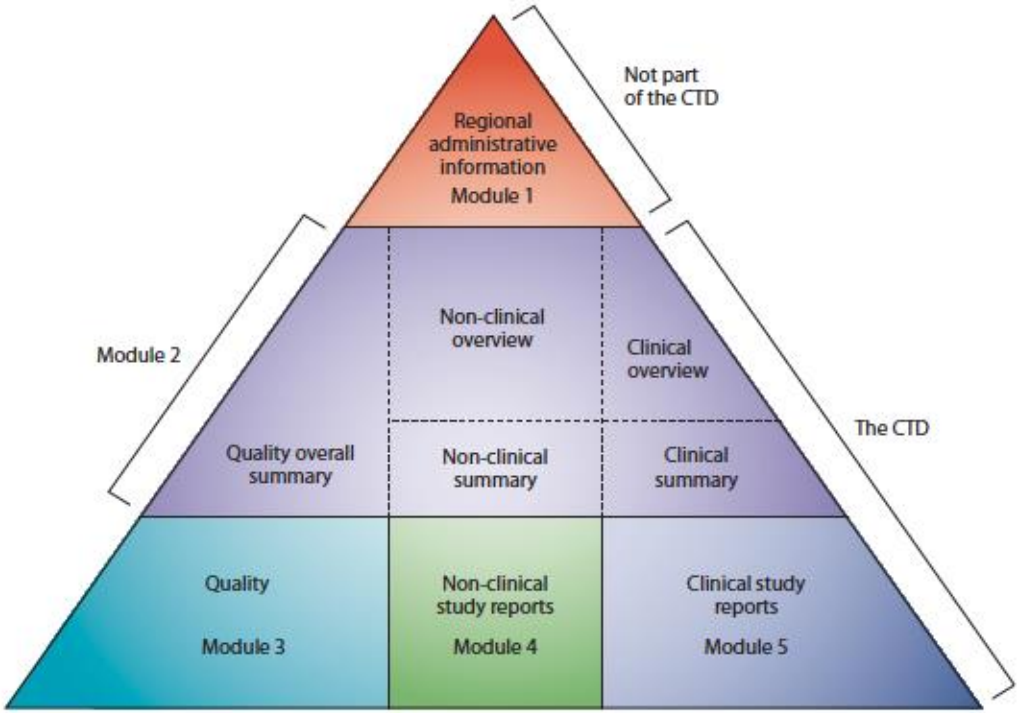
Estrategia regulatoria

Industria-Autoridad regulatoria



http://www.fda.gov/cder/handbook/develop.htm

Industria-Autoridad regulatoria



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

http://www.ich.org/products/ctd.html

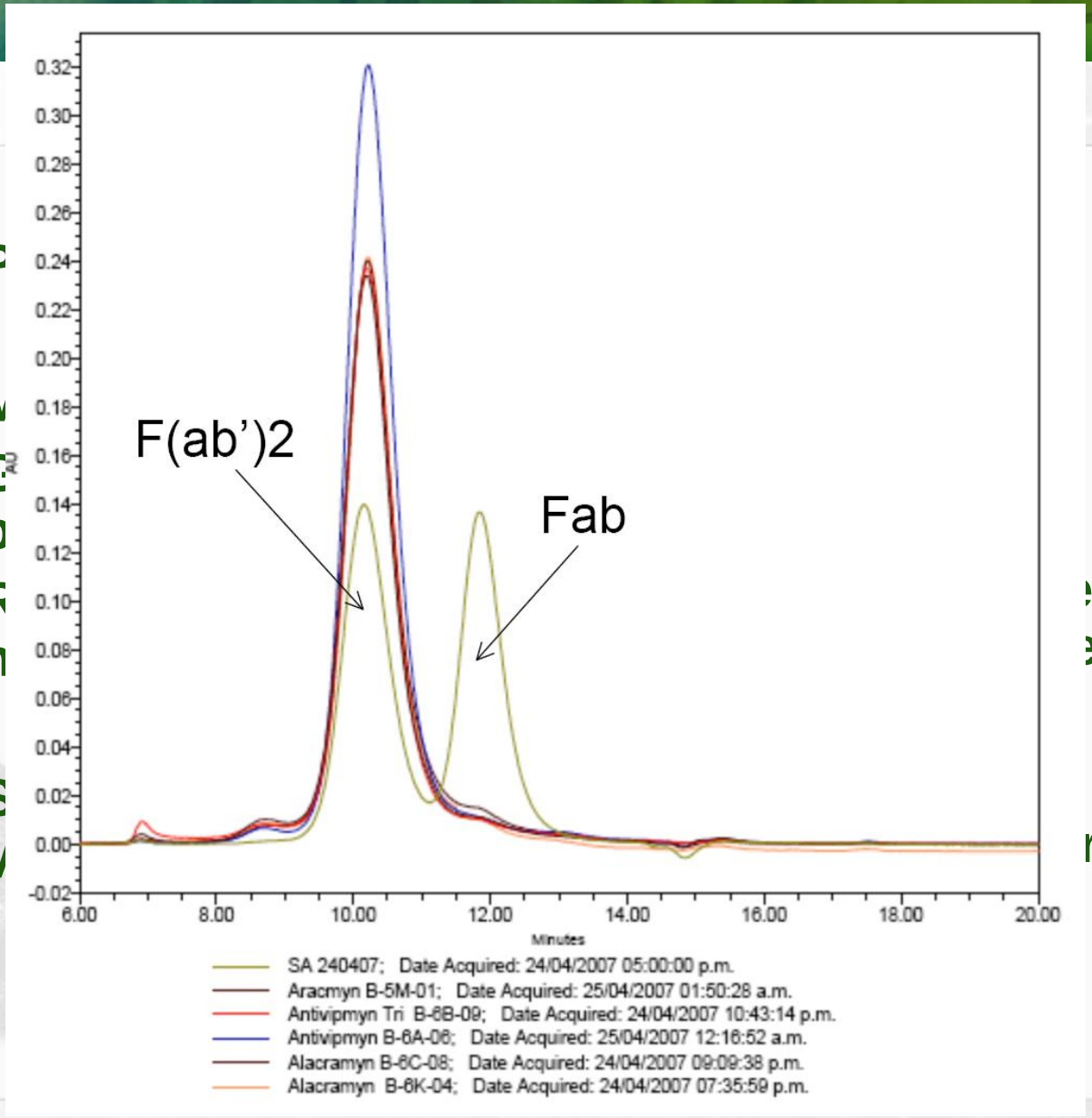
Manufactura

Sector servicios

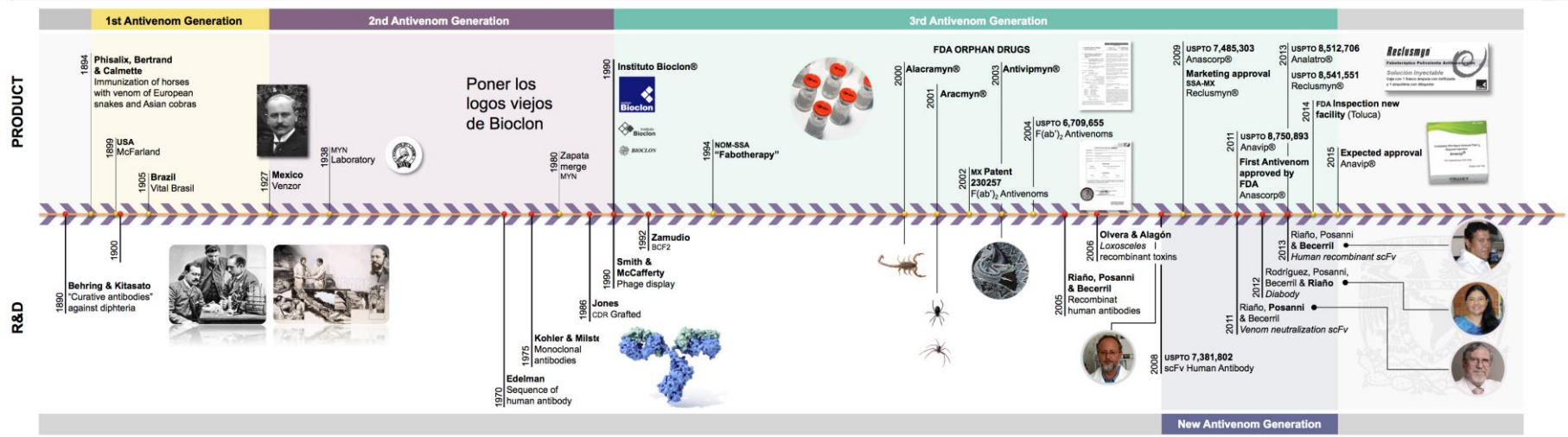
- Validación de procesos
- Planta de fabricación
- Good manufacturing practices (GMP).
- Reducción de carga viral
- Validación de métodos analíticos
- Desarrollo de metodología analítica específica (niveles de veneno-antiveneno).
- Transferencia de tecnología y metodología analítica.

Manufactura

- P
- M
- G
  p
- F
  h
- S
  V



Producto


1st Antivenom Generation
2nd Antivenom Generation
3rd Antivenom Generation
PRODUCT
R&D
1894 Phisalix, Bertrand & Calmette Immunization of horses with venom of European snakes and Asian cobras
1889 USA McFarland
1905 Brazil Vital Brasil
1927 Mexico Venzor
1938 MYN Laboratory
1890 Behring & Kitasato "Curative antibodies" against diphteria
1900
Poner los logos viejos de Bioclon
1980 Zapata merge MYN
1990 Instituto Bioclon®
1994 NOM-SSA "Fabotherapy"
1992 Zamudio BCF2
1990 Smith & McCafferty Phage display
1986 Jones CDR Grafted
1975 Kohler & Milst Monoclonal antibodies
1970 Edelman Sequence of human antibody
FDA ORPHAN DRUGS
2000 Alacramyn®
2001 Aracmyn®
2003 Antivipmyn®
2002 MX Patent 230257 F(ab')2 Antivenoms
2004 USPTO 6,709,655 F(ab')2 Antivenoms
2005 Riaño, Posanni & Becerril Recombinat human antibodies
2006 Olvera & Alagón Loxosceles recombinant toxins
2008 USPTO 7,381,802 scFv Human Antibody
2009 USPTO 7,485,303 Anascorp®
Marketing approval SSA-MX Reclusmyn®
2011 USPTO 8,750,893 Anavip®
First Antivenom approved by FDA Anascorp®
2013 USPTO 8,512,706 Analtro®
USPTO 8,541,551 Reclusmyn®
2014 FDA Inspection new facility (Toluca)
2015 Expected approval Anavip®
2013 Riaño, Posanni & Becerril Human recombinant scFv
2012 Rodríguez, Posanni, Becerril & Riaño Diabody
2011 Riaño, Posanni & Becerril Venom neutralization scFv
New Antivenom Generation

Time line

1st Antivenom Generation | **2nd Antivenom Generation**

PRODUCT

1894 **Phisalix, Bertrand & Calmette**
Immunization of horses with venom of European snakes and Asian cobras

1899 **USA**
McFarland

1905 **Brazil**
Vital Brasil

1927 **Mexico**
Venzor

1938 MYN
Laboratory

1980 Zapata merge
MYN

1990 Institu

R&D

1890 **Behring & Kitasato**
"Curative antibodies" against diphteria

1900

1970 **Edelman**
Sequence of human antibody

1975 **Kohler & Milstein**
Monoclonal antibodies

1986 **Jones**
CDR Grafted

1990 Smith
McCaf
Phage

Time line

3rd Antivenom Generation

PRODUCT

1990 **Instituto Bioclon®**

1994 **NOM-SSA**
"Fabotherapy"

FDA ORPHAN DRUGS

2000 **Alacramyn®**

2001 **Aracmyn®**

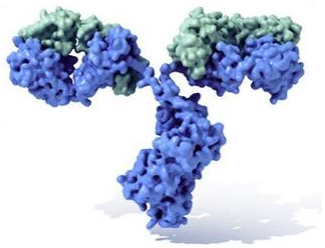
2003 **Antivipmyn®**

2004 **USPTO 6,709,655**
$F(ab')_2$ Antivenoms

2002 **MX Patent 230257**
$F(ab')_2$ Antivenoms

R&D

1986 **Jones**
CDR Grafted



1990 **Smith & McCafferty**
Phage display

1992 **Zamudio**
BCF2

2005 **Riaño, Posanni & Becerril**
Recombinat human antibodies

2006 Olvera & **Alagón**
Loxosceles | recombinant toxins

2008

Time line

3rd Antivenom Generation

PRODUCT

2009 **USPTO 7,485,303**
Anascorp®

Marketing approval
SSA-MX
Reclusmyn®

2013 **USPTO 8,512,706**
Analatro®

USPTO 8,541,551
Reclusmyn®

2014 **FDA Inspection new facility** (Toluca)

2011 **USPTO 8,750,893**
Anavip®

First Antivenom approved by FDA
Anascorp®

2015 **Expected approval**
Anavip®

R&D

& Alagón
les
nant toxins

2013 Riaño, Posanni & **Becerril**
Human recombinant scFv

2012 Rodríguez, Posanni, Becerril & **Riaño**
Diabody

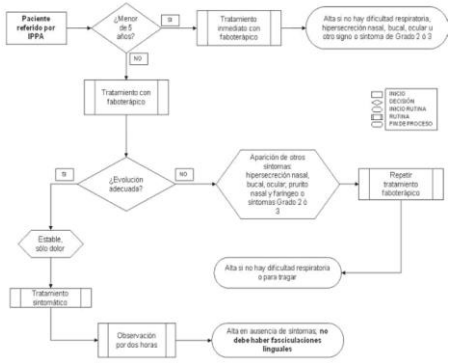
2011 Riaño, **Posanni** & Becerril
Venom neutralization scFv

2008 **USPTO 7,381,802**
scFv Human Antibody

New Antivenom Generation

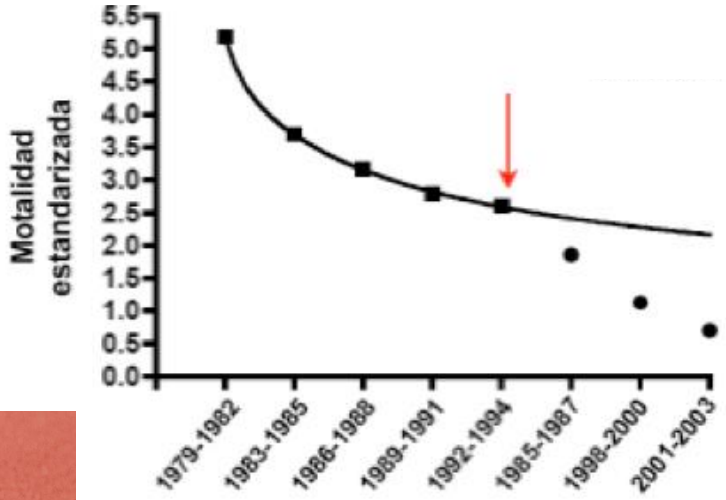
Picadura de alacrán en México

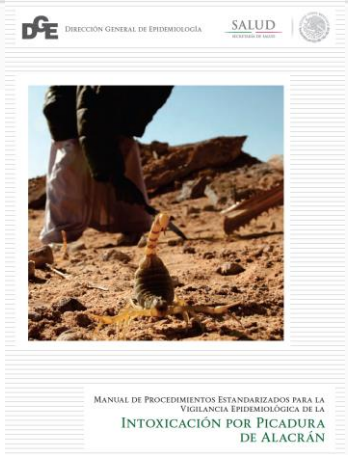
Sector Salud



Scorpion sting mortality in Mexico

1979 -2003





Alfredo Celis,[1] Ramón Gaxiola-Robles,[2] Elizabeth Sevilla-Godínez,[3] María de Jesús Orozco Valerio[4] y Jesús Armas[5]

Celis A, Gaxiola-Robles R, Sevilla-Godínez E, Orozco Valerio MJ, Armas J. Tendencia de la mortalidad por picaduras de alacrán en México, 1979-2003. Rev Panam Salud Publica. 2007;21(6):373–80.

Conclusiones

Organismos Internacionales

- **Las intoxicaciones por animales ponzoñosos son un problema mundial: OMS*.**

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Journal of Venomous Animals and Toxins including Tropical Diseases

LETTER TO THE EDITOR Open Access

Snakebite envenomation turns again into a neglected tropical disease!

Jean-Philippe Chippaux[1,2,3]

Abstract: On June 9th, 2017 WHO categorized snakebite envenomation into the Category A of the Neglected Tropical Diseases. This new situation will allow access to new funding, paving the way for wider and deeper researches. It should also expand the accessibility of antivenoms. Let us hope that it also leads to cooperation among stakeholders, aiming at improving the management of snakebites in developing countries.

* Snakebite as a Neglected Tropical Diseases (WHO, 2017). http://minutestodie.com/about-the-film/

Conclusiones

- **Vinculaciones formales y efectivas con:**
  - **Sector académico.**
  - **Industria.**
  - **Sector servicios.**
  - **CRO.**
  - **Sector Salud.**
  - **Autoridades regulatorias.**
  - **Organismos internacionales OPS/OMS.**

Muchas gracias!!!

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