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Factors involved in the resilience of incidence and decrease of mortality from scorpion stings in Mexico

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ABSTRACT

In Mexico, scorpion sting envenomation (SSE) is a significant public health issue that has engaged the attention of health authorities for more than a century. Rigorously characterized today, scorpion sting incidence is stable around 230 stings per 100,000 population, i.e. 300,000 annual stings treated in Mexican health centers and hospitals. Higher incidence is observed mainly in central and Pacific Mexico. Scorpion populations thrive in populated places, particularly in impoverished areas. Scorpion stings occur in houses. This could explain similar incidence according to gender and age. The number of scorpion stings has remained stable since the mid-2000s. In contrast, mortality, which was over 1500 deaths per year before the 1960s, underwent a dramatic drop after the 1970s, from 500 deaths per year to fewer than 50 annual deaths today. Case fatality rates have shown similar trend. We noted a significantly higher specific mortality in males than in females (0.199 and 0.168 per 100,000 respectively; $P < 1.9{\cdot}10^{-6}$). Three causes explained the drop in mortality and case fatality rate, a) ongoing improvement in hospital care, particularly in terms of supportive standardized treatments, b) the use of highly purified immunoglobulin F(ab')$_2$ fragments after 1995 and, c) increasing access to health services for most of the Mexican population. The authors retrace the history of the management of SSE, including the development of antivenoms, in Mexico between 1905 and today.

1. Introduction

Scorpion sting envenomation (SSE) is a public health issue, particularly in certain tropical regions of the world (Chippaux and Goyffon, 2008; Chippaux, 2012). All scorpions are venomous. The venomous apparatus, or telson, is located at the end of the metasoma (commonly known as the tail). It includes a vesicle made up of a pair of venom glands and a stinger or aculeus allowing the injection of venom into the prey or victim. Venom composition varies and can be very toxic to humans. Scorpions are nocturnal predators of arthropods, often cockroaches, and sometimes of small vertebrates such as lizards or juvenile rodents (Polis, 1990).

In Mexico, nearly 300 species of scorpions have been described, belonging to 8 families, and in which 21 are considered dangerous to humans (González-Santillán and Possani, 2018). The most important of these in terms of public health is the family Buthidae, which includes 2 genera, *Centruroides* Marx, 1890 and *Chaneke* Francke, Teruel and Santibañez-López, 2014 counting 50 species (Ponce-Saavedra et al., 2016). About 20 out these, all belonging to the genus *Centruroides*, are dangerous to humans (Riaño-Umbarila et al., 2017; González-Santillán and Possani, 2018).

Chowell et al. (2005) showed that the activity of scorpions is strongly associated with temperature and rainfall. Urbanization spreads over - and destroys - natural habitats of scorpions. However, some scorpion species find favorable conditions in the new environment and scorpion populations can grow and scatter (de Roodt, 2014; Lourenço, 2018). The majority of stings occur in urban or peri-urban areas (Dehesa-Dávila, 1986), especially inside houses (60% of stings treated in health centers) where scorpions may find refuge (Villegas et al., 1988; Dehesa-Dávila, 1989; Castillo Pérez et al., 2002). About a third of the stings occur in

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countryside, however, mainly during agricultural activities. More than half of stings occur between 6 p.m. and midnight (Galván Cervantes, 1966). Poor or unsanitary environment, as well as some construction materials, are attractants for scorpions and can be major factors affecting sting incidence (Castillo Pérez et al., 2002; Silva-Domínguez et al., 2019). Geographic distribution of scorpion stings can be heterogeneous for reasons that are unclear but that may result from both the way of life of scorpions and environmental and socioeconomic conditions (Castillo Pérez et al., 2002).

Morbidity and mortality depend on several factors (Chávez-Haro and Ortiz, 2015; Isbister and Bawaskar, 2014). Worldwide, scorpion sting morbidity results from the stimulation of autonomous centers, including sympathetic centers, by the direct action of the venom inducing massive release of catecholamines and vasoactive hormones. In North America, *Centruroides* scorpion venom also provokes a characteristic neuromotor syndrome that may include ineffective respiratory effort. In addition, in the presence of circulating mediators, patients may develop an inflammatory syndrome responsible for severe systemic effects involving, in particular, the cardiac and respiratory functions progressing towards life threatening cardiogenic shock or multi-organ failure (Chippaux, 2012; Isbister and Bawaskar, 2014). Consequently, management involves two complementary axes: antivenom administration to eliminate the venom accountable for triggering envenomation and supportive treatment to reduce cardiac and pulmonary damage and prevent multiorgan failure (Chippaux, 2012). The severity of the envenomation varies depending on the species of scorpion and the amount of inoculated venom. The effect of the venom on the victim is influenced by size, weight and state of health at the time of the sting. Finally, the timing and effectiveness of treatment influence the speed of patient recovery and the risk of fatal outcome (Dehesa-Dávila, 1989; Chowell et al., 2006; Chávez-Haro and Ortiz, 2015).

In Mexico, where the incidence of scorpion stings is one of the highest in the world, scorpionism is a long-standing public health concern (Cavaroz, 1865). The first antivenom used in humans to treat scorpion envenomation was innovated from the blood serum of immunized dogs, in Mexico in 1905 (Vergara Lope, 1906), and regular use of scorpion antivenom began in the late 1920s following the independent development of an equine antivenom (León de la Peña and Venzor, 1931). Scorpion antivenom sales for commercial export to the United States were first licensed in 1949 (Anonymous, 1951). These early antivenoms were relatively crude animal serum derivatives, and safety concerns led to physician reluctance to put them to routine use. Beginning in the mid-1990s, safety concerns were reduced following the introduction of antivenoms made from highly purified immunoglobulin $F(ab')_2$ fragments (Alagón, 2002).

Between 1940 and 1958, the average number of annual deaths from SSE was estimated at 1,775, i.e. a mortality of 7.1 per 100,000 population (Mazzotti and Bravo-Becherelle, 1963). It decreased to fewer than 500 deaths per year (0.9 deaths per 100,000 population) by the end of the 1970s, then decreased further to fewer than 50 annual deaths today, i.e. approximately 0.03 deaths per 100,000 population (Fig. 1). Celis et al. (2007) had shown that between 1979 and 2003 the decrease in mortality was statistically significant ($\beta = -0.195$; $P \leq 0.001$), with 86.5% total reduction for the period 2001–2003 compared to 1979–1982. In addition, in communities with fewer than 2500 inhabitants, mortality from scorpion stings was almost 12 times higher than in cities with more than 20,000 population.

The purpose of this study is to describe the evolution of scorpion sting incidence and mortality between 1979 and 2019, i.e. during the period covering the implementation of scorpion sting case reporting and development of antivenoms composed of highly purified and lyophilized immunoglobulin G (IgG) fragments. We will explain the dramatic fall in mortality over the past 40 years. We hypothesized that the latter depends on 3 factors: the improvement of supportive healthcare, development and large-scale distribution of effective and safe antivenoms (namely $F(ab')_2$) and increasing free access to health services for most of the Mexican population, particularly for the poor.

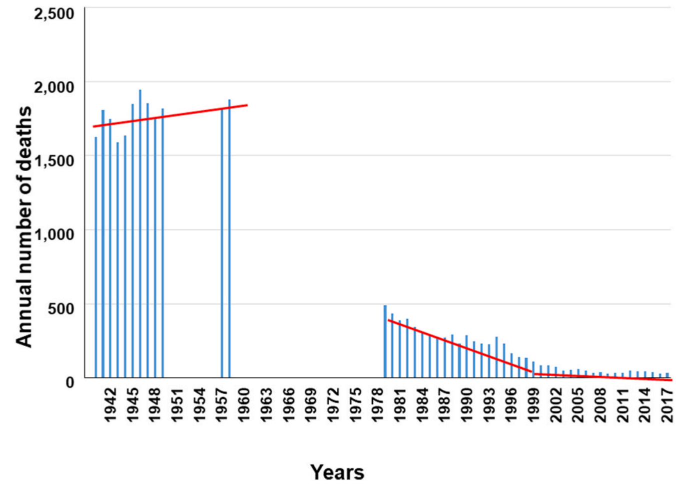

Fig. 1. Overview of scorpion sting death number in Mexico, 1940–2017. [Source: Mazzotti and Bravo-Becherelle, 1963; Boletín Epidemiológico/Sistema Nacional de Vigilancia Epidemiológica/Sistema Único de Información/Dirección General de Epidemiología]

2. Method

A bibliographic search was performed by querying MedLine (last access March 25th, 2019) using the keywords "Mexico AND scorpion*". From a total of 317 references, 37 were specifically related to the epidemiology and/or management of scorpion stings in Mexico. Some additional references in national or regional journals were obtained from articles found in MedLine bringing the total number of relevant papers to fifty. Furthermore, websites regarding a) the epidemiology of scorpion stings (using the words "health surveillance", "surveillance bulletin", "epidemiology surveillance", "scorpion stings envenomation", "scorpion stings death"), b) population demography ("using the words "population demography") and c) administrative and environmental geography (using the word "map ") were identified using the Google search engine for Mexico and using both languages, English and Spanish. Access to these websites was made between December 2018 and June 2019. The epidemiological data came from the various websites of

Table 1
Identification and exploration of accessed Websites.

Web site	Last access
Incidence	
https://www.gob.mx/salud/acciones-y-programas/direccion-general-de-epidemiologia-boletin-epidemiologico	24 April 2020
https://www.gob.mx/salud/acciones-y-programas/historico-boletin-epidemiologico	24 April 2020
http://www.epidemiologia.salud.gob.mx/anuario/html/anuarios.html	24 April 2020
https://www.gob.mx/busqueda?utf8=%E2%9C%93&q=Notificacio%CC%81n+Semanal+Casos+Nuevos++deEnfermedades	24 April 2020
https://www.gob.mx/salud/acciones-y-programas/direccion-general-de-epidemiologia-informes-semanales-para-la-vigilancia-epidemiologica	24 April 2020
Mortality	
https://datos.gob.mx/busca/dataset/estadistica-de-defunciones-registradas	25 March 2019
https://www.gob.mx/salud/acciones-y-programas/informacion-epidemiologica-publicaciones-de-mortalidad	25 March 2019
http://www.dgis.salud.gob.mx/contenidos/basesdedatos/std_defunciones_gobmx.html	4 Feb 2019
Demography and economy	
https://www.snieg.mx/cni/	5 Nov. 2019
https://www.snieg.mx/cni/indicadores.aspx?idOrden=1.2	5 Nov. 2019

the General Directorate of Epidemiology of the Ministry of Health. The list of the websites and the last access date to each are mentioned in Table 1.

The reference population for the calculation of incidence and mortality was the annual population provided by the Ministry of Health. We looked for a link between the incidence of scorpion stings and demographic (population density), and socioeconomic variables representative of the situation in each of the Mexican states, such as gross domestic product (GDP) and social lag index (SLI). SLI was defined by an aggregate of weighted socio-economic indicators of social deprivation (education, access to health services, basic infrastructure in housing, quality services, and space in housing and household assets) assessing social development and living conditions of households (Vargas-Chanes et Valdéz-Cruz, 2019).

All data were transferred and analyzed using Excel® software. The descriptions of the variables, estimation of trend curves and R^2 correlation indices were designed and calculated through Excel®. Trends were analyzed using simple regression. Comparisons were made using parametric tests (*t*-test and paired *t*-test, χ^2, and Spearman correlation) or non-parametric (Mann-Whitney), depending on the distribution of studied variables and number of cases/groups. We used the Spearman correlation because it evaluates the monotonic relationship between two continuous or ordinal variables as in the case of the average number or incidence of patients in relation to demographic or socioeconomic parameters. The significance level was equal to 0.05 and the means were expressed using a 95% CI. Statistical analyses were performed using Excel® and BiostatTGV online software (http://marne.u707.jussieu.fr/biostatgv/).

Topographic, physical and political maps were taken from the World Atlas of Wikimedia (https://commons.wikimedia.org/wiki/Atlas_of_the_world) and drawn on the basis of the data obtained in this study.

3. Results

Patients stung by a scorpion who consult health centers are systematically reported to the state epidemiological surveillance system, which in turn transmits the information to the Federal Ministry of Health. Health centers and public hospitals receive 70% of cases, the remaining 30% being distributed among various Mexican organizations or institutions (Fig. 2).

Incidence of scorpion stings regularly increased during the first 10 years of case reporting implementation from fewer than 45,000 stings in 1994 to over 250,000 stings after 2004, i.e. the reported annual incidence augmented from 50 to 250 scorpion stings per 100,000 population (Fig. 3). Scorpion sting incidence occurred predominantly near the Pacific Coast, in west Mexico, except in Baja California (Fig. 4), and in the

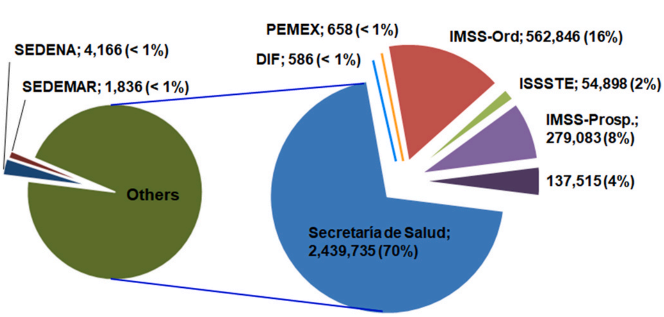

Fig. 2. Services and institution of first consultation and declaration for scorpion stings, 2006–2017: *Secretaría de Salud = National and State health centers; Instituto Mexicano del Seguro Social (IMSS); Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE); Sistema Nacional para el Desarrollo Integral de la Familia (DIF); Petróleos Mexicanos (PEMEX); Secretaría de Marina (SEMAR); Secretaría de la Defensa Nacional (SEDENA).*
[Source: Sistema Único de Información para la Vigilancia Epidemiológica/Dirección General de Epidemiología/SSA]

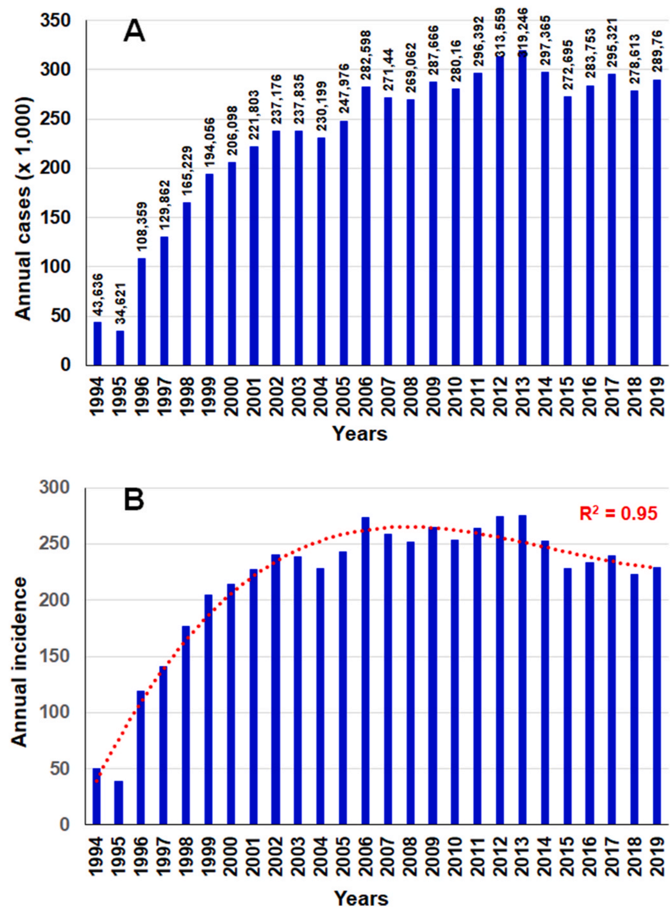

Fig. 3. Incidence of scorpion stings in Mexico, 1994–2019; A- Number of annual cases; B- Normalized annual incidence per 100,000 people.
[Source: Boletín Epidemiológico/Sistema Nacional de Vigilancia Epidemiológica/Sistema Único de Información/Dirección General de Epidemiología]

center of the country (Fig. 5). The seasonal distribution showed a clear predominance of the incidence of scorpion stings in summer when the average temperature is higher (Fig. 6), with greater seasonal variability in northern Mexico where the temperature differences are greater (Fig. 4).

The mean number of stings between 2003 and 2019 was 133,921 ± 5942 in males and 139,823 ± 7219 in females (sex ratio M/F = 0.96). The specific incidence according to gender was 240.1 per 100,000 males and 239.5 per 100,000 females ($P > 0.6$). There was a significant disparity across states (Table 2). The age-specific incidence varied little between children and adults regardless of age, except for a lower incidence in infants (Fig. 7).

Annual mortality fell dramatically between 1979 and 2017, the most recent year available in the databases of the Ministry of Health. It thus declined from 0.741 per 100,000 population in 1979 to 0.026 in 2017 (Fig. 8). There was a large disparity in mortality among states, parallel to the distribution of the incidence (Fig. 9). Mortality was significantly higher ($P < 1.9 \cdot 10^{-6}$) in males than in females with 0.199 per 100,000 males and 0.168 per 100,000 females respectively, between 1979 and 2017 (Fig. 10). Almost 90% of deaths occurred in children under 10 years old –80% in children under 5 –while this group represented less than 20% and 10% of scorpion stings respectively. People over the age of 60 were also vulnerable (Fig. 11).

The annual number of scorpion stings in each state was not correlated with population density ($P > 0.15$) and the mean incidence in states was not correlated with SLI ($P > 0.51$). On the other hand, the annual number of scorpion stings in each state was inversely correlated

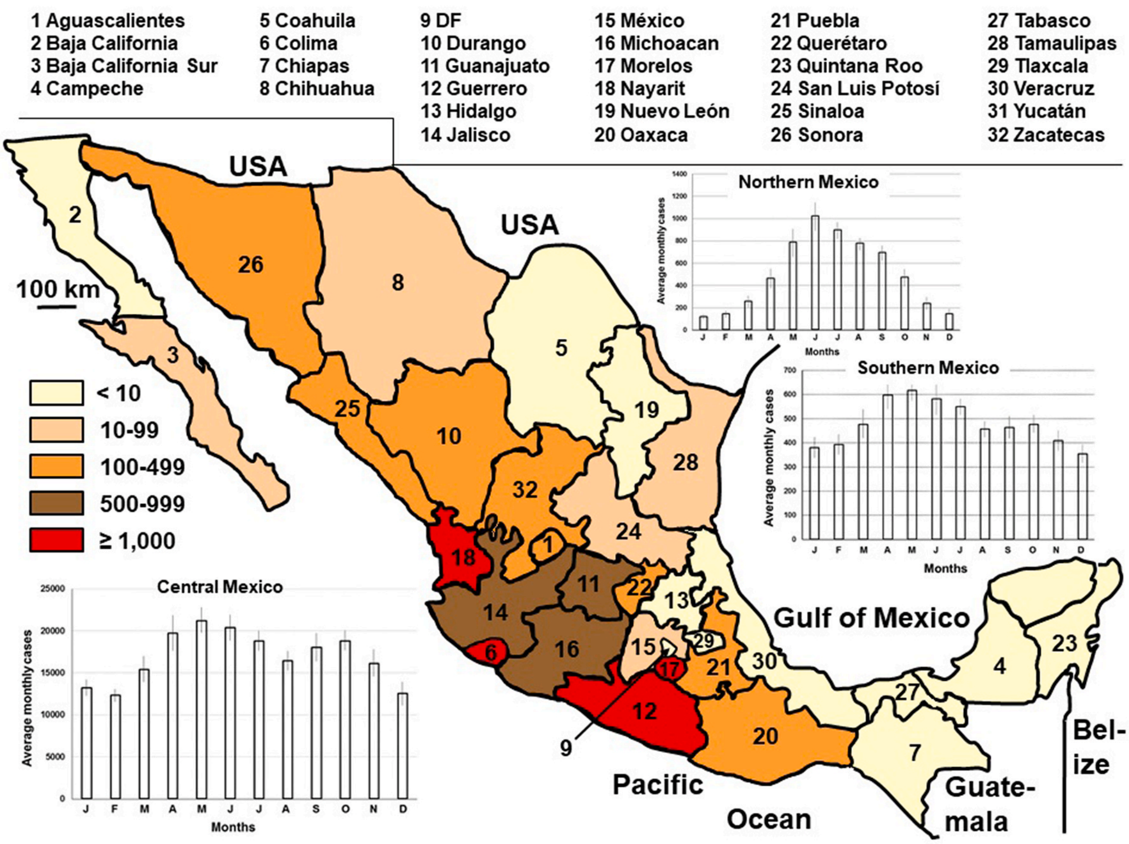

Fig. 4. Geographical distribution of scorpion stings in Mexico (average annual incidence by state and seasonal distribution in the 3 main geographic regions: North, Center and South Mexico).
[Source: Boletín Epidemiológico/Sistema Nacional de Vigilancia Epidemiológica/Sistema Único de Información/Dirección General de Epidemiología]

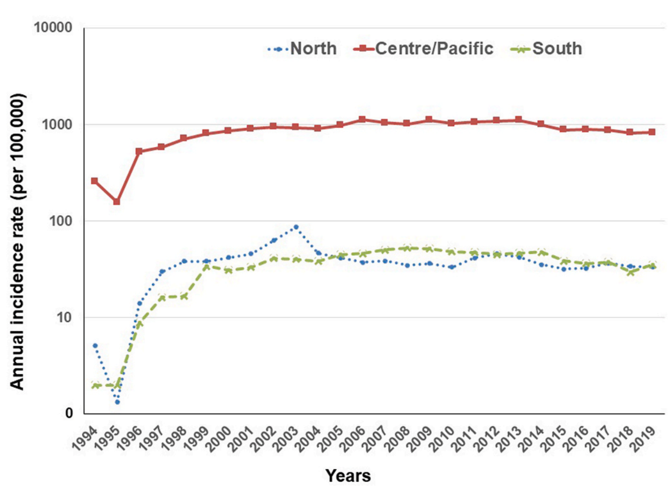

Fig. 5. Regional variation (North, Center and South) the scorpion sting incidence in Mexico.
[Source: Boletín Epidemiológico/Sistema Nacional de Vigilancia Epidemiológica/Sistema Único de Información/Dirección General de Epidemiología]

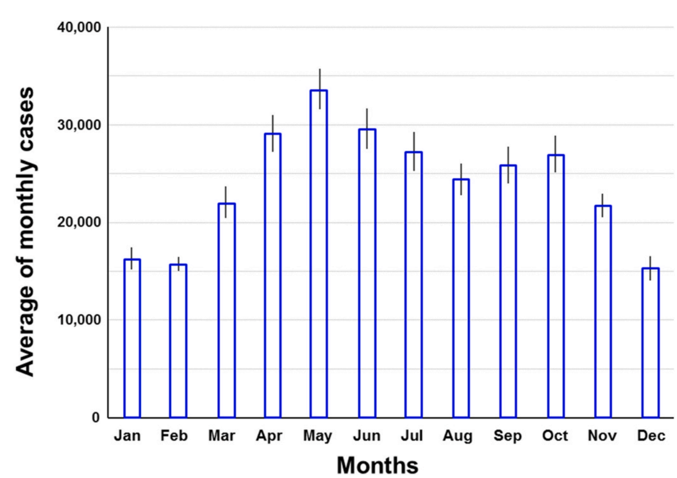

Fig. 6. Monthly incidence of scorpion stings throughout Mexico, 2006–2019 (see regional variations in Fig. 3).
[Source: Boletín Epidemiológico/Sistema Nacional de Vigilancia Epidemiológica/Sistema Único de Información/Dirección General de Epidemiología]

with the GDP (r = - 0.36; P < 0.046).

4. Discussion

This study showed an increasing incidence of scorpion stings during the first years after the onset of case reporting (Fig. 3) and a dramatic decline in mortality in recent decades (Fig. 8). Although there was no difference between the incidence of stings in males and females, the difference in mortality according to gender was highly significant suggesting either greater resistance in females or marked difference in scorpion species stinging males and females, possibly resulting from accidents occurring in distinct places and/or circumstances. The severity of envenomation in young children is well known (Chippaux and

Table 2
Notified scorpion stings incidence according to gender.

Region	Mexican States	Incidence in males	Incidence in females	Sex-ratio
Central/ Pacific	Aguascalientes	175 .0	174 .9	0 .95
North	Baja California	4 .3	4 .8	0 .91
North	Baja California Sur	11 .7	16 .8	0 .73
South	Campeche	6 .4	10 .7	0 .59
North	Coahuila	6 .8	8 .9	0 .75
Central/ Pacific	Colima	1832 .0	1475 .9	1 .23
South	Chiapas	6 .0	8 .0	0 .72
North	Chihuahua	11 .0	13 .0	0 .84
Central/ Pacific	DF	5 .3	6 .0	0 .80
North	Durango	337 .3	351 .5	0 .93
Central/ Pacific	Guanajuato	520 .5	580 .3	0 .83
Central/ Pacific	Guerrero	1457 .1	1394 .6	0 .99
Central/ Pacific	Hidalgo	6 .5	9 .2	0 .66
Central/ Pacific	Jalisco	731 .3	688 .3	1 .02
Central/ Pacific	México	60 .9	61 .8	0 .94
Central/ Pacific	Michoacan	740 .7	719 .5	0 .97
Central/ Pacific	Morelos	1874 .2	1742 .1	1 .01
Central/ Pacific	Nayarit	1437 .0	1212 .1	1 .18
North	Nuevo Lon	3 .7	5 .2	0 .70
South	Oaxaca	129 .5	158 .3	0 .75
Central/ Pacific	Puebla	248 .3	256 .0	0 .89
Central/ Pacific	Querétaro	240 .4	266 .6	0 .85
South	Quintana Roo	7 .8	11 .5	0 .70
Central/ Pacific	San Luis Potosi	10 .0	14 .9	0 .64
North	Sinaloa	300 .1	364 .2	0 .82
North	Sonora	148 .0	222 .5	0 .67
South	Tabasco	1 .9	2 .7	0 .69
North	Tamaulipas	8 .8	13 .1	0 .66
Central/ Pacific	Tlaxcala	4 .1	5 .1	0 .75
Central/ Pacific	Veracruz	2 .9	3 .6	0 .76
South	Yucatan	2 .3	3 .5	0 .63
Central/ Pacific	Zacatecas	248 .9	248 .6	0 .96
	Mexico	254 .0	252 .4	0 .96

Goyffon, 2008; Bahloul et al., 2010). This may be explained by a higher plasma concentration of venom in children for the same amount of venom inoculated (Krifi et al., 1998) and a higher diffusion of venom in some vital organs, in particular the heart and lungs (Nunan et al., 2003).

The epidemiological data were inherently limited because they were based on the collection and transmission of information from the registers of health centers and death certificates. First, the results depended on the quality of the records and the reliability of the data collection and transmission. Second, some variables or details were missing, in particular on the severity of the envenomation (morbidity) and precise anatomic location of the scorpion stings, which might account for the difference in mortality according to gender. The morbidity and severity of SSE vary depending on several factors. The danger of scorpions is related to the species, i.e. environmental conditions, accident circumstances and clinical assessment of the severity of envenomation according to the observer and criteria applied, which are poorly standardized and not consensual. In addition, the registration of each case –and possibly death– was recorded in the health center where the

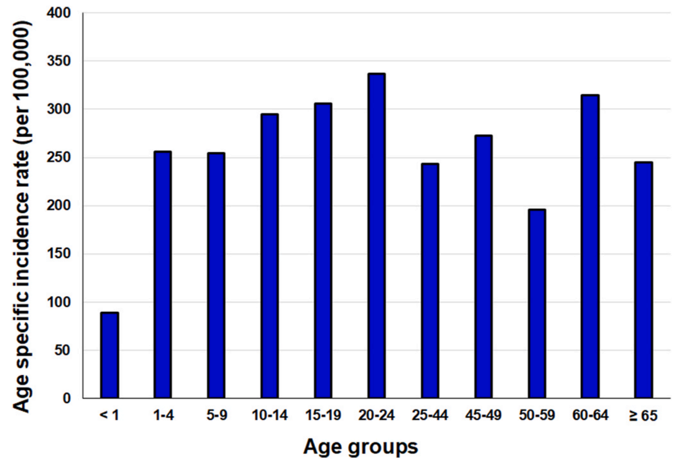

Fig. 7. Specific incidence of scorpion stings according to patient's age, 2006–2018 [SUIVE/DGE/Secretaría de Salud/Estados Unidos Mexicanos].

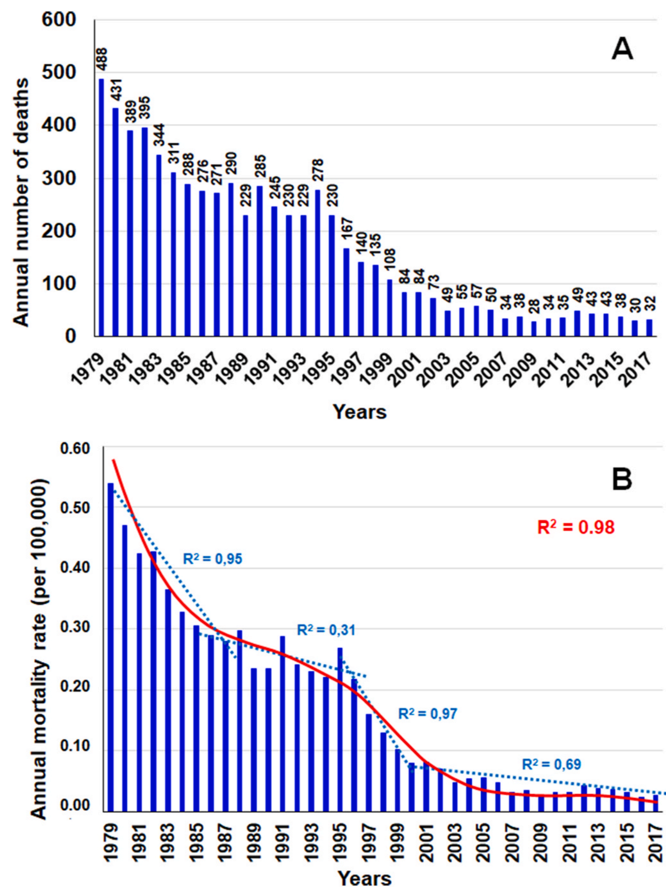

Fig. 8. Scorpion sting mortality in Mexico (1979–2017); A- Number of annual deaths; B- Normalized annual mortality per 100,000 people.
[Source: Información Epidemiológica/Publicaciones de Mortalidad/Dirección General de Epidemiología/Dirección General Adjunta de Epidemiología]

patient was treated or, possibly, the one where he/she died. The scorpion sting was considered to occur in the same state as that where the declaration was made, which may not always be the case. However, this bias probably has minimal consequences. Finally, the availability of statistical data varied depending on the year. Mortality was available beginning in 1979, while incidence was not specified before 1994. Incidence according to gender and age was obtained only for the periods

Fig. 9. Geographical mortality of scorpion stings in Mexico, 1979–2017.
[Source: Información Epidemiológica/Publicaciones de Mortalidad/Dirección General de Epidemiología/Dirección General Adjunta de Epidemiología]

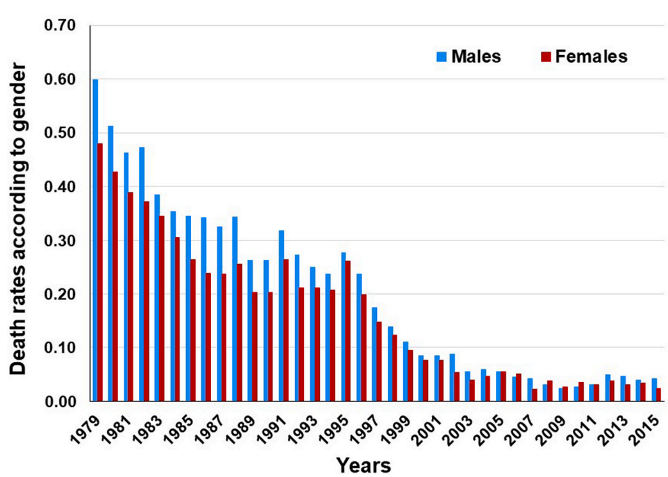

Fig. 10. Specific scorpion sting mortality according to patient's gender, 1979–2017.
[Source: Información Epidemiológica/Publicaciones de Mortalidad/Dirección General de Epidemiología/Dirección General Adjunta de Epidemiología]

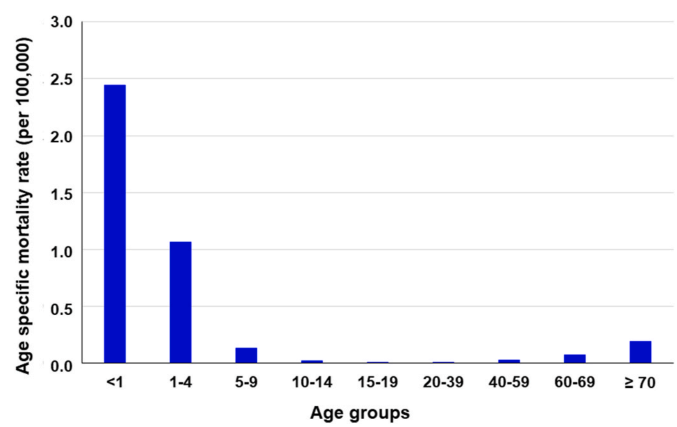

Fig. 11. Specific scorpion sting mortality according to patient's age, 1979–2017.
[Source: Información Epidemiológica/Publicaciones de Mortalidad/Dirección General de Epidemiología/Dirección General Adjunta de Epidemiología]

2006–2019 and 2006–2018, due to the heterogeneity –or absence– of data for the other years.

Despite these limitations, the data obtained were consistent and they enabled, on the one hand to characterize scorpionism in Mexico, one of the countries where the prevalence is the highest, and on the other hand to study the trends in incidence and mortality intending to determine the causes.

The remarkable increase in cases between the onset of scorpion sting reporting and today –actually between 1994 and 2006– can have two explanations which, probably, are cumulative: improvement in the quality of case reporting and patients' motivation to attend health centers after scorpion sting. The gradual improvement in the quality of the data collection that started in 1994 would have stabilized in the mid-2000s (Fig. 3). It resulted from the implementation of new procedures and their rigorous application in accordance with the decentralization of the health information system in Mexico. In addition, hospital presentations of mild SSE were likely to have increased spontaneously since the health authorities –and the media– focused public attention on this health issue, prompting the patients to come for treatment. However, the motivation of people stung by a scorpion can vary depending on several parameters (danger of local scorpions, distance from and reputation of health center, free management for low income patients, sociocultural pressures, treatment-seeking behavior) which result from local culture, education and circumstance, in particular the place of the sting, i.e. in urban or rural areas. One can assume that motivation mainly affects asymptomatic or minimally severe stings. Regardless of the pain, a minority of scorpion stings have severe systemic symptoms and very few –apart from SSE in young children– are life-threatening. In Durango, Galván Cervantes (1966) described the increasing incidence of asymptomatic scorpion stings between the start and the end of his study (1955–1964) from 53% to 70% while mortality remained under 1% during the same period. Chowell et al. (2006) in Colima in 2000–2001, reported that 50% of scorpion stings were mild, while 17% were considered serious and mortality was 0.03%. In Guerrero, severe envenomation represented 44% of the stings in the 1980s (Villegas et al., 1988), while 19% patients presented with symptomatic envenomation between 1999 and 2005 (Lagunas-Flores and Lagunas-Jaimes, 2009), illustrating some variability in conditions, perceptions or criteria of envenomation severity. Such information is lacking in the case reporting. However, an increase in the incidence –mainly linked to recruitment bias and concerning mild cases– has consequences on the calculation of the case fatality rate. In contrast, the calculation of mortality depends on the number of deaths relative to the general population and is not affected by changes in incidence.

Death from SSE results from many factors. The danger, abundance and geographical distribution of scorpions as well as their behavior, in particular their proximity to dwellings or places of high human activity, are crucial factors (Chippaux and Goyffon, 2008; González-Santillán and Possani, 2018; Lourenço, 2018; Ponce-Saavedra et al., 2016; Riaño-Umbarila et al., 2017; Silva-Domínguez et al., 2019) which largely explain the distribution of SSE mortality in Mexico (Fig. 9). In addition, the management of SSE, and perhaps prevention of contact, are critical elements that help explain the evolution of mortality.

While mortality was stable, or even increased slightly during the 40s and 50s (Fig. 1), it showed that starting in the 1970s –or perhaps before, since we do not have data between 1960 and 1978– a dramatic fall in four steps (Fig. 8). The strong decreasing slope between 1979 and 1988 is followed by a slightly decreasing slope between 1989 and 1996, then a further strong decrease from 1997 to 2003 and finally, after 2004 an asymptotic plateau as if the lower limit of mortality had been reached. In addition, case fatality rate was over 0.6% in the early 1990s. It fell sharply to less than 0.2% in 1996 and continued to decline to 0.01% from the end of the years 2000 (Fig. 12). The decline by tier suggested a

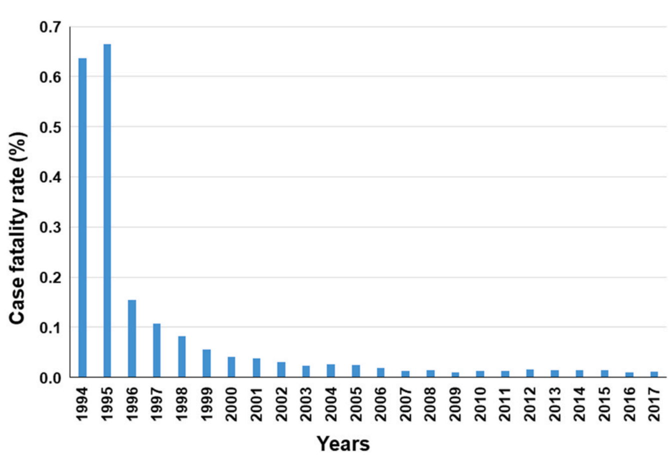

Fig. 12. Case fatality rate of scorpion stings in Mexico, 1994–2017. [Source: Información Epidemiológica/Publicaciones de Mortalidad/Dirección General de Epidemiología/Dirección General Adjunta de Epidemiología]

set of successive causes. The conjunction of the decrease in mortality and case fatality rate makes it possible to formulate some hypotheses which are not exclusive: a) reduction in the population of scorpions, in particular the dangerous species; b) change in human population behavior and scorpion sting circumstances; c) increasing availability of or demand for healthcare; and d) improvement in healthcare.

A spontaneous reduction in scorpion populations has never been reported, probably due to their strong resistance and adaptability to environment changes. Spreading of insecticide undertaken for malaria control, for example, seemed to have contrasting and controversial effects on scorpion populations. While Ramsey et al. (2002) have shown the effectiveness of pyrethroids (up to 83% reduction of scorpions in houses and 77% around houses), several previous or retrospective studies in Mexico and Brazil have indicated that chemical control was poorly efficient over the long term and even suggested that it may have had a dispersive effect on scorpions (Galván Cervantes, 1966; Albuquerque et al., 2009). In any case, the increasing incidence in the current study, even if we take into account case reporting biases, showed the resilience of scorpion populations, if not their growth, and persistence of similar exposure to risk, both quantitatively and qualitatively. Numerous studies in Mexico and elsewhere have shown that urbanization and suburban development, especially when the environment is precarious or poor, are not associated with a decline in scorpion populations. Scorpion populations adapt well in this type of environment (Castillo Pérez et al., 2002; de Roodt, 2014; Reckziegel and Pinto, 2014; Furtado et al., 2016; Araújo et al., 2017; Riaño-Umbarila et al., 2017; Lourenço, 2018; Silva-Domínguez et al., 2019).

A change in the behavior of rural and urban populations –at least in the sense of reducing risk and exposure– was unlikely. The local and general characteristics of the incidence did not seem to have changed intrinsically since 1979. In particular, they did not change in relationship to geographic distribution, population growth, gender or age (data not shown). We did not observe a correlation between the incidence of scorpion stings and population density or SLI. On the other hand, the correlation between the annual number of scorpion stings in each state and the GDP could reflect a higher risk among populations with limited resources. Several authors have pointed out poor environment as risk factors for scorpion stings, which is consistent with low economic resources. Silva-Domínguez et al. (2019) showed a significant relationship between the incidence of scorpion stings and lack of cleanliness of housing, agricultural professions, and roofing infrastructure in unsound materials, suggesting that preventive measures should be based on the improvement of roofing materials and of housekeeping. However, this should not conceal the considerable influence of climate on scorpion dispersion and development (Chowell et al., 2005; Lourenço, 2018).

Therefore, it seems that in the face of increasing incidence –or the better measure of it– health strategies have greatly improved the management of SSE, and that this improvement has resulted in a significant drop of case fatality rate and mortality. The stability of the incidence while the mortality decreases could be explained either a) by a replacement of dangerous scorpions by less dangerous species, which has never been observed and even is contradicted by numerous entomological and epidemiological studies (Galván Cervantes, 1966; Dehesa-Dávila, 1989; Dehesa-Dávila and Possani, 1994; Castillo Pérez et al., 2002; Ponce-Saavedra et al., 2016; Riaño-Umbarila et al., 2017; González-Santillán and Possani, 2018; Silva-Domínguez et al., 2019), or b) through improved care and/or better access to care.

Morbidity due to SSE is due on one hand to the direct action of the venom and, on the other, to the secondary systemic impact of patient's defensive responses (Chippaux, 2012; Isbister and Bawaskar, 2014). The main purpose of antivenom is to remove venom from the body in order to stop the original cause of envenomation. As complement, supportive care intends to reduce secondary symptoms of the envenomation and prevent multiorgan failure (Chippaux, 2012). Severe envenomation necessitates intensive supportive care. The improvement of the health system and the development of hospitals with emergency and resuscitation services certainly contributed to the decrease in mortality for various diseases including SSE. Scorpion sting management gradually improved with better knowledge of the composition and mode of action of venoms. This has become more accurate and appropriate since the 1960s, as can be assessed from the therapeutic recommendations mentioned in the literature (Galván Cervantes, 1966; Dehesa-Dávila, 1986; Montoya-Cabrera, 1996; Alagón, 2002; Alagón et al., 2003; Lagunas-Flores and Lagunas-Jaimes, 2009).

The efficacy and safety of antivenoms are controversial (Galván Cervantes, 1966; Foëx and Wallis, 2005; Lagunas-Flores and Lagunas-Jaimes, 2009). However, recent studies have shown their benefit, provided they are correctly manufactured and used (Dehesa-Dávila and Possani, 1994; Boyer et al., 2009). In severely envenomed children, intravenous administration of a specific antivenom composed of highly purified IgG F(ab')$_2$ fragments resolved the clinical syndrome within 4 h in all children compared with 15% in those who did not received it. In addition, the need for supportive care was reduced to less than 30 min in the antivenom group versus almost 10 h in the others, and the venom disappeared from the plasma in less than an hour versus more than 4 h in the control group (Boyer et al., 2009).

The history of antivenoms in the world and in Mexico has been detailed by Boyer (2013). Since the discovery of antivenoms by Phisalix and Bertrand (1894) and Calmette (1894), there have been 3 generations (Table 3; Fig. 13). The first consisted of the whole serum of the immunized animal (Calmette, 1907). It was gradually replaced by the second generation from 1907, composed of IgG concentrated by precipitation using an ammonium sulfate solution (Pick, 1902) then improved (Gibson, 1905; Brazil, 1907, 1914; 1916; Homer, 1918; Grasset, 1932). The third generation, still used today, is obtained by enzymatic digestion of IgG (Parfentchev, 1936, 1938; Pope, 1939). Marketed in the 1940s (Grasset and Christensen, 1947), they were generalized after the 1960s with great differences in quality.

In Mexico, the development of antivenoms against scorpion venoms evolved in 4 phases (Table 3; Fig. 13): a) the proof of concept of antivenom controlling scorpion venom, in 1905 by Vergara Lope (1906), b) manufacture of a 2nd generation antivenom in 1928 (León de la Peña and Venzor, 1931; Cervera, 1936), the industrial production and marketing of which began in 1938 by MyN laboratory (Chavez Haro, 2007), c) industrial manufacture of 3rd generation antivenom from 1980 by Zapata laboratory, bought by Profam in 1986 then by Bioclon in 1990, and d) provision of highly purified F(ab')$_2$ from 1995 (Espino-Solis et al., 2009). These highly purified specific antibodies resulted from a patented process for the thorough purification of IgG F(ab')$_2$ fragments (Chavez Haro, 2007).

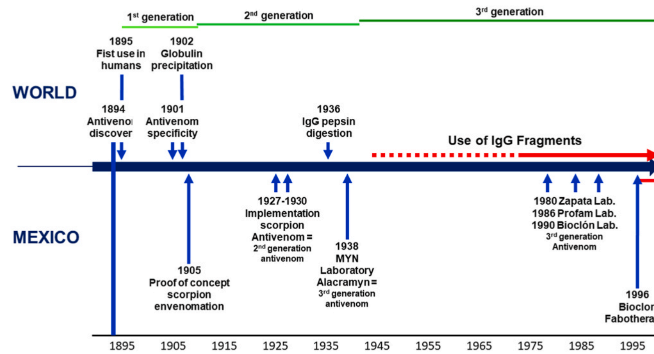

Fig. 13. Brief sketch of the history of antivenoms in the world and Mexico from the origins (1894) to now.

While technological progress of the manufacture of antivenoms aimed at increasing efficiency, it has also resulted in greater safety. Tolerance mainly depends on the manufacturing process of the antivenom and those composed of poorly purified IgG fragments are poorly tolerated (Chippaux et al., 2015). Safe antivenom can be distributed in isolated peripheral health centers, lacking sophisticated means of resuscitation (Boyer et al., 2013a). Thus, administered earlier, antivenom efficiency is significantly increased and the need to use strong supportive treatments is reduced (Dehesa-Dávila, 1989; Boyer et al., 2013b).

The delivery of antivenom gradually increased between 1995, when the first batches of highly purified F(ab')$_2$ were released, and 2007, when the annual number of distributed vials stabilized. The sales curve for antivenom between 1995 and 2007 is the reverse of the dramatic drop in mortality, suggesting an inversely proportional relationship between both (Fig. 14).

Once purified antivenom was standardized and validated, it was necessary to ensure its general use and accessibility and its manufacture in sufficient quantity. Medical treatment with SSE is expensive, estimated in the late 2000s at almost US $ 600 (Granja Bermúdez et al., 2009), which is out of reach of many patients. The latter, if they do not

Table 3
History of antivenoms in the world and Mexico from the origins (1894) to now.

Years	World event	Mexico event	Remarks	References
1894	Antivenom discovery			Calmette, 1894; Calmette (1894)
1995	First human administration of antivenom		First generation of antivenom: whole serum	Calmette, 1896
1901	Antivenom specificity		Development of local antivenoms worldwide	Brazil (1914)
1902	Globulin precipitation		Procedure simplifications and improvement will take place until 1920	Pick (1902); Gibson, 1905; Brazil (1907)
1905		Scorpion antivenom	Proof of concept of scorpion antivenoms	Vergana Lope (1906)
1906			Second generation of antivenom: globulin precipitate	Brazil, 1907; Grasset (1932)
1924	Anavenom discovery			Ramon (1924)
1926		Development of the 2nd generation of antivenom		Cervera (1936); Monroy-Velasco (1961)
1930			First commercial whole IgG scorpion antivenom in Mexico (MyN)	Monroy-Velasco (1961); Taub (1964); Russell & Lauritzen (1966)
1936	Enzyme digestion of globulins			Parfentchev (1936), 1938; Pope (1939)
1947	First commercial 3rd generation of antivenoms		Third generation of antivenom: purified IgG fragments.	Grasset & Christensen (1947)
1958–1960	Discovery of IgG structure			Edelman & Porter
1970s			Enforcement of enzyme digestion to most commercial antivenoms started during the 70s	
1980		Marketing the 3rd generation of antivenom		Dehesa-Dávila (1989)
1995		Marketing Fabotherapy	Highly purified F(ab')$_2$ scorpion antivenom distributed in Mexico (Bioclon)	Espino-Solis et al. (2009); Alagón, 2002

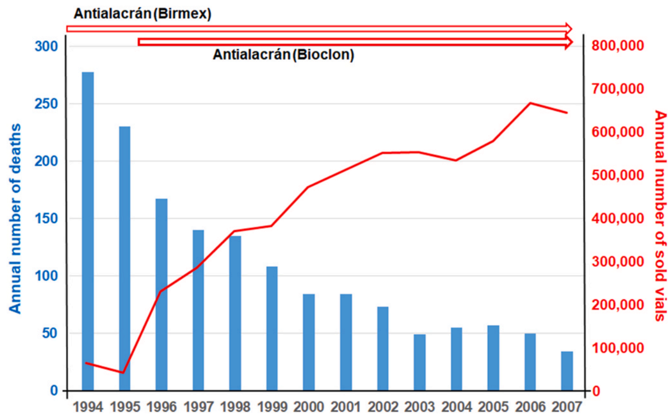

Fig. 14. Evolution of antivenom sales against scorpion envenomation ('Antialacrán' and 'Alacramyn') and mortality from scorpion stings between 1994 and 2007.

have social security coverage or appropriate insurance, may hesitate to seek care, which delays, or even precludes, treatment. Mexican health coverage is provided by different social mechanisms. The Mexican healthcare system has gradually improved since the creation of the General Hospital of Mexico City in 1905, establishing of the Mexican Social Security Institute (IMSS) in 1943, Institute of Security and Services Social Workers of the State (ISSSTE), then various social funding programs until the creation of the Social Health Protection System (SPSS) in 2003, which allow free access to healthcare for around 75% of the Mexican population, especially among the poorest (Gómez-Dantés et al., 2011).

In hospitals and health centers of the Ministry of Health, antivenoms are purchased by the government. In addition, several social organizations provide antivenoms free of charge to covered patients, including ISSSTE which supports workers in Mexican States, IMSS which covers workers in companies not belonging to the government, the national system of integral development of families DIF and other autonomous organisms including the Mexican Petrol Company (PEMEX), the Ministry of Defense (SEDENA), the Ministry of the Navy (SEMAR), etc. (Fig. 2). These allocations involve more than 95% of the use of antivenom. On the other hand, in private health facilities, patients pay for the administered antivenoms and may be reimbursed by insurance companies. Unfortunately, we do not have precise data on the severity of SSE cases, especially those requiring immunotherapy, and the use of antivenoms, including the number of vials used for each treatment.

Two basic factors aimed at reduce mortality due to SSE from the 1970s. On the one hand, improving the management of SSE through more effective treatments and, on the other hand, better access to healthcare. The latter results from a proactive health policy allowing underprivileged populations to benefit from appropriate care. The improvement in treatment involved both advances in intensive care and more effective and earlier immunotherapy. Access to highly purified IgG fragments at the end of the 1990s (Fig. 14), allowing greater safety, was a key element in extending immunotherapy to more patients, resulting in a reduction in severity of SSE with early treatment.

5. Conclusion

Scorpion stings occur mainly in inhabited places showing low population density and unsanitary or economically unstable environment. Populations with low or moderate resources seem to be more impacted. The incidence increased during the 10 first years of scorpion sting reporting between 1994 and 2005, resulting from the implementation and transmission of data collection and, to a lesser extent, increasing hospital presentation of asymptomatic sting or mild envenomation.

Although scorpion sting incidence is currently stable, mortality showed a dramatic decline by steps over the past forty years (Fig. 8). First, from the 1960s, the effectiveness of treatment protocols, particularly in emergency wards, gradually improved, resulting in considerable decline of mortality thanks to effective supportive healthcare. Then, the development of better antivenom in sufficient quantity from the late 1990s (Fig. 14) improved clinical evolution of severe SSE by promoting rapid elimination of the venom, reducing the length of hospital stays and the quantities of symptomatic drugs administered. Finally, throughout this period, the accessibility of healthcare increased due to the improvement of the Mexican social system which allowed a very large number of patients to rapidly benefit from appropriate treatment. The number of deaths that remain, around 30 per year, mainly among very young children, seems hard to reduce. This objective could be achieved by intervening in the exposure to the risk of scorpion stings, in particular by cleaning up the outskirts of cities and around the houses.

This study presents a rational explanation of the mortality reduction due to the management of SSE, which could prompt health authorities of countries located in regions of the world exposed to scorpion stings, such as North Africa, the Middle East or South Asia, to adopt an effective strategy to better control this scourge.

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Ethical statement

This manuscript presents a retrospective epidemiological study performed following the standard procedure of scientific ethics excluding the use of personal medical records and laboratory animals.

CRediT author statement

Chippaux Jean-Philippe: Conceptualization, Methodology, Data curation and organization, Formal analysis, Writing - original draft, Writing - review & editing, validation of the manuscript. **Celis Alfredo:** Conceptualization, Methodology, Data curation and organization, Formal analysis, Validation, Writing - review & editing, validation of the manuscript. **Boyer Leslie:** Validation, Writing - review & editing, validation of the manuscript. **Alagón Alejandro:** Data curation and organization, Writing - review & editing, validation of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JPC has carried out clinical trials in Africa and South America as a research director at the French National Research Institute for Sustainable Development (IRD), involving drugs, vaccines and antivenoms, for which IRD received support either from World Health Organization or manufacturers (Merck, Sharp & Dohm, Sanofi Pasteur, Bioclon and Inosan). He reports no current financial conflict of interest. CA reports no conflict of interest. LVB has carried out clinical trials while employed by the State of Arizona, involving antivenoms from Therapeutic Antibodies, BTG, and Bioclon, for which the University of Arizona received support from the manufacturers. She has conducted clinical research using antivenoms from Inosan, for which University of Arizona grant funds were used to purchase antivenom. She reports no current financial conflict of interest. AA helped to carry out clinical trials and wrote BLAs while employed by the Universidad Nacional Autónoma de México (UNAM), involving antivenoms from Therapeutic Antibodies, BTG, and Bioclon, for which the UNAM received support from the manufacturers and AA received support as a consultant for Bioclon. Both supports ended in mid-2013. He reports no current financial conflict of interest.

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