

# Mortality trend by dengue in Mexico 1980 to 2009

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## ABSTRACT

**Objective.** To describe the mortality of dengue in Mexico during 1980 to 2009. **Material and methods.** Dengue mortality data for Mexico were obtained from Instituto Nacional de Estadística, Geografía e Informática. We used standardized and non-standardized dengue mortality rates per 1,000,000 people and determined the mortality trend. The groups were based on International Classification of Diseases coding criteria (ICD-9 E061 and ICD-10 A91X). The results were stratified by age groups and the frequencies of dengue deaths were compared using relative risk (RR) with its 95% confidence interval. **Results.** During 1980 to 2009 in Mexico, 549 deaths due to dengue were reported. We found an important variation in the mortality rates during the years studied. We were able to identify three periods: 1980 to 1992, 1994 to 2000, and 2001 to 2009. The mortality rates found are from 0.88/1,000,000 through 0.00/1,000,000. The average mortality rates by decade: 1980 to 1989: 0.53/1,000,000; 1990 to 1999: 0.06/1,000,000; 2000 to 2009: 0.12/1,000,000. In the analysis of mortality by community size during 2000 to 2009, we observed in the small communities with < 2,499 people, the risk is 1.25 times higher than in those with more than 20,000 people. **Conclusions.** We found, in general, a sustained decline in the number of deaths by dengue over the last 30 years in Mexico. However, a slow increase was observed since 1994, which may be related to the circulation of DENV2 and DENV3, among other factors. We need to strengthen prevention programs in smaller communities (< 2,499) where we found a higher risk of mortality due to dengue.

**Key words.** Mortality. Dengue. Mexico.

## Mortalidad por dengue en México durante 1980 a 2009

## RESUMEN

**Objetivo.** Describir la mortalidad por dengue en México durante 1980 a 2009. **Material y métodos.** A partir de las bases de datos del Instituto Nacional de Estadística, Geografía e Informática, se estimaron tasas estandarizadas y crudas de la mortalidad. El análisis se llevó a cabo con las muertes codificadas según la novena y décima clasificación internacional de enfermedades códigos E061 y A91X. La tendencia general y las muertes por dengue se estratificaron por tamaño de localidad y grupo de edad. Las frecuencias de las muertes por dengue se compararon mediante riesgo relativo (RR) y se tomó como significancia estadística el intervalo de confianza de 95%. **Resultados.** Durante 1980 a 2009 se reportaron un total de 549 muertes por dengue en México. Se encontraron variaciones importantes en cuanto a las tasas de mortalidad durante los 30 años de estudio. Se identificaron tres grandes periodos: 1980 a 1992; 1994 a 1999 y de 2001 a 2009. Las tasas encontradas fueron desde 0.81/1,000,000 habitantes hasta 0.00/1,000,000. El promedio de las tasas de mortalidad por década fueron: 1980 a 1989: 0.53/1,000,000 habitantes; 1990 a 1999: 0.06/1,000,000 habitantes; 2000 a 2009: 0.12/1,000,000 habitantes. En el análisis del riesgo de morir según tamaño de la localidad, se encontró que las personas de comunidades pequeñas (< 2,499 habitantes) presentaron un riesgo 1.25 (IC95% 1.24 a 1.27) veces mayor de morir de dengue relativo aquellas con más de 20,000 habitantes. **Conclusión.** Existe un decremento importante de la mortalidad por dengue en las tres décadas estudiadas. A pesar de eso, se ha presentado un incremento paulatino desde 1994. Esto se asociaría con la circulación de DENV2 y la introducción en México del DENV3, entre otras macrodeterminantes. Es necesario fortalecer acciones de prevención en las comunidades pequeñas (< 2,499 habitantes) donde se pudo apreciar un mayor riesgo.

**Palabras claves.** Mortalidad. Dengue. México.

## INTRODUCTION

Around 50 million people world-wide are infected annually by the dengue virus (DENV). Of those, approximately 500,000 develop its severe form, hemorrhagic dengue fever (DHF), which has a mortality rate that can reach > 5%.<sup>1</sup> Even though the real magnitude of the disease has not been determined, it is estimated that around 2,500 million people live in risk areas. One of this is the rural area with small communities where we can find ecological, social and demography factors for dengue transmission.<sup>2</sup> Due to climate change, a notable increase in that number is expected in the next years.<sup>3</sup> Global warming has broadened the reproductive niches of the principal vector, the mosquito *Aedes aegypti*. Because of this, the number of areas of risk, and ultimately the number of susceptible individuals, has increased.<sup>4,5</sup>

Dengue is a mosquito-borne disease, caused by serologically related but antigenically distinct single-strand positive sense RNA virus. The viruses have been grouped into four serotypes: DENV-1 through DENV-4, belonging to the genus *Flavivirus* (family *Flaviviridae*). To date, many virulent strains have been identified with different transmission capacity, and simultaneous circulation of several serotypes and genotypes in the same region has been reported.<sup>6,7</sup>

Since the 1970s, large epidemics due to DENV have been present in Latin America, including Mexico.<sup>8</sup> In Mexico during the year 1995, circulation of the four DENV was reported<sup>7</sup> and the number of cases reported has increased.

In week 40 of 2009, there were 29,993 confirmed cases of dengue.<sup>9</sup> For week 33 of 2010, the epidemiological bulletin confirmed 14,069 cases of individuals with dengue in Mexico: 11,314 cases of Dengue Fever (DF); 2,755 cases of DHF; and four deaths.<sup>10</sup>

Information on dengue has increased notably in the last decade, but many aspects remain to be investigated. The Integrated Management Strategy proposed by the World Health Organization (WHO) aims at strengthening national programs, with the goal of reducing morbidity and mortality. Also, the lines of investigation outlined by the AHO/WHO, through the Program for Research and Training in Tropical diseases, are based on the active observation of the epidemiology of the disease.<sup>8</sup> One of these lines of investigation is defining the burden of the disease, the economic and social impact of dengue. In spite of its importance in public health in Mexico, the behavior of the mortality trend of this problem has not been studied. This is the objective of our work: to describe the behavior of mortality by dengue in Mexico from 1980 to 2009.

## MATERIAL AND METHODS

This is a cross-sectional ecological study which analyzed the aggregate data from the Mortality database on line of the National Institute of Statistics, Geography, and Information (*Instituto Nacional de Estadística, Geografía e Informática, INEGI*) for the years 1980 to 2009.<sup>11</sup> These studies assess the existence of an association between the level of exposure to a risk factor and the rate of the disease under consideration from data aggregated at the level of geographic unit; synthetic estimators summarize the information recorded in each of the units considered.<sup>12</sup> The mortality data were classified and analyzed with the software Visual FoxPro 6.0, Excel 2007 and SPSS 13.0. For analysis, only records with the following codes were used: E061 of the 9th International Disease Classification (IDC-9),<sup>13</sup> and A91X of the 10th International Disease Classification (IDC-10).<sup>14</sup>

The variables analyzed were the following: age, sex, size of locality, and year of the event. Mortality rates by dengue were calculated as the total number of deaths by dengue occurring in a given period, divided by the number of person-years in the period. The denominator for the rates was projected linearly<sup>15</sup> from the population registered in the General Population Census of 1980,<sup>16</sup> 1990,<sup>17</sup> and 2000<sup>18</sup> and the General Population Counts of 1995<sup>19</sup> and 2005.<sup>20</sup> For the mortality analysis, both raw and standardized rates for the population were used (per 1,000,000 inhabitants).<sup>21</sup> The rates were standardized, according to the General Population Census for the year 2000,<sup>18</sup> were grouped by age:

- Less than 1 year of age.
- From 1 to 4 years of age.
- From 5 to 9 years of age.
- From 10 to 19 years of age.
- From 20 to 39 years of age.
- From 40 to 59 years of age.
- 60 years of age and over.

This classification was used before by Celis, *et al.* (2007), in a cross-sectional ecological study in Mexican population.<sup>22</sup> Mortality was grouped into three decades: 1980 to 1989, 1990 to 1999, and 2000 to 2009. To describe the difference between groups and the mortality rates by sex, we used ANOVA and a value  $p \leq 0.05$  for statistical significance. To estimate the relative risk (RR) and its 95% confidence interval (95% CI) between two groups adjusted regressions were used. It was defined, as the frequency of the exposed factor  $X_1$ , related exposed factor  $X_0$ ; or  $y_1/y_0$  so that:  $y_0 = a + bx_0$

and  $y_1 = a + bx_1$ ; then, the relative risk can be estimated as:<sup>23</sup>

$$RR = \frac{y_1}{y_0} = \frac{a + bx_1}{a + bx_0}$$

The DENV serotype reported in the 30 years of study were optioned through the papers of Díaz, *et al.* (2006), Vázquez-Pichardo, *et al.* (2011) and the Ministry of Health of Mexico.<sup>7,24,25</sup>

## RESULTS

During the 30 years studied, 549 deaths due to dengue were registered at the national level. Mortality behavior during the period studied showed broad variations, among which three patterns can be identified: mortality rates from 1980 to 1992 reach 0.88/100,000 and then decline to 0.00/1,000,000; from 1994 to 2000, the mortality has the same pattern, reach to 0.13/1,000,000 and decline again to 0.00/1,000,000; during the last period, 2001 to 2009, we found an upward trend that reaches a mortality rate of 0.39/100,000 (Figure 1, Table 1). In the analysis by decade, generally the same pattern in the mortality rates was found. The average mortality rates were:

- 1980 to 1989, 0.53/1,000,000.
- 1990 to 1999, 0.06/1,000,000.
- 2000 to 2009, 0.12/1,000,000.

The mortality rate does not show different behavior according to the rates by sex; ANOVA test: between groups: sum of squares 0.004,  $df = 1/58$ ,  $f = 0.56$ ,  $p = 0.81$  (Table 1).

The findings reported by Díaz, *et al.* (2006), Vázquez-Pichardo, *et al.* (2011) and the Ministry of Health of Mexico;<sup>7,24,25</sup> have been inserted into figure 1. An increase can be seen with each introduction of a DENV, especially DENV2 and DENV3.

Table 2 shows the mortality distribution by community size during the three decades. For the period 1980 to 1989 the highest risk were found in the communities with less than 2,499 people, compared with those over 20,000 people (RR 14.93 95% CI 14.80 to 15.06). In the decade of 1990 to 1999 the highest risk was still in the communities with less than 2,499 people compared with those over 20,000 people, but the risk dropped significantly (RR 2.29, 95% CI 2.27 to 2.31). The same pattern was observed for the decade of 2000 to 2009 for those communities with less than 2,499 people, the risk keep dropping (RR 1.54 95% CI

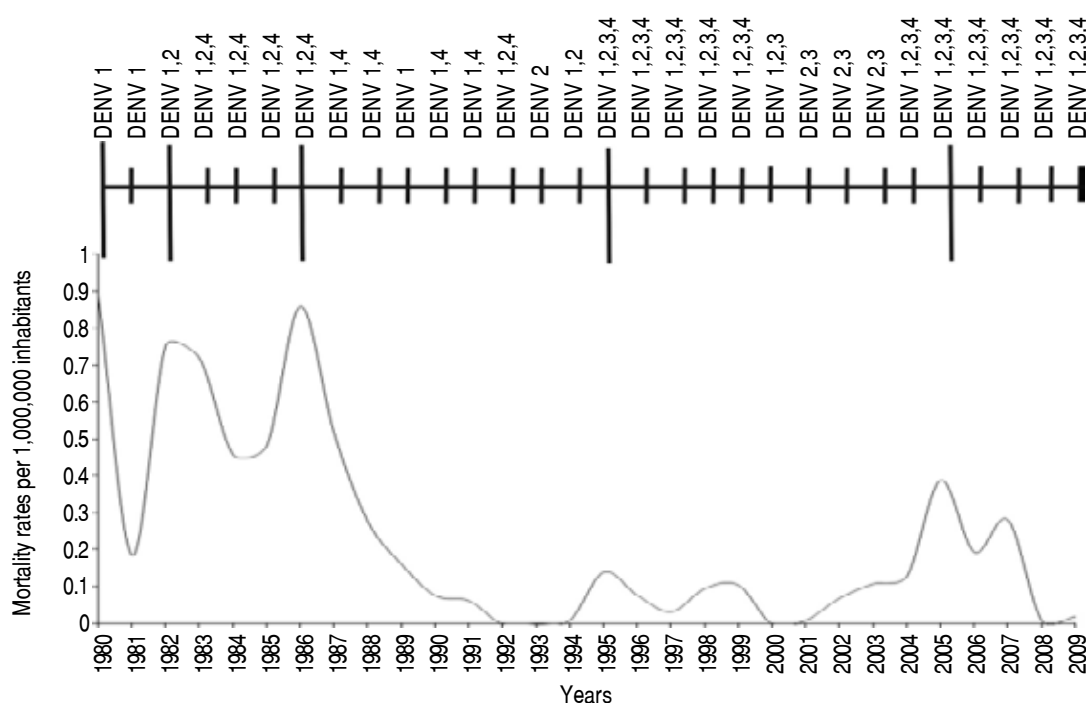


Figure 1. Mortality trend\* by dengue and serotype reported of DENV\*\* in Mexico 1980-2009. Source: mortality database on line of the Nacional Institute of Statistic, Geography, and Information (INEGI). \*Mortality rates per 1,000,000 inhabitants; standardized according to the General Population Census for the year 2000 (INEGI). \*\*Source: Díaz, *et al.* (2006), Vázquez-Pichardo, *et al.* (2011) and Minister o Health of Mexico ([cenavece.salud.gob.mx](http://cenavece.salud.gob.mx)).

Table 1. Mortality rates\* for dengue en Mexico by sex, three decades.

Year	National mortality rates	Mortality rates in men	Mortality rates in women
1980	0.89	0.88	0.84
1981	0.31	0.45	0.17
1982	0.75	0.91	0.60
1983	0.72	0.70	0.74
1984	0.46	0.39	0.52
1985	0.48	0.59	0.38
1986	0.86	0.94	0.78
1987	0.52	0.47	0.56
1988	0.27	0.33	0.20
1989	0.12	0.08	0.15
1990	0.08	0.05	0.10
1991	0.06	0.03	0.10
1992	0.00	0.00	0.00
1993	0.00	0.00	0.00
1994	0.01	0.00	0.02
1995	0.14	0.14	0.14
1996	0.08	0.08	0.08
1997	0.03	0.00	0.06
1998	0.10	0.11	0.08
1999	0.11	0.13	0.08
2000	0.00	0.00	0.00
2001	0.01	0.02	0.00
2002	0.07	0.02	0.12
2003	0.11	0.04	0.17
2004	0.13	0.16	0.10
2005	0.39	0.36	0.42
2006	0.19	0.21	0.18
2007	0.28	0.26	0.30
2008	0.01	0.02	0.00
2009	0.02	0.04	0.00

ANOVA: between groups; men and women: Sum of squares 0.004, df = 1/58, f = 0.56, p = 0.81. Average rates and standard deviation by decades: 1980-1989: 0.53 (DS  $\pm$  0.27). 1990-1999: 0.06 (DS  $\pm$  0.05). 2000-2009: 0.12 (DS  $\pm$  0.13). \*Mortality rates per 1,000,000 inhabitants and standardized according the general population census 2000 (INEGI).

1.24 to 1.26) when compared with the communities over 20,000 people.

Table 3 presents the mortality rates and the relative risk by age group. For the total period, individuals less than one year of age presented a risk of death 13.48 (95% CI 13.36 to 13.60) times greater than those in the 5- to 9-year-old age group. Likewise, the 60-and-over age group presented a risk of death 23.60 (95% CI 23.39 to 23.80) times that observed in the 5- to 9-year-old age group. Comparing the mortality rate by groups of age in the decades of 1980-1989 *vs.* 2000-2009, an important reduction in the mortality rates in all the groups with different percentages was found. The biggest change was found for the group of 60 years and over with 92.08%, closely followed for the group of 1 to 4 years with 91.83%, and the less than 1 year of age, with 89.50%. Two groups with small percentage changes in the mortality rates were identified: the group of 10 to 19 years of age with 13.31% and the group of 20 to 39 years of age with 10.84%. On the other hand, when we compared the decades 1990-1999 to 2000-2009, an important increase in mortality rates for the age group of 10-19, 20-39 and 40-59 years were found.

## DISCUSSION

In Mexico and Central America, the number of cases of DF has doubled in the last 30 years. The same pattern holds for cases of DHF. This can be verified with the data published for our region by San Martín. This same study reports a downward trend in lethality, severe cases (DHF), of the total number of deaths. For the period of 1980 to 1989 a lethality of 6.4% was reported, followed by 2.4% for 1990 to 1999, and of 0.7 for the period of 2000 to 2007. Like San Martín, our

Table 2. Description of the mortality for dengue according the communities size by decade in Mexico 1980-2009.

	Community size	Population	Cases (n)	Rate*	RR**	95% CI***
1980 to 1989	1 to 2,499	22,548,104	293	12.99	14.93	14.60 to 15.01
	2,500 to 19,999	11,026,752	52	4.72	5.43	5.38 to 5.47
	20,000 and over	33,272,977	29	0.87	1	-
1990 to 1999	1 to 2,499	23,289,924	26	1.17	2.29	2.27 to 2.31
	2,500 to 19,999	12,959,877	8	0.67	1.27	1.25 to 1.28
	20,000 and over	44,999,844	22	0.49	1	-
2000 to 2009	1 to 2,499	24,723,590	38	1.54	1.25	1.22 to 1.26
	2,500 to 19,999	15,229,080	16	1.05	0.85	0.85 to 0.86
	20,000 and over	57,530,742	71	1.23	1	-

\*Mortality rate per 1,000,000 inhabitants. \*\*RR: relative risk. \*\*\*95% CI: 95% confidence interval.

**Table 3.** Description of the mortality by dengue according age groups during each of the decades 1980 to 2009 in Mexico.

	Age group	Cases (n)	Mortality rate*	RR**	95% CI***
1980 to 1989	Less than 1 year	37	20.45	16.36	16.22 to 16.50
	1 to 4	24	3.03	2.42	2.40 to 2.45
	5 to 9	13	1.25	1	-
	10 to 19	32	1.75	1.40	1.39 to 1.41
	20 to 39	45	2.15	1.72	1.70 to 1.74
	40 to 59	60	6.41	5.13	5.08 to 5.17
	60 though highest	161	34.24	27.39	27.15 to 27.63
1990 to 1999	Less than 1 year	0	0.00	0	-
	1 to 4	2	0.23	1.21	1.20 to 1.22
	5 to 9	2	0.19	1	-
	10 to 19	3	0.14	0.74	0.73 to 0.74
	20 to 39	12	0.43	2.26	2.24 to 2.28
	40 to 59	11	0.85	4.47	4.43 to 4.51
	60 though highest	22	3.87	20.37	20.19 to 20.55
2000 to 2009	Less than 1 year	4	2.15	11.32	11.70 to 11.42
	1 to 4	2	0.25	1.32	1.30 to 1.33
	5 to 9	2	0.19	1	-
	10 to 19	29	1.52	8.00	7.93 to 8.07
	20 to 39	43	1.92	10.11	10.02 to 10.19
	40 to 59	31	3.13	16.47	16.33 to 16.62
	60 though highest	14	2.71	14.26	14.14 to 14.39
Total (1980 to 2009)	Less than 1 year	41	21.71	13.48	13.36 to 13.60
	1 to 4	28	3.42	2.12	2.11 to 2.14
	5 to 9	17	1.61	1	-
	10 to 19	64	3.30	2.04	2.03 to 2.06
	20 to 39	100	4.19	2.60	2.58 to 2.63
	40 to 59	102	9.51	5.91	5.86 to 5.96
	60 though highest	197	37.99	23.60	23.39 to 23.80
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<sup>a</sup> Change (%)			80's vs. 00's	90's vs. 00's	
	Less than 1 year		-89.50	0.00	
	1 to 4		-91.83	5.91	
	5 to 9		-84.70	3.46	
	10 to 19		-13.32	959.39	
	20 to 39		-10.84	351.03	
	40 to 59		-51.16	266.69	
	60 though highest		-92.08	-29.96	

\*Mortality rate per 1,000,000 inhabitants. \*\* RR: relative risk. \*\*\*95% CI: 95% confidence interval. <sup>a</sup>Rate change between decades 1980-1989 vs. 2000-2009 and 1990-1999 vs. 2000-2009.

data shows a statistically significant downward trend in mortality by dengue in Mexico.<sup>6</sup> This could be due, in large part, to the strategies implemented at the beginning of the 1980s, including the establishment of a system of epidemiological surveillance for vector-borne diseases, as well as to the incorporation of Manual Standard Number 40 for the prevention and control of dengue in primary health care.<sup>26</sup> Manual Standard

Number 40 was subsequently legislated to establish the official standard for epidemiological surveillance, prevention, and control of vector-borne diseases in 1994<sup>27</sup> and 2000<sup>28</sup>. Additionally, manuals for the monitoring, management, control, and treatment of dengue were distributed, promoted, and applied, with mandatory enforcement, throughout the Mexican territory.<sup>29-32</sup> The result of this was a successful strategy

for primary health care in Mexico, and the decrease of mortality by dengue. In countries that have achieved a decrease in mortality by dengue, it has been mainly on account of the establishment of programs of awareness and prevention, such as the development of training programs for the care of patients with DHF. Among these countries are Cuba, El Salvador, Brazil, and Thailand.<sup>33,34</sup>

Although not all the determinants of the increase or decrease in mortality by dengue are subject to the previous explanation, when the trends in mortality by dengue in Mexico are analyzed and associated with the chronological appearance of different DENV according to the studies of Díaz<sup>7</sup> and Vázquez-Pichardo,<sup>24</sup> an interesting pattern emerges. During 1980 to 1982, the probable cause of DENV deaths was DENV1. With the introduction of DENV2 in 1982, there was another increase in mortality that remained until 1986. Additionally, during this period DENV1, 2, and 4 coexisted. In 1987 the most notable decline in deaths by dengue began, coinciding with the absence of DENV2. During 1992 and 1993, there were no registered deaths, despite the reintroduction of DENV2. In 1994, an increase in the death trend begins with the appearance for the first time of DENV3, which remained present until the last year analyzed. The pattern of emergence and reemergence of the four DENV, and in particular the circulation of various genotypes, serotypes, and quasi-species in a determined area, has been associated with a greater number of severe cases and with an increase in mortality.<sup>7,33</sup>

The origin and evolution of the DENV that have circulated in Mexico, together with mortality, can be explained in the following manner. During the first upward trend in mortality by dengue (1980), the serotype DENV1, genotype 1298/YUKATAN-MX/80, was present. The American, Asiatic, and African genotypes of DENV1 were present as well during the period studied.<sup>7,35</sup>

The DENV2 probably involved in the deaths from 1983 to 1995 were the genotypes 421/MEXICO/83, 1482/MEXICO/84, 131/SONORA-MX/92 and 328298/REYNOSA-MX/95. In 1997, the Asiatic genotypes were introduced, which would explain to a certain extent the increase in severe cases, and a greater number of deaths.<sup>7</sup>

As for the 1994 reintroduction in America of DENV3 and its introduction in Mexico in 1995, these genotypes are more closely related to the African strains from Mozambique and Somalia than to the Asiatic strains.<sup>7</sup> However, there are other authors who suggest that the strain of DENV3 reintroduced in America in 1994 has Asiatic origins. This is the predominant serotype associated to fatalities. It could be one of the

explanations for the scope in the number of deaths over the last two decades. We can explain with this theory concerning a prior dengue infection which may set the stage for more deadly infections by a different serotype in the future. This point of view is supported by several seroepidemiological studies.<sup>6</sup>

The DENV4 that have been identified in Mexico come from common ancestors, the genotypes S44754/Tahiti/79 and 5489/New Caledonia/81.<sup>7</sup> The coupling of DENV2 of Asiatic origin and DENV3 of Asiatic or African origin is what appears to have been the cause in the increase of deaths from 1994 to 2009.

One of the macro-determinant factors which the aggregated database allows the exploration of is the size of the communities where the deaths occurred. This shows the social structure of the vulnerable individuals, the availability of basic public services such as access to health care.<sup>22</sup> The present study shows that small villages, of less than 2,499 inhabitants, are those with the greatest risk of death, more than 24 million people in Mexico alone.<sup>2,20</sup> The majority of these types of villages do not have basic services, such as garbage collection, drainage, or running water.<sup>29</sup> This generates ideal conditions for the reproduction of the vector.<sup>35,36</sup> Without denying the influence of other environmental, geographic, or political factors that may also be at play,<sup>37,38</sup> low socioeconomic levels and bad living conditions appear to act as direct or indirect factors in the number of cases of dengue. This situation is not exclusive to Mexico; it is linked with poverty and social inequality. Given this scenario, how can these communities be influenced to organize and battle against the vector when their cultural and economic level does not allow it, and they are more preoccupied with survival?<sup>39</sup> Measures as simple as placing covers over water containers would reduce in large extent the reproduction of the vector, diminishing mosquito density, and therefore reducing the number of cases of dengue, and ultimately, mortality.<sup>36,40</sup>

Our data demonstrates that mortality by age group seems to be towards the extremes of life, with highly elevated risks in the less-than-one-year and the over-60-years age groups. But in analyzing the rates in the 1980-1989 *vs.* 2000-2009, we found an important downward trend and the proportional decrease of > 89% in death rates for both age groups. Although all the age groups had important changes in rates, when we compared the decades 80's *vs.* 00's, the same pattern was reported in Thailand from 1980 to 2000.<sup>41</sup> But even with this downward trend in all age groups, a small reduction in the rates for those 10 to 19 and 20 to 39 was found. Also, when we compared the mortality rates for the decades 1990-1999 to 2000-2009 the impact

of mortality on these age groups is more evident. Proposed theories to explain the change in the age distribution include: severe cases and consequent mortality is based on demographic transition, along with a decrease in the virulence of the infection;<sup>41</sup> control of the household mosquito elimination programs, which may affect mosquito population towards non-residential areas and thereby infecting the mobile working population.<sup>42</sup> However, it is still unclear what factors may explain the change in the ages of severe cases of dengue and deaths.<sup>41</sup>

Our study has the implicit limitation of ecological studies based on mortality records. This reduces the number of variables to explore, assigning risk to groups instead of individuals.<sup>12</sup> Moreover, the validity of the results depends on the quality of the records, and it is well known that in small communities, an elevated number of undetermined deaths are reported.<sup>43</sup> As the risk of death by dengue found in small communities was the highest, the effect of this bias in information may be important. Additionally, diagnostic problems, with a large number of patients with unconfirmed cases, remain as probable causes increasing underreporting.

## CONCLUSIONS

During the 30 years analyzed in our study, we observed a change in the epidemiological paradigms of the disease; specifically, an important reduction in deaths in Mexico, through the establishment of standards and programs of vigilance and control. Considering the increase in the number of deaths associated with the cause, and in the development of an effective vaccine against dengue, the vigilant actions and attention to the environment to achieve the reduction in mortality rates must be intensified.

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*Recibido el 30 de septiembre 2011.*

*Aceptado el 27 de junio 2012.*