“Considerations for the introduction of the vaccine against dengue: From evidence to the policy”

Pablo Kuri Morales
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Epidemiology overview of *Aedes spp* infections in Mexico

**Dengue (1978 – present)**
- All 4 serotypes circulating in the country
- 30,000+ cases / year
- 10+ deaths / year
- Only two states disease – free

**Chikungunya (mid 2014 – present)**
- 2014: 222 confirmed cases
- 2015: 11,577 cases
- 2016: 80 cases (Feb 19, 2016)
- 28 states reporting cases

**Zika (late 2015 – present)**
- 93 confirmed cases
**Epidemiological surveillance**

## Confirmed cases of Dengue Fever and Dengue Hemorrhagic Fever in Mexico, 2014 – 2016*

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>DF Cases</td>
<td>43,663</td>
<td>23,374</td>
<td>21,201</td>
<td>768</td>
<td>-36.8</td>
</tr>
<tr>
<td>DHF Cases</td>
<td>18,667</td>
<td>8,647</td>
<td>5,464</td>
<td>381</td>
<td>-9.3</td>
</tr>
<tr>
<td>Total cases</td>
<td>62,330</td>
<td>32,021</td>
<td>26,665</td>
<td>1149</td>
<td>-16.7</td>
</tr>
<tr>
<td>Deaths</td>
<td>170</td>
<td>76</td>
<td>42</td>
<td>0</td>
<td>-44.7</td>
</tr>
<tr>
<td>Lethality</td>
<td>0.56%</td>
<td>0.88%</td>
<td>0.77%</td>
<td>0.00</td>
<td>-12.5</td>
</tr>
</tbody>
</table>

- We observe a 16.3% decrease of total Dengue cases and a reduction of both mortality and lethality.
- 50% of all cases occurred in 5 states: Veracruz, Sonora, Jalisco, Guerrero and Michoacan.

* Data up to the Source: SINA/DGE/SALUD/Sistema Especial de Vigilancia Epidemiológica de Dengue.
Virological surveillance

Incidence and isolated serotypes from DF cases by state, Mexico, 2015

States with the circulating serotype

<table>
<thead>
<tr>
<th>Serotype</th>
<th>DENV-1</th>
<th>DENV-2</th>
<th>DENV-3</th>
<th>DENV-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>DENV-1</td>
<td>27</td>
<td>21</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>DENV-2</td>
<td>1,379</td>
<td>496</td>
<td>74</td>
<td>124</td>
</tr>
</tbody>
</table>

- Seven states have four serotypes circulating
- Six states have three serotypes

Public Health Laboratory
- Virological surveillance
- Weekly updated online data

The state of Colima shows an incidence over 162.55

* Incidence per 100 thousand inhabitants

Source: SINAVE/DGE/SALUD/Sistema Especial de Vigilancia Epidemiológica de Dengue.
Integrated management strategy for Dengue prevention and control

Technical components:

1. Epidemiology—> Comprehensive Surveillance and outbreak preparedness
2. Entomological Surveillance
3. Laboratory support
4. Healthcare, patient care
5. Integrated vector management
6. Environmental management
7. Vaccine preparedness for eventual release

Planning, decision making, implementation and impact measurement:

1. Incidence rate reduction
2. Entomological risk control
Architecture of a integrated management system

- National Surveillance System (SINAVE)
  - Information platforms
    - Epidemiological
      - Clinical
      - Microbiological
    - Entomological
    - Environmental Control
  - Prioritization of intervention areas
    - Risk assessment: mapping
  - Informed decision making
    - Control actions
      - Implementation
    - Dengue Vaccine
  - Incidence & mortality
  - Vector control
    - IMPACT
Vector control actions

Mexico invest more than 800 mdp (42 million of dollars*)

Entomologic and epidemiologic surveillance

Health Promotion

Vector Control Healthcare

* 1 dollar = 18.20 pesos
Results:

- Organophosphate susceptibility
- Carbamate susceptibility
- Pyrethroid susceptibility

Conclusions:

- Susceptibility towards carbamates and organophosphates, resistance towards both Type I and II Pyrethroids.
May-Sep 2012
Creation of the Dengue Group of experts (DGE) and 4 meetings were held. Expert

Jan-Dec 2013
Exchange of information between Sanofi and COFEPRIS to begin the regulatory process

January 2014
The document “Creating a Public Policy for vaccine introduction” is published

June-Sep 2015
Three meetings of the Dengue group expert (DGE), and one meeting with the International experts who made some recommendations.

July 2015
International meeting of Dengue Vaccine Introduction (DVI) in the World Health Organization in Geneve

DEC 2015
Issuance of Sanofi Pasteur’s vaccine registration by COFEPRIS
Considering the high impact dengue fever has in the country, and the possibility of implementing a vaccine against the disease, the Mexican Secretariat of Health developed a strategy to define the public policy towards the matter, involving participating institutions from:

- **Public Sector**: Create an evidence-based proposal to future administration of the dengue vaccine once it become available.
- **Academic Sector**: A group of experts was integrated to fulfill the task.
- **Private Sector**
- DGE meetings since 2012. In 2015 two general meetings have been held.
- 71 participants from 22 national institutions.
- International Experts observed our process and made some recommendations.
- Glaxosmithkline, Merck, Sanofi-Pasteur and Takeda (Inviragen) have presented their progress.
Dengue vaccine, implementation process

Two clearly differentiated processes

Vaccine Sanitary Registration

COFEPRIS

Security Efficacy Quality

Vaccine Public Policy

NHS CONAVA

Cost / Benefit

Cost / Effectiveness

Dengue Expert Group

Where are we now?
On December 9th, 2015, Mexico was the first country of the world to obtained the sanitary registration to the dengue vaccine.


Mexico is for the first time part of a select group of 28 countries with an agency capable of manufacturing, distributing, reviewing and commercializing vaccines worldwide.
Dengue Group of Experts

Six working groups

- Epidemiological information/Burden of disease
- Legal and regulatory affairs
- Technical aspects
- Economy and financial aspects
- Social communication Health Promotion Diffusion
- Health care
Technical aspects

- Burden of disease (incidence, prevalence, disability, hospitalizations and mortality).
- Vaccine efficiency, quality and safety.
- Comparison with other interventions.
- Economic and financial criteria.
  - Budget Impact Analysis in the institutions of the National Health System.
  - Cost-effectiveness and cost-benefit analysis.

Programmatic and feasibility aspects

- Presentation of the vaccine.
  (monovalent or combined, single or multiple dose, liquid or lyophilized)
- Vaccine supply.
  (sufficient, timely and regular)
- Cold chain.
  (enough storage capacity at all levels)
- Safe vaccination.
  (patient, vaccinator, environment)
- Vaccinators and supplies for vaccination, training, supervision and monitoring.
Characteristics of the registry

The conclusion of this regulatory process and the recommendations issued by the National Institute of Public Health, the Coordinating Committee of National Institutes of Health and High Specialty Hospitals and COFEPRIS (Federal Commission for the Protection against Sanitary Risk) registration issued for dengue vaccine CYD-TDV with the following characteristics:

1) **Chimeric tetravalent vaccine** (for serotypes I, II, III and IV), made from live attenuated dengue (CYD-TDV).

2) It is aimed to **population previously exposed** to dengue virus between 9 and 45 years old.

3) Application in **populations where dengue is endemic** and seroprevalence desirably is equal to or **greater than 60%**.

This vaccine has an average **efficiency of 60.5%** for the prevention of **dengue** and **93.2%** for the prevention of **severe dengue**.
Some of the recommendations:

- The introduction of the vaccine should be in phases.
- Implement regional evaluation programs.
- Reinforce the surveillance system with an appropriate diagnostic and laboratory support.
- Seroprevalence studies.
- Enhance training in clinical management of cases.
The plan should include the following:

- Introduction the vaccine in the national vaccine scheme.
- Establish a system of record surveillance in sentinel sites for population-based registry, identification, hospitalization, serious illness dengue and hemorrhagic dengue.
- Establish population-based studies to evaluate the efficacy and safety of the vaccine, as well as hospitalization and cases of hemorrhagic dengue.
- Implement ongoing pharmacovigilance program of COFEPRIS, through a passive reporting.
- Carry out seroprevalence studies in representative populations of sentinel sites.
- Additionally a working group to monitor this will be created, in which the information gathered from the measures described above will be discussed. This will be monthly to determine corrective measures in case of detecting any risk to the population.
Considerations

- It is required to have financial capacity to provide vaccine to areas and groups considered as priorities.

- Ensure a strong prevention and control program before the introduction of a vaccine.

- A single measure is not enough for eliminating a vector borne disease.

- To avoid severe cases and deaths will always be a Public Health concern.

- A vaccine against dengue requires strengthened and comprehensive control programs to achieve a greater impact.
Considerations

- The vaccine introduction requieres assertive actions of social communication and health promotion.
- Never before dengue topic was positioned like now.
- Today we have one “dengue vaccine” and probably in the next 5 years we will have more alternatives.
- Anti vaccination growing trends requieres assertive and effective communication.
- Commercial interest should not be involved in decision-making.
- The available resources of the National Dengue Program should not be considered for the purchase of the vaccine.
- The vaccine will never substitute the vector control and personal measures.
Next steps

- Gather a group of experts
- Cost of the vaccine
- Definition of the cost-benefit and cost-effectiveness
- Identify endemic areas to introduce a pilot vaccination program
- Implement an epidemiological surveillance system postvaccinal
  - Active surveillance
  - Passive surveillance
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