

Assessment of dengue vaccine effectiveness and impact for different rollout strategies

Diana P. Rojas and Ira Longini

Center for Inference and Dynamics of Infectious Diseases

Emerging Pathogens Institute

University of Florida

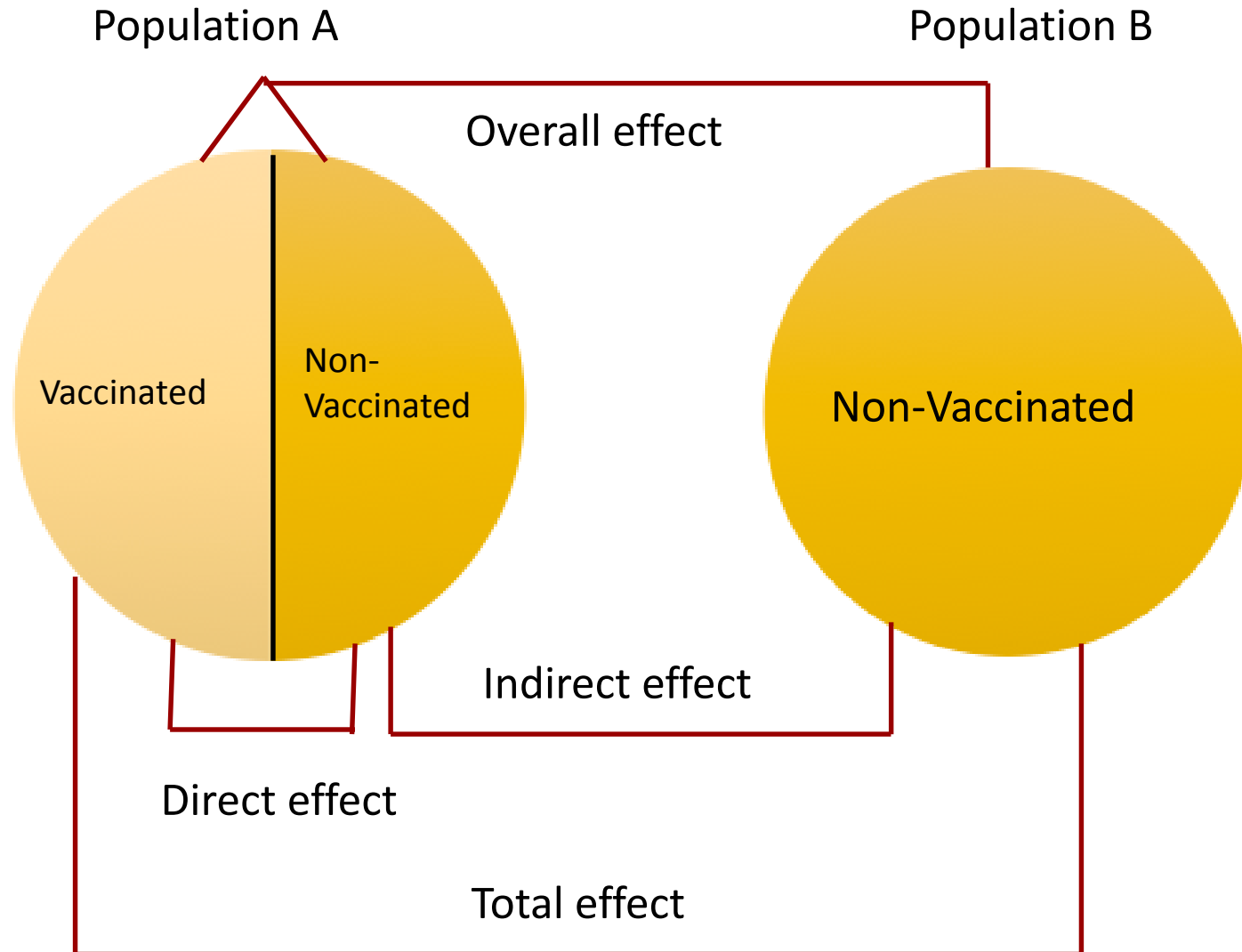
November 4th 2015
First Regional Dengue Symposium
Rio de Janeiro, Brazil



This talk

- Effects of vaccination programs
- Vaccine effects of interest
- Study designs to evaluate effectiveness of vaccines
- Design for evaluation of effectiveness of CYD dengue vaccine in the Yucatan, Mexico.
- Other thoughts

1. Effects of vaccination programs





2. Vaccine effects of interest

- Vaccine Effect on Susceptibility: VE_S
- Vaccine Effect on Clinical Disease: VE_P
- Vaccine effect for susceptibility to disease: VE_{SP}
- Vaccine Effect on Infectiousness: VE_I
- Total Vaccine effect: VE_T
- Indirect effect of vaccination in those not vaccinated
- Total effect of vaccination in those vaccinated
- Overall population level effects



3. Study designs

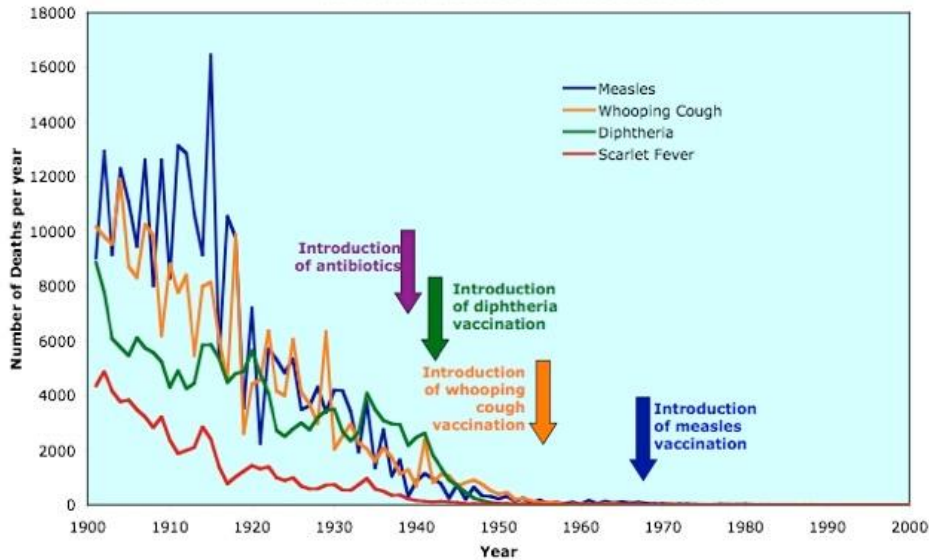
3.1. Observational studies

Pre and post-vaccination comparisons of incidence rates:

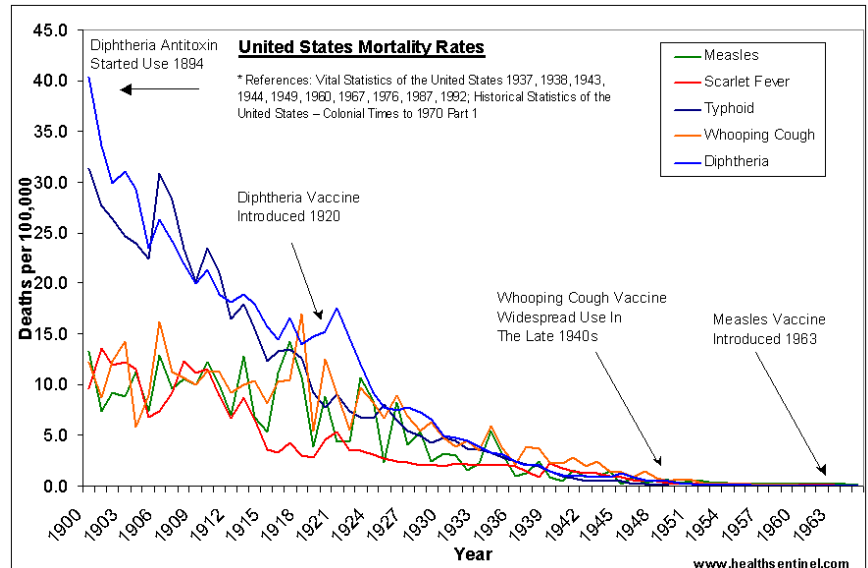
- Change in incidence or attack rates in target population (Overall effect)
- Stratifies by vaccination status (Indirect and total effect)
- Reduction in incidence rates in age groups that did not receive vaccine (Indirect effect)
- Reduction in incidence greater than vaccine coverage (Overall effect)
- Change in age distribution of the disease

3. Study designs

Deaths in England & Wales from four diseases and different medical interventions



Source: www.healthsentinel.com



www.healthsentinel.com



3. Study designs

3.1. Observational studies

Pre and post-vaccination comparisons of incidence rates:

Considerations:

- Good data on dengue cases and possibility to estimate denominators.
- Vaccination status of reported cases
- Level of vaccine coverage and age-specific vaccine uptake.



3. Study designs

3.2. Group randomized Studies

- Ideal way to evaluate vaccine effectiveness
- Several communities are randomized to receive the vaccination strategy and the other communities serve as controls.
- Outcomes in the vaccinated communities would be compared with the control communities.
- This design allows to estimate: Direct effect, Indirect effect, Overall effect and total effect.



3. Study designs

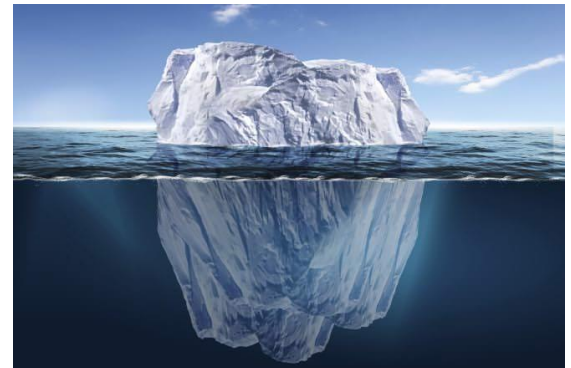
3.2. Group randomized studies considerations:

- Questions of interest: Scientific or public health question
- Vaccination strategy: Target populations to vaccinate (age-groups), control vaccine? or routine vector control.
- Clinical endpoints: Symptomatic cases, severe cases, hospitalizations?, suspected, probable or confirmed cases.
- Study population and subpopulations: Determined by the vaccine characteristics, scientific evidence and the ability to conduct large-scale study in the population.
- Sources of transmission: Transmission patterns of dengue and sources of exposure in a population is required in anticipating possible detection of indirect effects.

3. Study designs

3.2. Group randomized studies considerations:

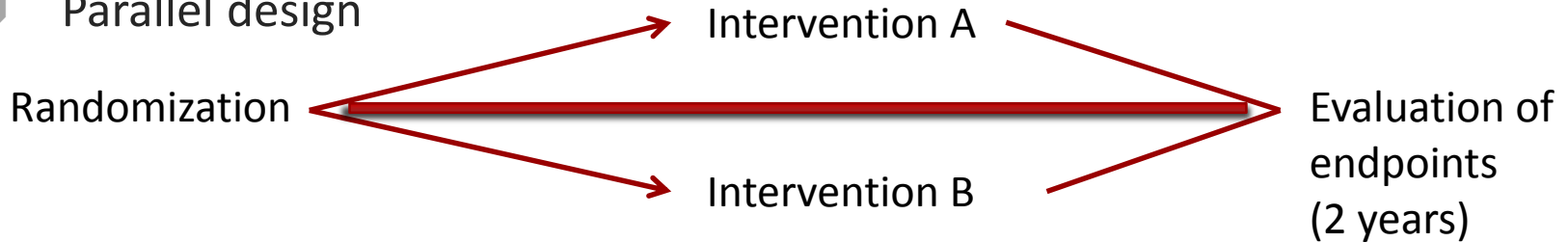
- Case ascertainment: Underreporting in dengue: two or more sources of data are needed (enhanced surveillance, active surveillance)
- Randomization unit at the group level: Temporal order of the randomization strategy. Identify randomization unit: State, City, neighborhoods, households, schools. Groups need to be transmission-dynamically separate to avoid contamination across units.
- Randomization schemes: Completely randomized, Stratified or matched pairs.



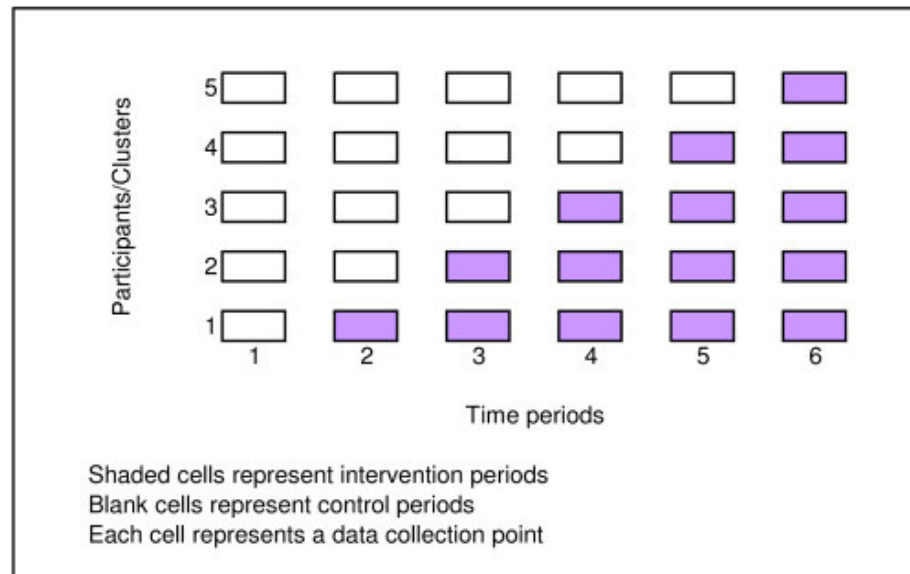
3. Study designs

3.2. Group randomized studies

➤ Parallel design



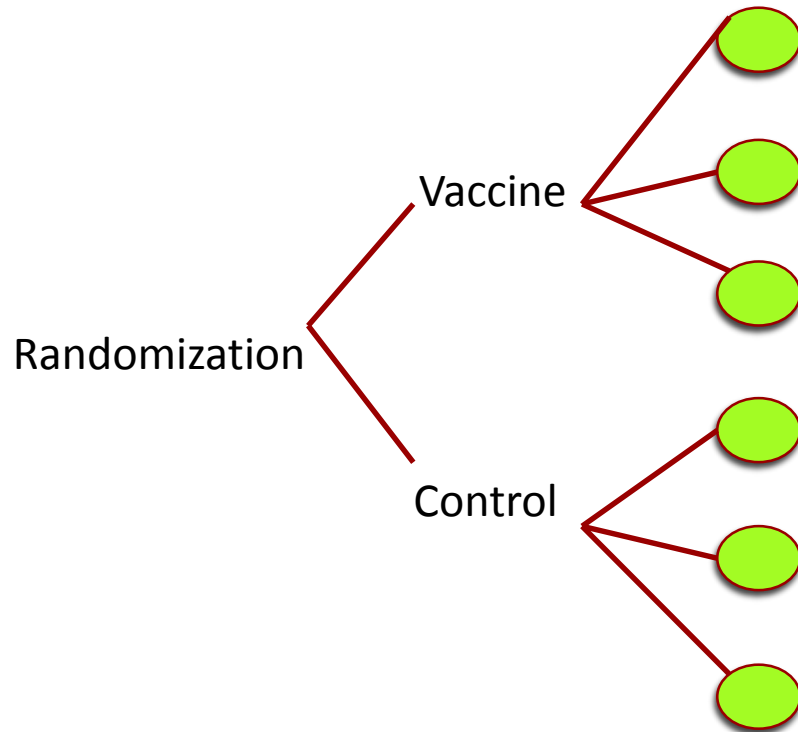
➤ Stepped wedge



3. Study designs

3.2. Group randomized studies

➤ Cluster Randomized



Unit of
randomization:
Cluster

Unit of analysis:
Clusters

4. Dengue transmission baseline field studies in the Yucatan, Mexico.



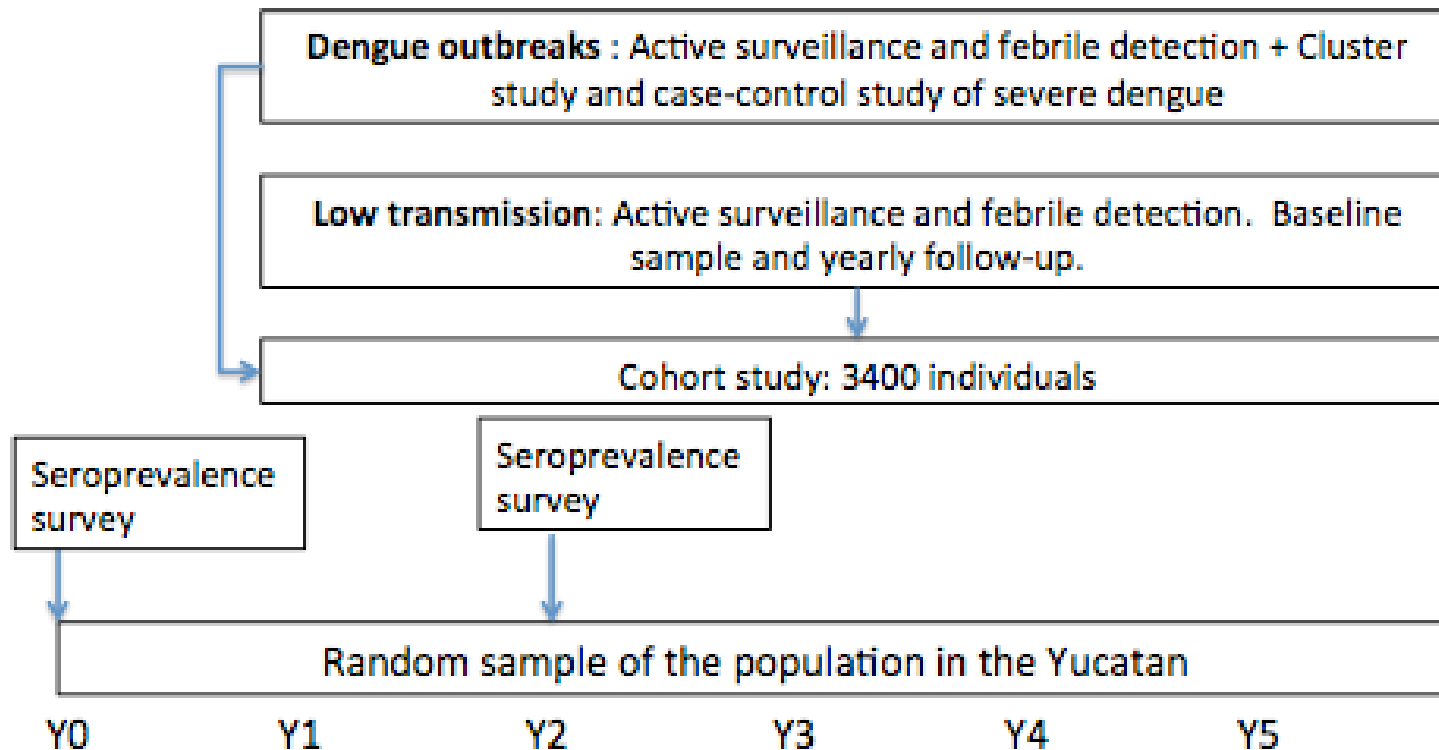
Population: 1.956 million (INEGI)
106 municipalities

http://www.explorandomexico.com/photos/maps/full-yucatan_1.gif



Funded by Sanofi Pasteur.

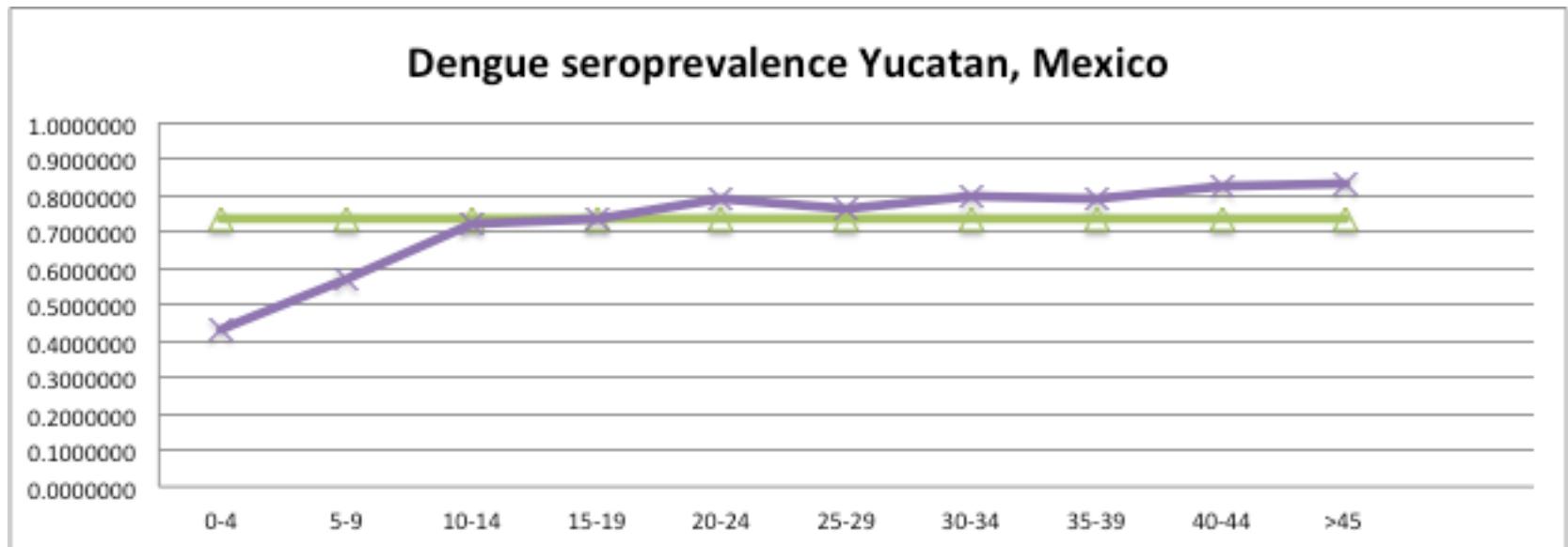
4. Dengue transmission baseline field studies in the Yucatan, Mexico



Contact tracing: Using cell phones and questionnaires to assess possible sources of transmission.

Mapping blocks and neighborhoods from most the cities in the Yucatan.

4. Dengue transmission baseline field studies in the Yucatan, Mexico

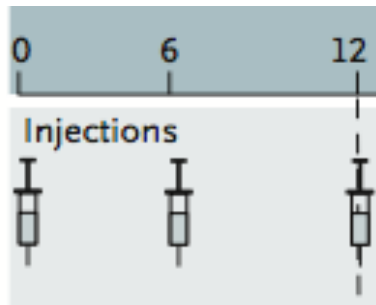


5. Cluster-randomized design for evaluation of CYD sanofi dengue vaccine in the Yucatan

Measures of interest:

- Primary: Overall effect: Cluster randomization
- Direct effect: Depends on vaccination strategy
- Indirect effect: In those not eligible to be vaccinated.

Vaccine: CYD dengue vaccine





5. Cluster-randomized design for evaluation of CYD sanofi dengue vaccine in the Yucatan

Vaccination strategy: According to the decision of the country.

- Vaccine will be licensed: ≥ 9 year olds.
- Target population: 9 year olds.
- To maximize overall or indirect effects: Vaccinate as many people as possible in clusters or could add catch-up (30 or 45 year olds) or adding another age group.
- Clusters randomized to vaccination or not, vaccination+catch-up Vs. vaccination targeting one age group.
- Smaller contact groups: Vaccinate everyone (9 year olds and older) in the household or schools.
- Good registry of people who get the dengue vaccine



5. Cluster-randomized design for evaluation of CYD sanofi dengue vaccine in the Yucatan

Recruitment:

- It depends on the strategies planned by the Government.
- Governments agree with the strategy consent maybe not be necessary (Steeped-wedge Vs. Parallel design).
- Decide the cluster unit (households, neighborhoods, schools, municipalities).

Clinical endpoints:

- Discussion with dengue experts.
- Suspected cases Vs. confirmed cases (IgM, NS1, RT-PCR?) or total cases, severe cases, hospitalizations? Surveillance in specific age groups (<9 year olds, infants), asymptomatic?
- Epi surveillance Vs. active surveillance

Aedes Aegypti

DOUTOR,
ESTOU EM UMA
CRISE DE
IDENTIDADE!

HORAS SOU
DENGUE.

E AINDA TEM
UM TAL DE
ZICA.

OUTRAS
CHIKUNGUNYA.



QUAL
DELES VOCÊ
É AGORA?

Dabon

5. Cluster-randomized design for evaluation of CYD sanofi dengue vaccine in the Yucatan

Sources of transmission:

- Baseline risk populations (IR, entomologic baseline, vector control measures, mobility)

Clustering of transmission

- Identify dengue hotspots in the municipalities.
- Avoid contamination with other febrile diseases: CHIKV, ZikaV...

Choice of clusters:

- Size clusters, number of expected cases per cluster and number of clusters.
- To aim for 30- 40 clusters or more.
- Clusters: Households, schools, neighborhoods, localities, municipalities, states?



5. Cluster-randomized design for evaluation of CYD sanofi dengue vaccine in the Yucatan

Case ascertainment:

- Surveillance system has to be able to ascertain cases. Enhanced surveillance, active surveillance. Proportion of confirmed cases, underreporting, include all the potential case reporters.
- Yucatan: School –based cohort with families with active surveillance (absenteeism , 1800-call)
- Enhanced surveillance: Include contact tracing of every case: Phone and addresses surveillance system. GIS. (add vaccination status)
- Potential contamination across clusters as well as the role of networks in estimating effects of vaccination.



5. Cluster-randomized design for evaluation of CYD sanofi dengue vaccine in the Yucatan

Stepped wedge Vs. parallel study:

- Time: 2-5 years
- Placebo (or another vaccine)
- Seasonality: Could limit choice of steps.



5. Cluster-randomized design for evaluation of CYD sanofi dengue vaccine in the Yucatan

Randomization:

- Completely randomized: The order of introduction of the intervention is randomized without any consideration of variability among groups.
- Stratified: stratify by pre-randomization group-level covariates of interest (transmission characteristics) and then randomize within strata.
- Matched pairs: Randomize the intervention within pairs.



5. Other thoughts

- The importance of vector control to evaluate effectiveness of dengue vaccine.
- Effectiveness of IVM
- Entomologic surveillance
- Entomologic insecticide resistance
- Integrated evaluation of effectiveness



6. Conclusions

- Different study designs to evaluate dengue vaccine effectiveness.
- Each country is autonomous to pick the study design that fits its needs and capability of running the study.
- Observational studies are implicit with the current status of the epidemiological surveillance.
- Cluster-randomized stepped wedge design Vs Parallel design will be the optimal study design to assess the effectiveness of the dengue vaccine.

Acknowledgments

Fred Hutchinson Cancer Research Center - UW

- Elizabeth Halloran
- Leora Feldstein

Instituto Nacional de Salud Publica de Mexico

- Hector Gomez Dantes

Universidad Autonoma de Yucatan

- Team Familias sin dengue.
- Pablo Manrique
- Norma Pavia

Secretaria de Salud de Yucatan

Fulbright – Colciencias doctoral scholarship.





THANK YOU