CEMI 17: actualités sur les arboviroses

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and
pulation

Challenges for research and development of a dengue vaccine

- No vaccine available despite research started over 60 years ago
- Main challenges
  - **No animal model for the disease**
  - **Four different viral serotypes**
  - **Theoretical risk of immunopotentiation after sequential infections**
    - tetravalent vaccine needed
  - **Live attenuated vaccine technology to optimise protection**
  - **No known correlate of protection**
    - Efficacy studies needed
  - **Industrialization of the production process and consistent large-scale manufacturing**

Most Advanced Dengue Vaccine Strategies

- Leading Dengue Vaccine Candidates:
  - Advanced candidates based on classic approaches
  - Current candidates largely based on molecular biology

Developer	Technology	Pre-clinical	Phase I	Phase II	Phase III
Sanofi Pasteur	Chimeric YF17D attenuated virus				
GSK/WRAIR	Classic attenuated virus			X	
InViragen	Chimeric Den 2 attenuated virus				
Hawaii Biotech	Recombinant subunit				
NIH	Chimeric Den 4 attenuated virus				
GSK/Fiocruz/WRAIR	Inactivated virus adjuvanted				

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SP dengue Vaccine Development History

- 1994: Partnership with the Vaccine Development Centre, University of Mahidol, Bangkok, Thailand
- 1998: First contact with Acambis, Cambridge, USA, developer of a molecular biology technology
- 2001: Proof of concept of a live attenuated vaccine (LAV) against dengue in two doses and a booster
- 2001: Beginning of the development of a live attenuated vaccine obtained by genetic recombination at Sanofi Pasteur laboratory
- 2004: The classical live vaccine approach is abandoned due to reactogenicity and under-attenuation of serotype 3. The choice is made to focus on the development of the second generation LAV

Acambis

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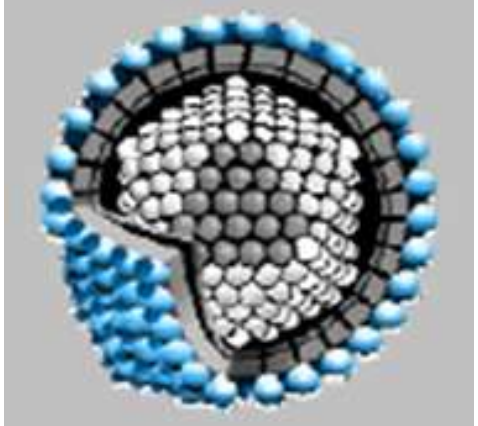
SP Vaccine: Vaccine construct and non-clinical evaluation

Chimeric approach

YF 17D Vaccine

Dengue Virus



YF vaccine: Live attenuated

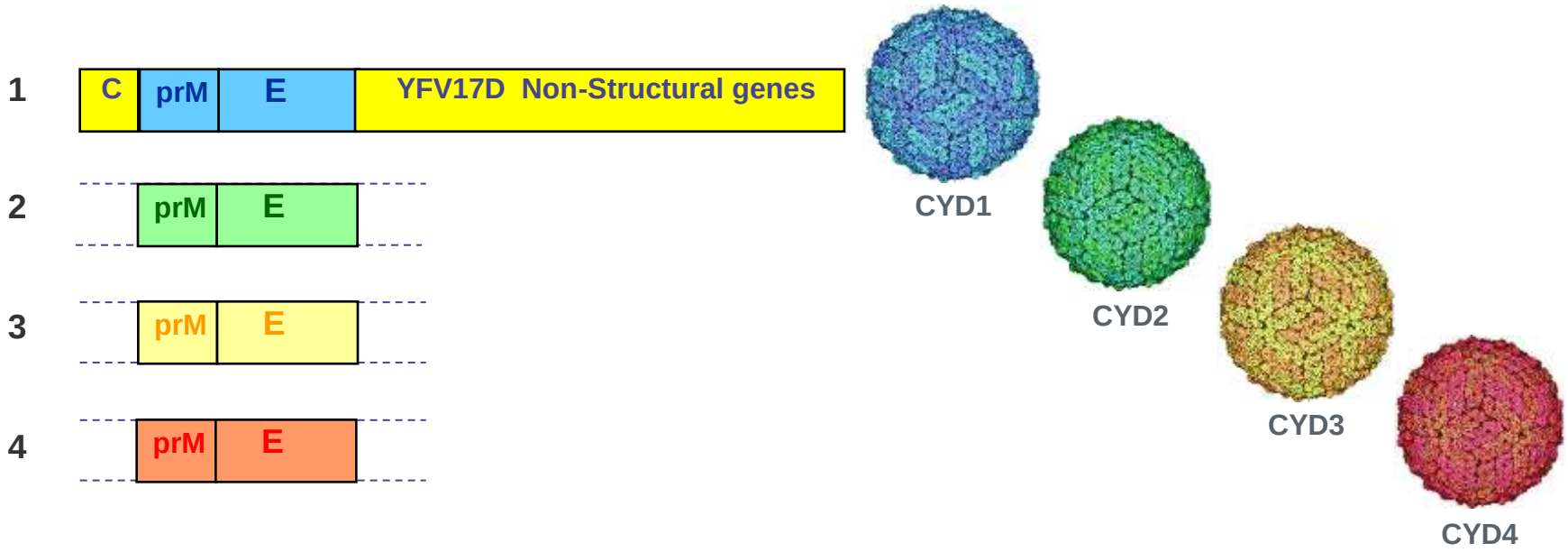
- Decades of use show reversion to virulence is unlikely
- Low error-prone polymerase resulting in high genetic stability

Dengue virus: Wild Type

- Serotype differences linked to protein differences at surface
- Envelope E proteins trigger production of neutralizing antibodies

CYD Dengue Vaccine: Tetravalent Combination of Chimeric LAV

- **Four genetic constructs are created, one for each serotype**
- **All are based on same YF 17D backbone**
- **Insertion of E and prM genes, isolated from each serotype**



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Nonclinical Safety Evaluation

Systemic and local toxicity No vaccine-related toxicological findings	✓
Biodistribution Limited distribution/replication without persistence of the virus	✓
Shedding No viral shedding in urine, feces, saliva and at the injection site	✓
Neurovirulence No neurotropism (SC route) Less neurovirulent than well characterized YF vaccine (IC route)	✓
Viscerotropism No liver infection in hamsters and monkeys, while a few foci exist for YF-17D in monkeys Chimeric viruses display lower growth than YF-17D in hepatic cells	✓

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Dengue Vaccine Candidate's Current Company Target Product Profile

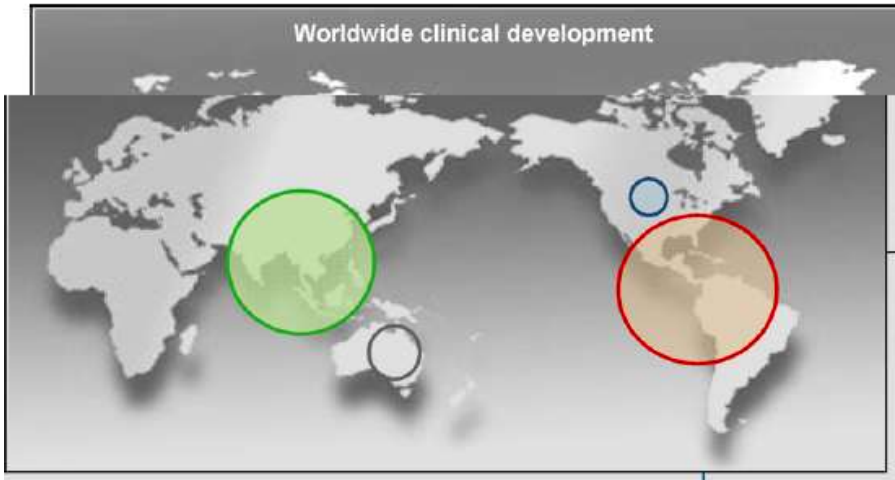
- **Description:** Live attenuated virus, tetravalent (4 vaccinal strains cultured in serum free Vero cells)
- **Pharmaceutical form:** Powder and solvent for suspension for injection (0.5 ml)
- **Route of administration:** Sub-cutaneous
- **Schedule:** 3 injections 0 - 6 - 12 months
- **Dosage:** 5 ± 1 log10 CCID50 of each serotype for one dose
- **Storage:** +5°C
- **Indication:** Prevention of symptomatic dengue disease i.e. covering the spectrum from Dengue Fever to severe Dengue cases due to serotypes 1, 2, 3 or 4.
- **Populations:** Children as of 24/9 months of age and adults living in endemic areas, people working in (traveling to) endemic areas
- **Priority:** Endemic countries (Asia/Pacific, Latin America, Caribbean)

SP Vaccine: Clinical Trial update

Dengue Specific Guidelines Used in Development of CYD Dengue Vaccine

- Guidelines for the clinical evaluation of dengue vaccines in endemic areas
  - **WHO/IVB/08.12, 2008**
- Guidelines for the production and quality control of candidate tetravalent dengue virus vaccines (live)
  - **WHO Technical Report Series, No. 932, 2006 Annex 1 (under revision)**
- Guidelines for plaque reduction neutralization testing of human antibodies for dengue viruses
  - **WHO/IVB/07/07, 2007**

Expanded Phase I/II Clinical Program (Endemic Population)



Ongoing / completed **Phase II** studies

Safety and Immunogenicity (S&I) PoC - efficacy

Asia, Latin America, USA

Ongoing / planned **Phase III** studies

Efficacy, Lot to lot consistency, S&I , Co-admin.

Asia, Latin America, Australia

Conclusions from completed Phase I / Phase II studies

Safety

- No safety signals
- No mild dengue-like syndrome
- Reactogenicity profile comparable to control vaccine
- No increase in reactogenicity
  - in dengue or YF17D / JE - immune subjects
  - in younger subjects (2-11 yr)
  - after a 2nd or a 3rd dose

Immunogenicity (Neut. Abs)

- Non-endemic Populations
  - Balanced response (against all 4 serotypes) after 3 doses
  - Higher seroconversion in children
  - Higher immunogenicity in flavivirus-exposed individuals
- Endemic Populations
  - Balanced responses after 3 doses
  - Higher immunogenicity in dengue-exposed individuals

Source: Bruno Guy et al. From research to phase III: Preclinical, industrial and clinical development of Sanofi Pasteur tetravalent dengue vaccine Vaccine. 2011 Sep 23;29(42):7229-41.

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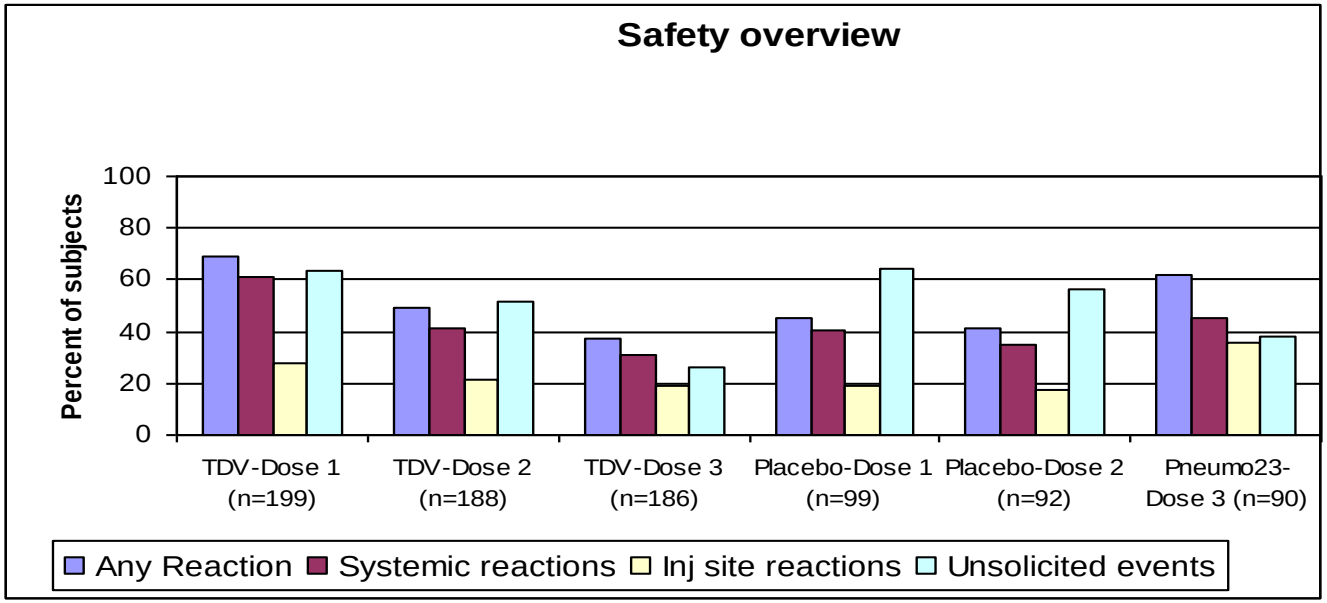
Ph II safety and immunogenicity of CYD vaccine in 2-11 year old children in Peru

- Phase II blind-observer Peru
- Age 2-11 years, N=300
- YF-primed subjects (1 to 7 years before enrolment)
- Schedule 0- 6- 12 m
- Design
  - **Group 1 (n=200)**
    - CYD dengue vaccine (TDV) (≈5 log10 CCID50 of serotypes 1, 2, 3, 4)
  - **Group 2 (n=100)**
    - Placebo – Placebo – Pneumo23
  - **Subset of subjects (n=130)**
    - Vaccine viremia and biological parameters
    - D7 and D14 after first and second vaccinations

Lanata C. et al. poster presentation ASTM&H 2010

Overview of safety in Ph II study with CYD vaccine in 2-11 year old children in Peru



- Satisfactory safety profile comparable to observations from other Phase II trials
- No increase of reactogenicity in subjects previously vaccinated with YF vaccine
- Trend towards decrease of reactogenicity with subsequent dosing of the dengue vaccine as observed in the previous studies

Lanata C. et al. poster presentation ASTM&H 2010

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Overview of immunogenicity in Ph II study with CYD vaccine in 2-11 year old children in Peru

- > 94% seropositive for each serotype after two or three vaccinations
- > 90% seropositive for all of the four serotypes after two or three vaccinations

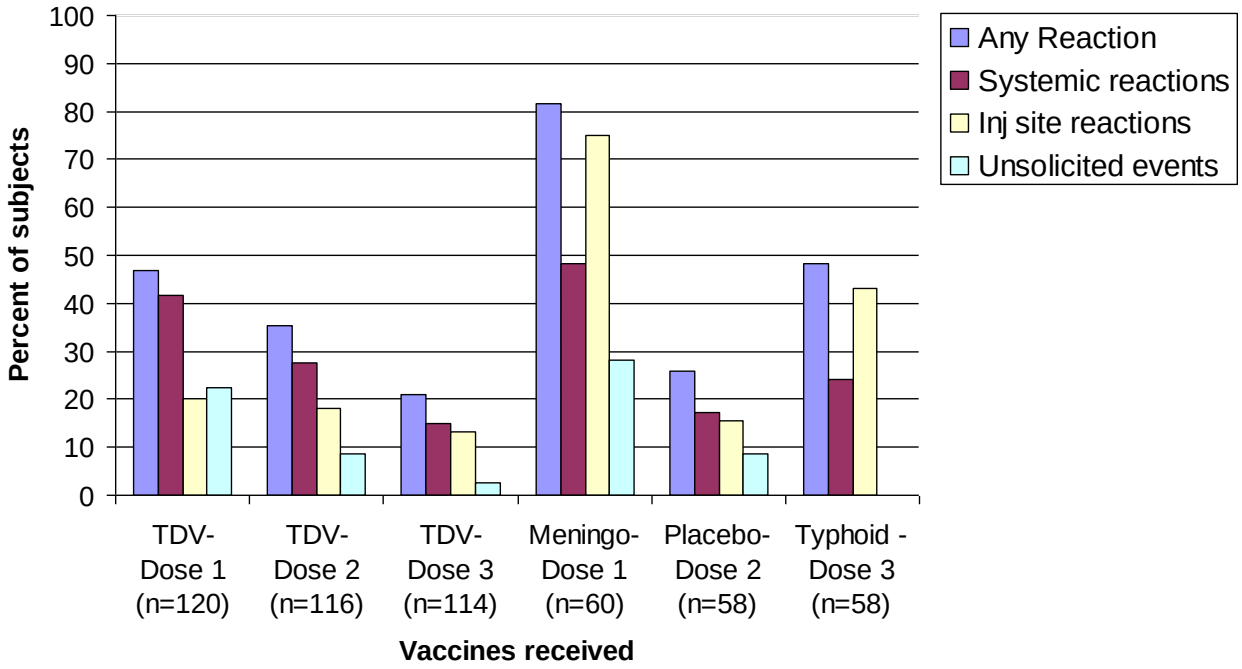
Higher immunogenicity after 3 doses ahscega va y4-□l□rfteold□en □accve-

Ph II safety and immunogenicity of CYD vaccine in 2-45 year old in Vietnam

- Phase II randomized, blind-observer (1st and 2nd Vaccination) single blind (3rd vaccination)
- Age 2-45 years
- N=180
  - **120 children (2-11 y), 30 adolescents (12-17 y), 30 adults (18-45 y)**
- Schedule 0- 6- 12 m
- Design
  - **Group 1 (n=120)**
    - CYD dengue vaccine (TDV) (≈5 log10 CCID50 of serotypes 1, 2, 3, 4)
  - **Group 2 (n=60)**
    - Meningo A+C, Placebo (NaCl), Typhoid Vi
- Status
  - **Follow-up (year 1) ongoing**

Viviani S. et al XIVth Conference on Vaccine Research 2011

Overview of safety in Ph II study with CYD vaccine in 2-45 year old in Vietnam



- Satisfactory safety profile comparable to observations from other Phase II trials
- Reactogenicity slightly higher after dengue vaccine compared to placebo (i.e. solicited systemic reaction)
- Trend towards decrease of reactogenicity with subsequent dosing of the dengue vaccine as observed in the previous studies

Viviani S. et al XIVth Conference on Vaccine Research 2011

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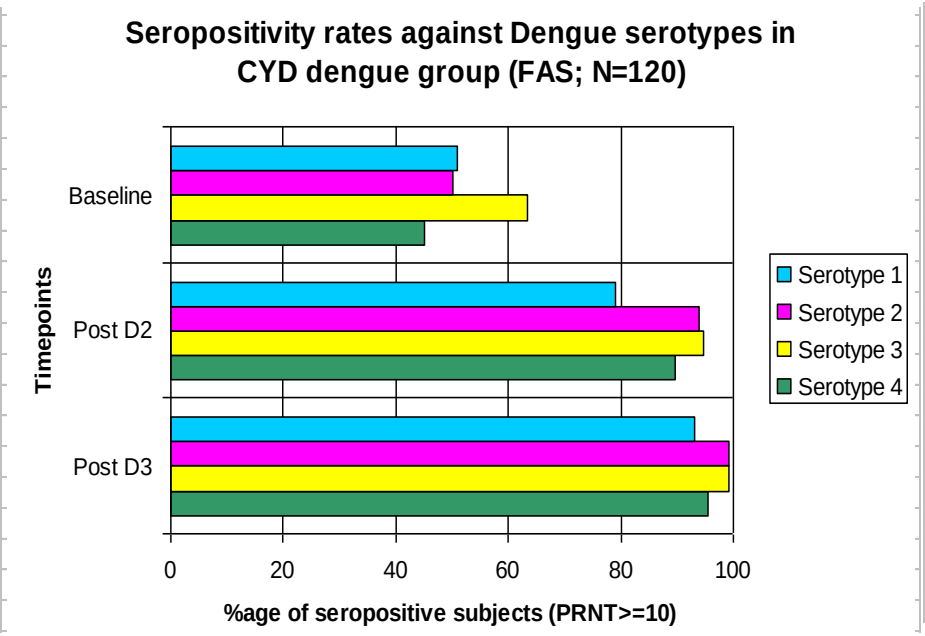
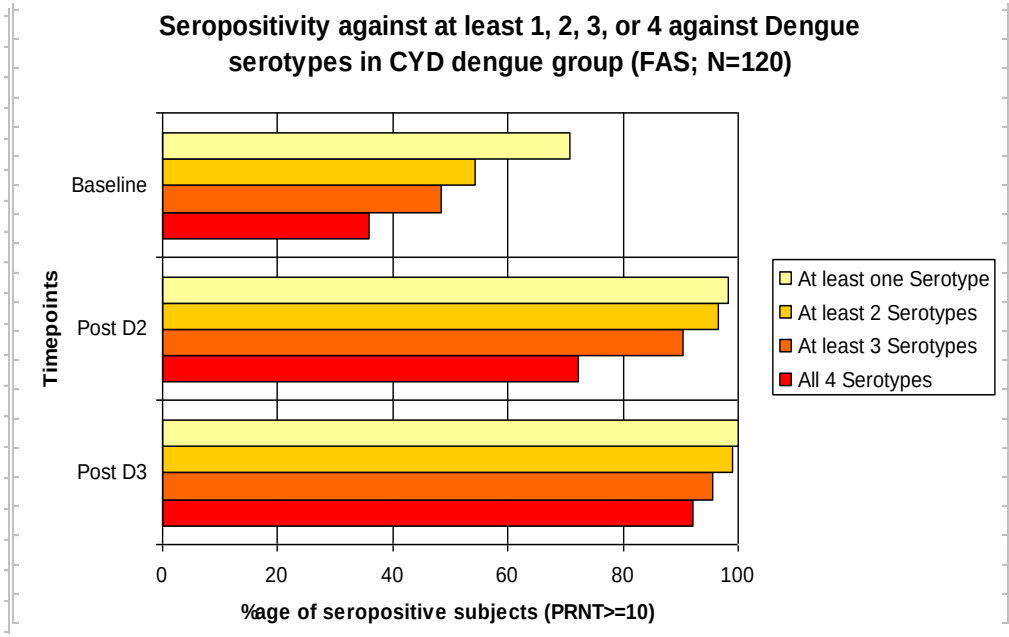
Overview of immunogenicity in Ph II study with CYD vaccine in 2-45 year old in Vietnam





- High seropositivity rates against all 4 serotypes at baseline
- 92% of subjects seropositive against all 4 serotypes following 3 doses of CYD dengue vaccine
- Improvement of seropositivity against all 4 serotypes by the 3rd dose

Balanced immune response against all 4 serotypes following 3-dose schedule

Viviani S. et al XIVth Conference on Vaccine Research 2011

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Overview of safety and immunogenicity

- Safety
  - By January 2012, more than 23,000 people have received at least one
  - Reactogenicity profile comparable to control vaccines
  - No safety concern and satisfactory safety profile
- Immunogenicity
  - Balanced immune response against all 4 serotypes after 3 doses of tetravalent Dengue vaccine
  - Higher immune responses observed in children
  - Consistent higher immune response in subjects previously exposed to Dengue infection and to JE or YF vaccination
  - Stepwise increase of seropositivity rates against each serotype with 3 dose

Demonstrating Efficacy of Dengue Vaccine to Prevent Symptomatic Dengue Infection

Phase III Expanded Efficacy Study Latin America

- Countries: Colombia, Mexico, Honduras, Puerto Rico, and Brazil
- Age group: 9-16 years
- N subjects: 20,000

Phase III Expanded Efficacy Study Asia

- Countries: Thailand, Indonesia, Malaysia, Viet Nam, Philippines
- Age group: 2-14 years
- N subjects: 10,000

CYD23 First Efficacy Study

- Country: Thailand
- Age group: 4-11 years
- N subjects: 4,000

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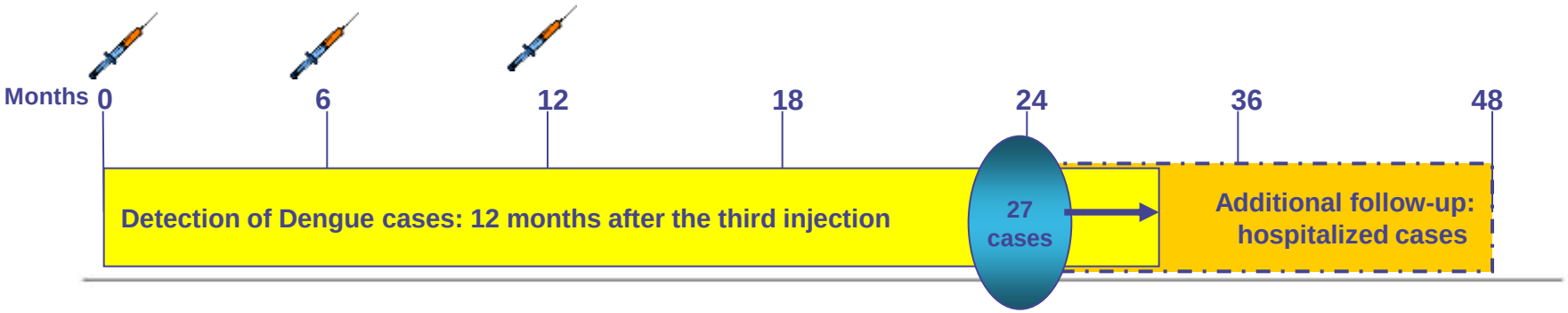
First worldwide efficacy trial in 4-11 years Thai Children

- Study site: Ratchaburi, Thailand (57 schools, 28 vaccination sites)
- Sample size: Based on 70% efficacy, lower bound of 0% and attack rate of 1.3%
- Primary endpoint: To assess the efficacy of dengue vaccine after 3 injections in preventing symptomatic, virologically* confirmed dengue cases, regardless of the severity, due to any of the four serotypes
- Safety follow up: review by IDMC every 2 weeks, last safety review : Q1 2012
  - **Subsets: immunogenicity n=300; viraemia n=100; reactogenicity n=1050**
- Results in Q4 2012

Population	Group 1 (Dengue Vaccine)	Group 2 (Control/placebo)	TOTAL
Children (4-11 years)	2668	1334	4002



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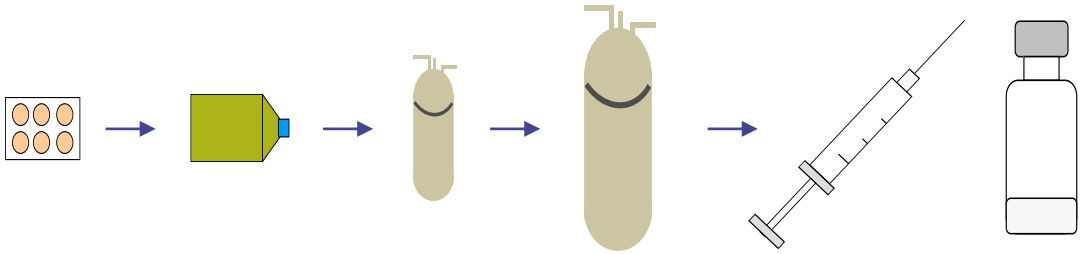
* According to WHO Guidelines for the evaluation of dengue vaccines in populations exposed to natural infection. TDR/IVR/DEN/01

Main Characteristics of our vaccination / supply Industrialization strategy

- Production of 4 vaccine strains (active substances) coming from 4 virus seed lots
- Identical manufacturing process for the 4 serotypes
- Proprietary stabilizer for the finished product
- Absence of raw material from animal origin: Use of sanofi pasteur serum-free Vero cell banks for viral culture
- No preservative, no adjuvant, no antibiotics
- Typical control profile for a live attenuated viral vaccine based on current GMP regulations and WHO Guidelines
- Starting in October 2010 of S&I and consistency Phase III trials with commercial scale lots

Facilitating Access to Vaccine:
Early Scale Up and Industrial Development



Quality Control

Bulk Manufacturing

Utilities

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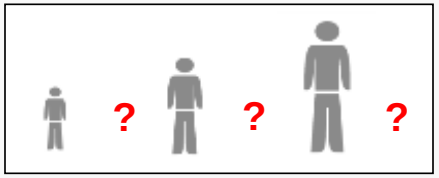
Challenges for introduction

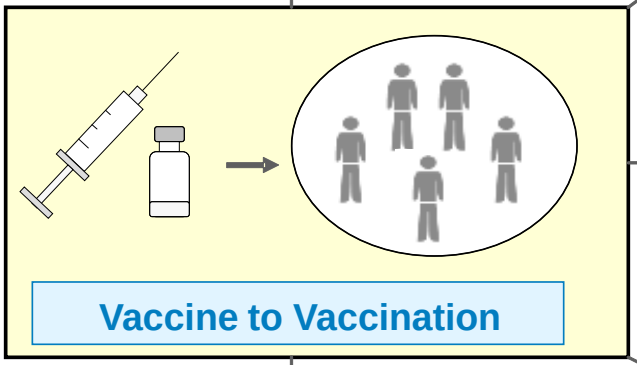
Dengue is underreported

• Improve surveillance

Dengue epidemiology varies

• Adapt vaccination programs to local/ regional specificities

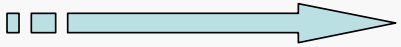




Vaccine to Vaccination

Longterm Phase IV studies

• Plan PhaseIV studies to address effectiveness and long-termsafety

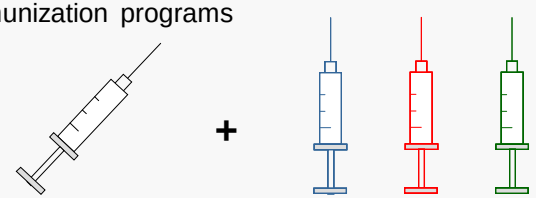


Dengue vaccination will be part of an integrated control approach

• Anticipate the logistic needed behind vaccination programs

Dengue: an additional vaccine

• Include dengue vaccine in national immunization programs



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Conclusion

- Innovative approaches were needed to develop a dengue vaccine that is safe and immunogenic to all 4 serotypes
- Results from large and extensive pre-clinical and clinical evaluation (phase I and II)
  - **No safety concern and satisfactory safety profile**
    - By January 2012, more than 23,000 people have received at least one dose of Sanofi Pasteur's dengue vaccine across age groups and regions
  - **Broad and balanced immune response against all 4 serotypes observed in children and adults from endemic and non-endemic areas after 3 doses (0, 6, 12 months)**
- Tetravalent dengue vaccine ongoing large scale Phase III Efficacy Trials in major endemic areas.
- First results of efficacy 4Q 2012
- Highly coordinated product and industrial development to facilitate access to the dengue vaccine
- First dossier submission expected in 2013 for pediatric/adult in endemic countries

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Francois Sillan : Pharmacovigilance
Germano Ferreira : Epidemiology

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