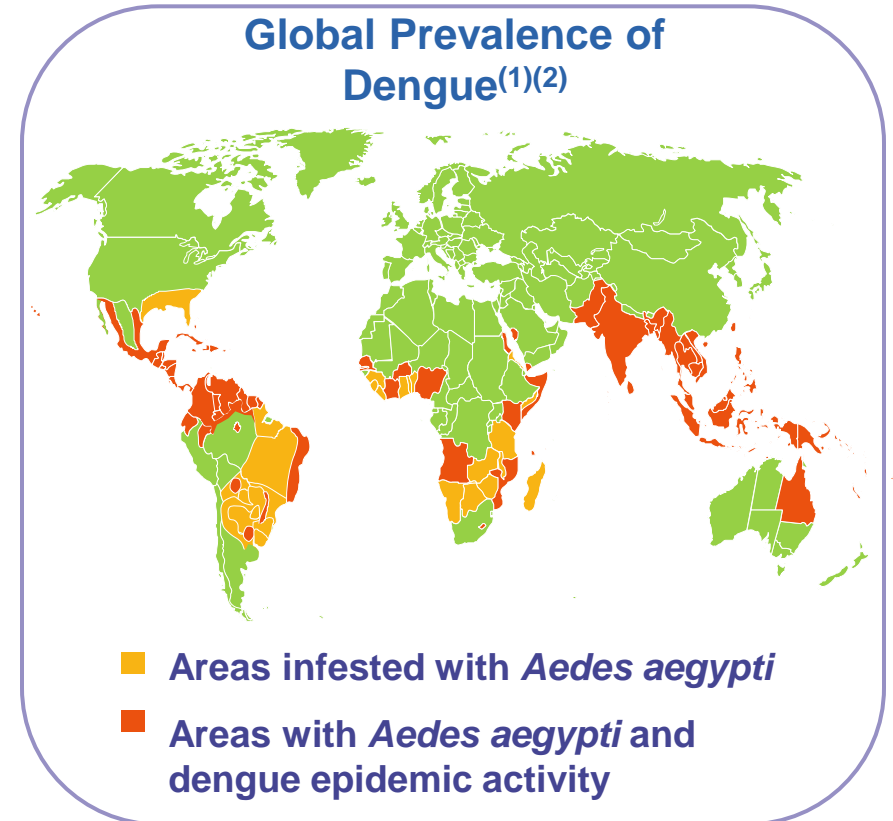


Présentation du candidat vaccin contre la dengue

*Rémy Teyssou, Valentine Delore, Jean Lang
CEMI 17: actualités sur les arboviroses
16 Mars 2012 – Institut Pasteur*

Dengue Disease: A Major Public Health Concern

- **Mosquito-borne disease**
- **2nd most widespread tropical disease after Malaria**
 - 1st in Latin America and Asia Pacific
- **Almost 40% of world population is at risk**
- **Each year:**
 - 50-100 million infected
 - 500,000 severe disease (90% children)
 - CFR 2.5%
- **Increasing geographic spread and burden of disease**
- **No effective drug treatments**
- **No effective prevention**



(1) Beatty M et al. *AM J Trop Med Hygiene* 81, 5:231 2009
(2) WHO 2009

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 immunopotential 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				
InViragen	Chimeric Den 2 attenuated virus				
Hawaii Biotech	Recombinant subunit				
NIH	Chimeric Den 4 attenuated virus				
GSK/Fiocruz/WRAIR	Inactivated virus adjuvanted				

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

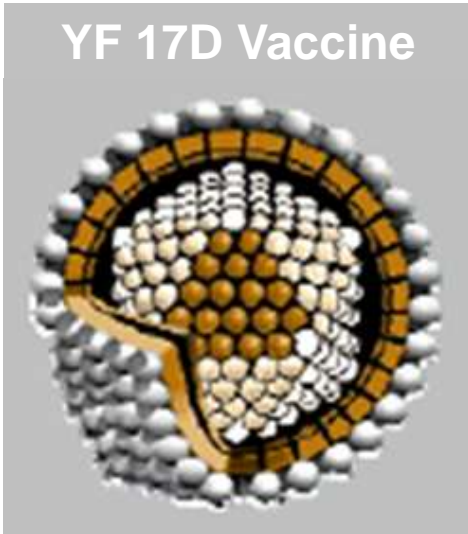


Acambis

SP Vaccine: Vaccine construct and non-clinical evaluation

Chimeric approach

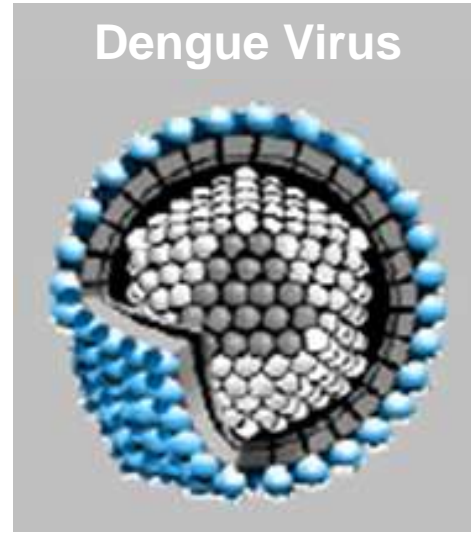
YF 17D Vaccine



YF vaccine: Live attenuated

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

Dengue Virus

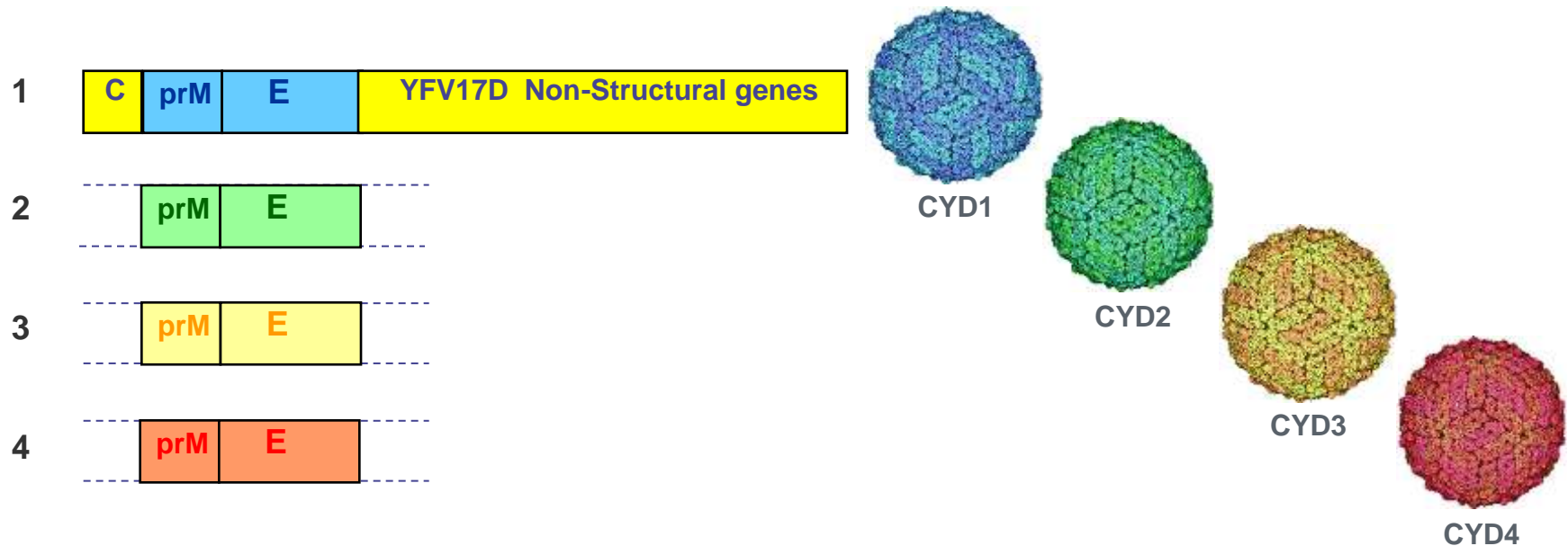


Dengue virus: Wild Type

- 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



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	✓

Dengue Vaccine Candidate's Current Company Target Product Profile

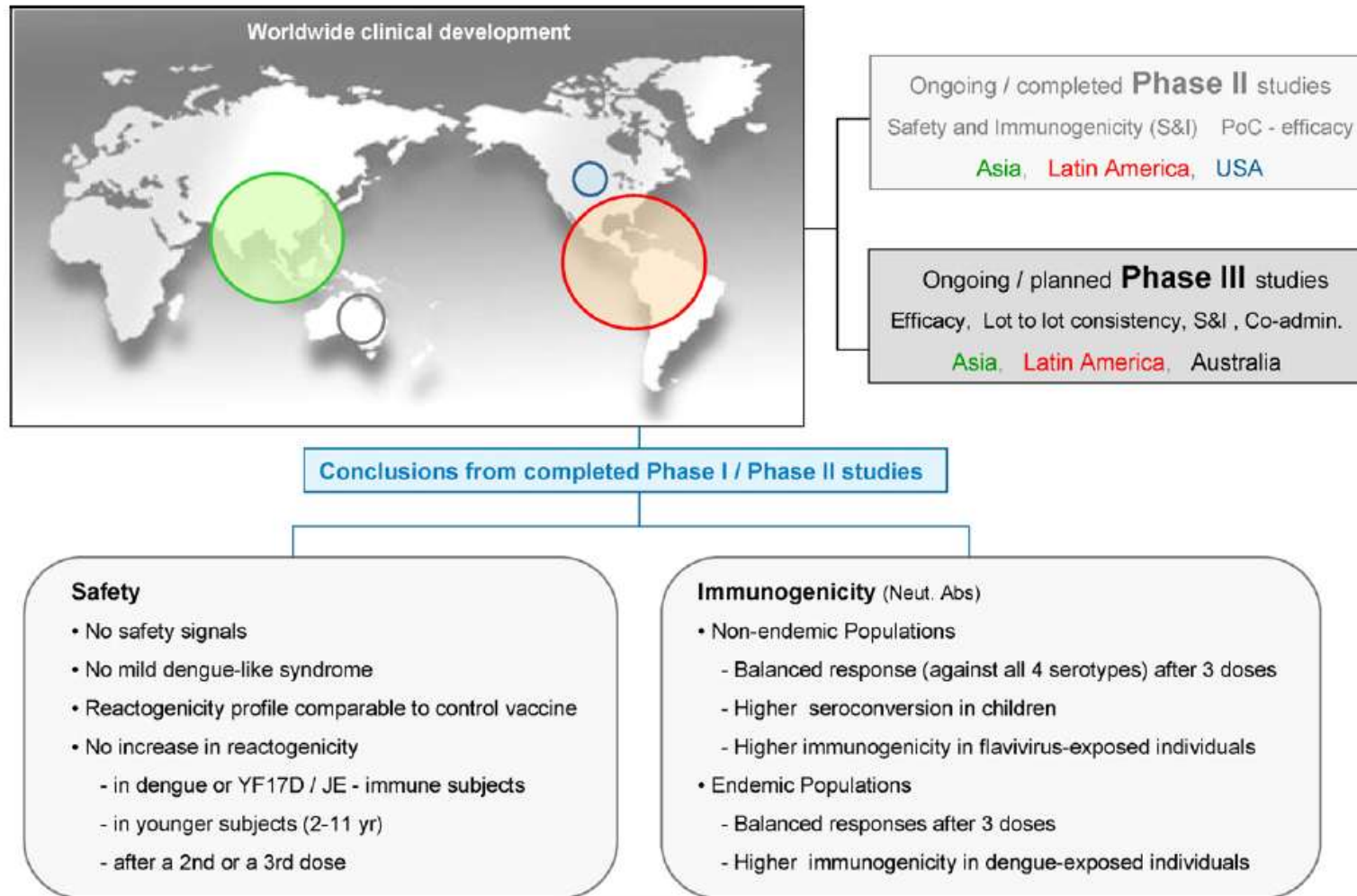
- **Description:** Live attenuated virus, tetravalent (4 vaccinal strains cultured in serum free Vero cells)
- **Pharmaceutical form:** Powder and solvent for suspension for injection (0.5 ml)
- **Route of administration:** Sub-cutaneous
- **Schedule:** 3 injections 0 - 6 - 12 months
- **Dosage:** 5 ± 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

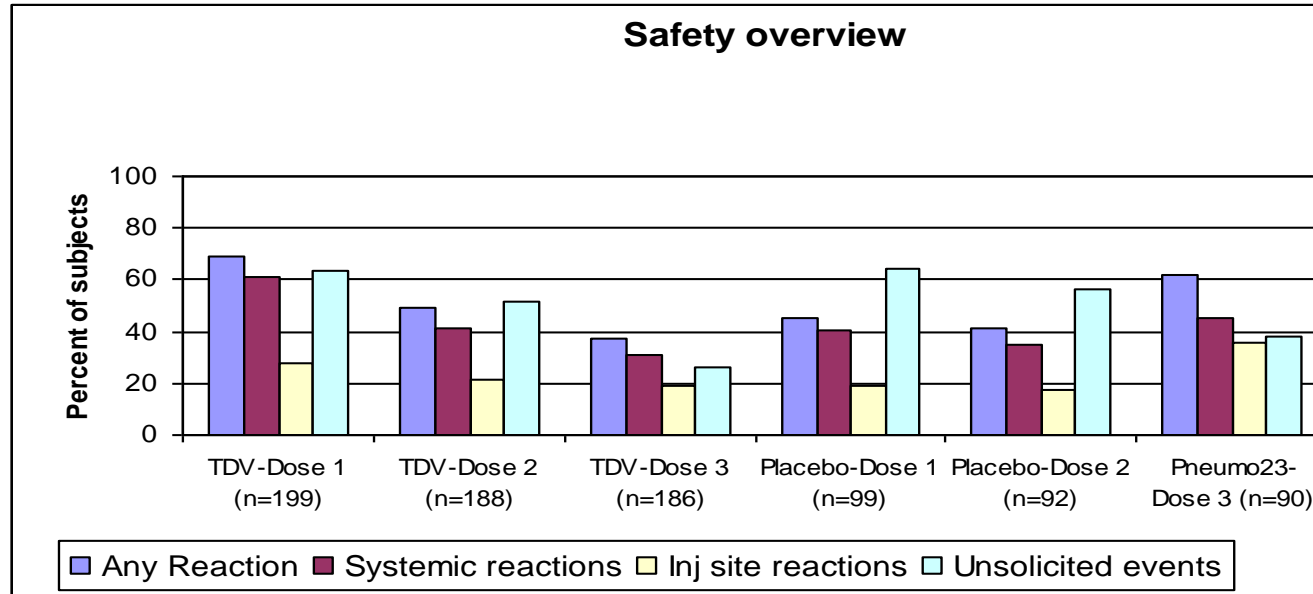
Expanded Phase I/II Clinical Program (Endemic Population)



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

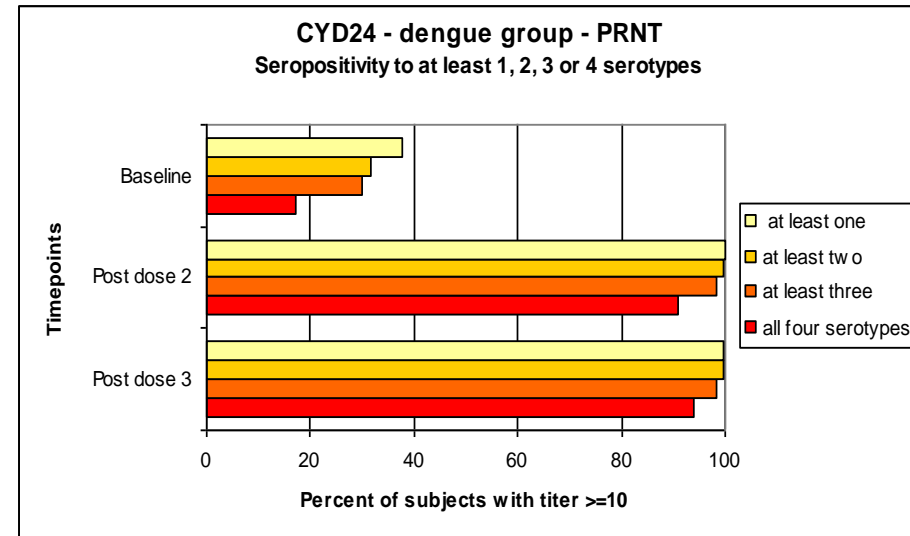
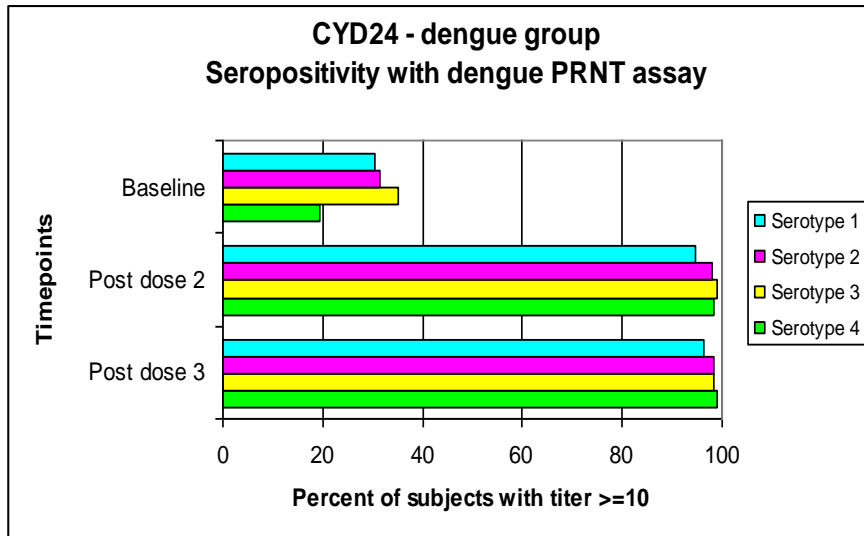
- Phase II blind-observer Peru
- Age 2-11 years, N=300
- YF-primed subjects (1 to 7 years before enrolment)
- Schedule 0- 6- 12 m
- Design
 - **Group 1 (n=200)**
 - CYD dengue vaccine (TDV) ($\approx 5 \log_{10}$ CCID₅₀ of serotypes 1, 2, 3, 4)
 - **Group 2 (n=100)**
 - Placebo – Placebo – Pneumo23
 - **Subset of subjects (n=130)**
 - Vaccine viremia and biological parameters
 - D7 and D14 after first and second vaccinations

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

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



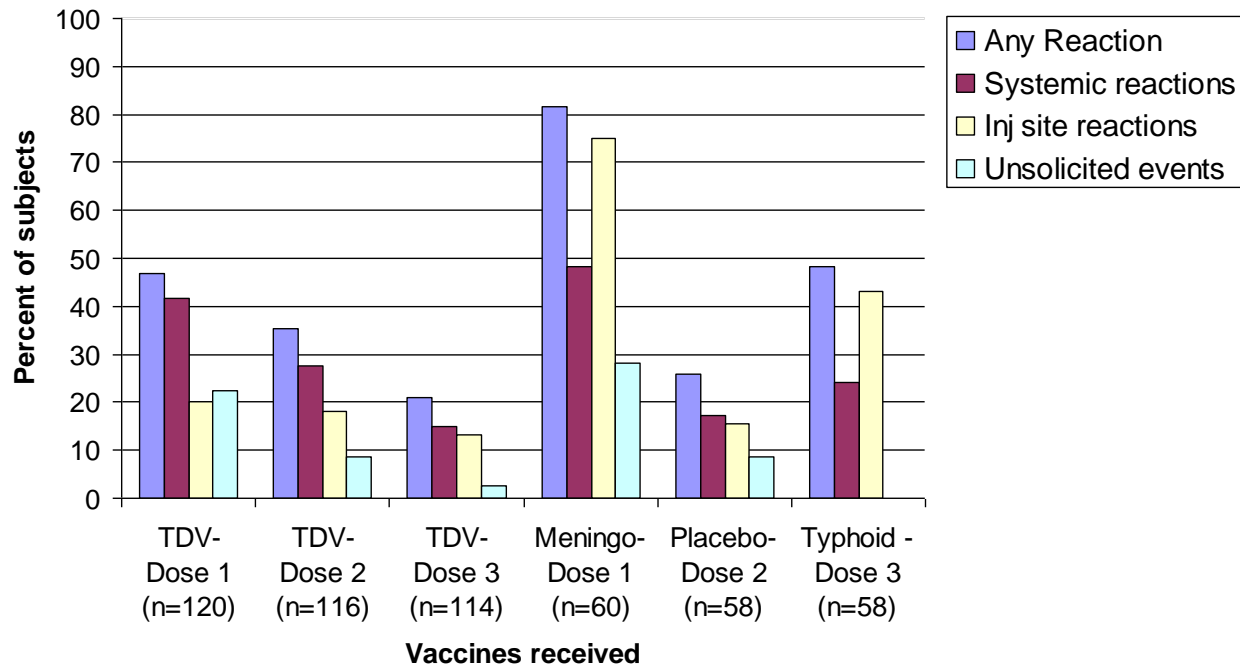
- > 94% seropositive for each serotype after two or three vaccinations
- > 90% seropositive for all of the four serotypes after two or three vaccinations

Higher immunogenicity after 3 doses administered to a population having already received a YV vaccine compared to FV naïve population

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) ($\approx 5 \log_{10}$ CCID₅₀ of serotypes 1, 2, 3, 4)
 - Group 2 (n=60)
 - Meningo A+C, Placebo (NaCl), Typhoid Vi
- Status
 - Follow-up (year 1) ongoing

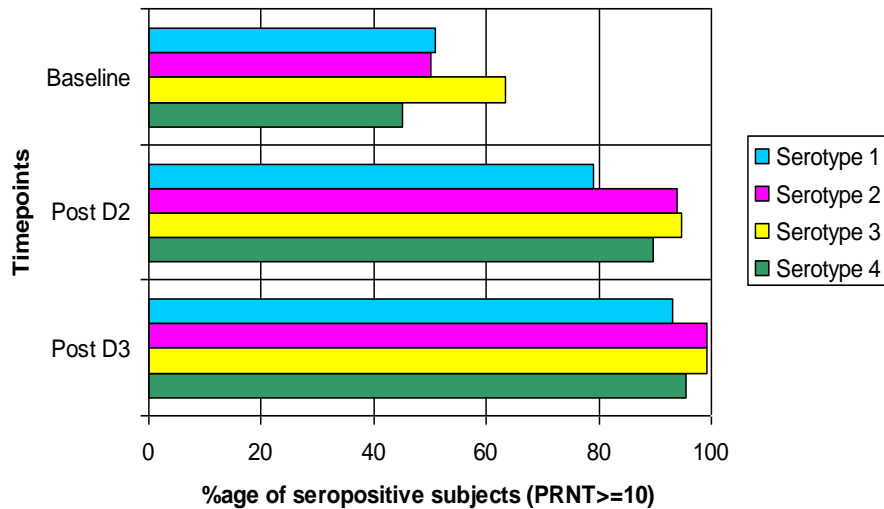
Overview of safety in Ph II study with CYD vaccine in 2-45 year old in Vietnam



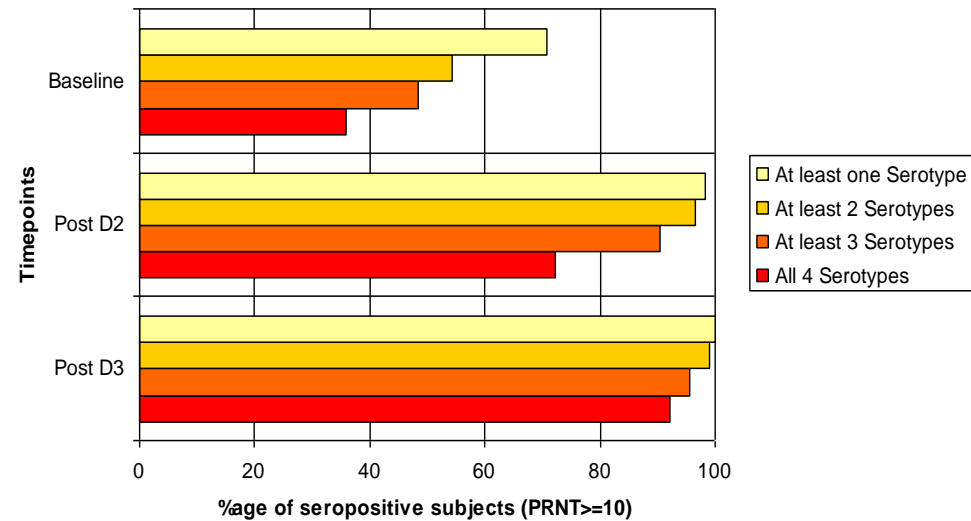
- Satisfactory safety profile comparable to observations from other Phase II trials
- Reactogenicity slightly higher after dengue vaccine compared to placebo (i.e. solicited systemic reaction)
- Trend towards decrease of reactogenicity with subsequent dosing of the dengue vaccine as observed in the previous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

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

Seropositivity rates against Dengue serotypes in CYD dengue group (FAS; N=120)



Seropositivity against at least 1, 2, 3, or 4 against Dengue serotypes in CYD dengue group (FAS; N=120)



- 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

Overview of safety and immunogenicity

● Safety

- By January 2012, more than 23,000 people have received at least one dose of Sanofi Pasteur's dengue vaccine
- 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

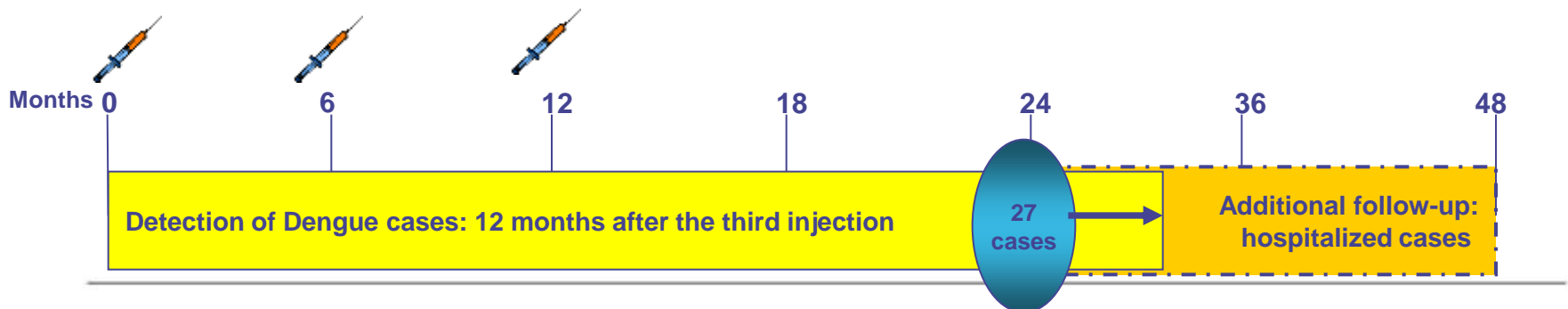
CYD23 First Efficacy Study

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

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

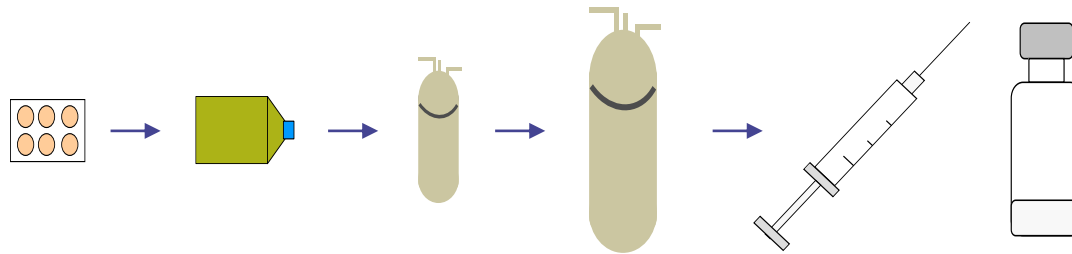
Population	Group 1 (Dengue Vaccine)	Group 2 (Control/placebo)	TOTAL
Children (4-11 years)	2668	1334	4002



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

Challenges for introduction

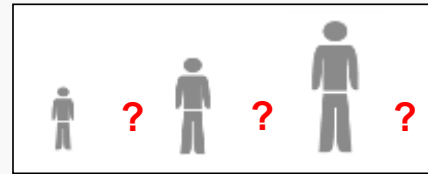
Dengue is underreported

- Improve surveillance



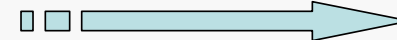
Dengue epidemiology varies

- Adapt vaccination programs to local/ regional specificities



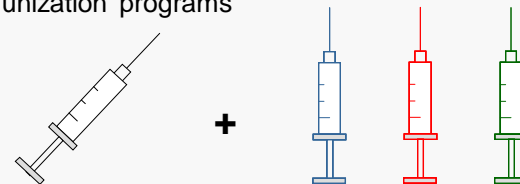
Longterm Phase IV studies

- Plan Phase IV studies to address effectiveness and long-term safety

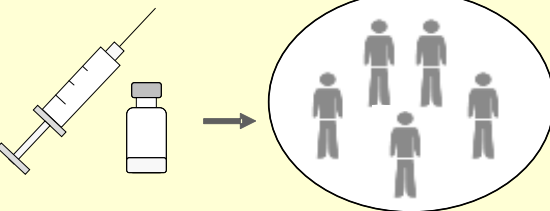


Dengue: an additional vaccine

- Include dengue vaccine in national immunization programs



Vaccine to Vaccination



Dengue vaccination will be part of an integrated control approach

- Anticipate the logistic needed behind vaccination programs

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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Germano Ferreira : Epidemiology



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