Clinical Development Plan

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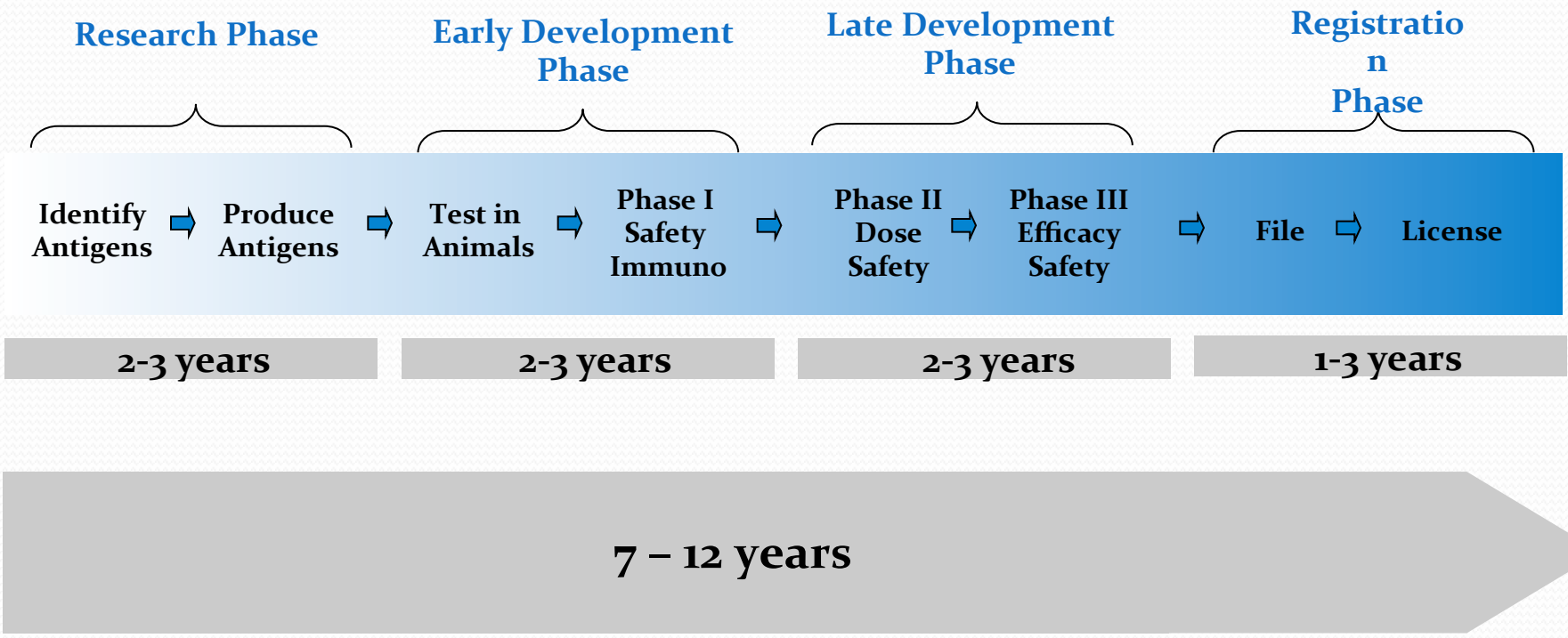
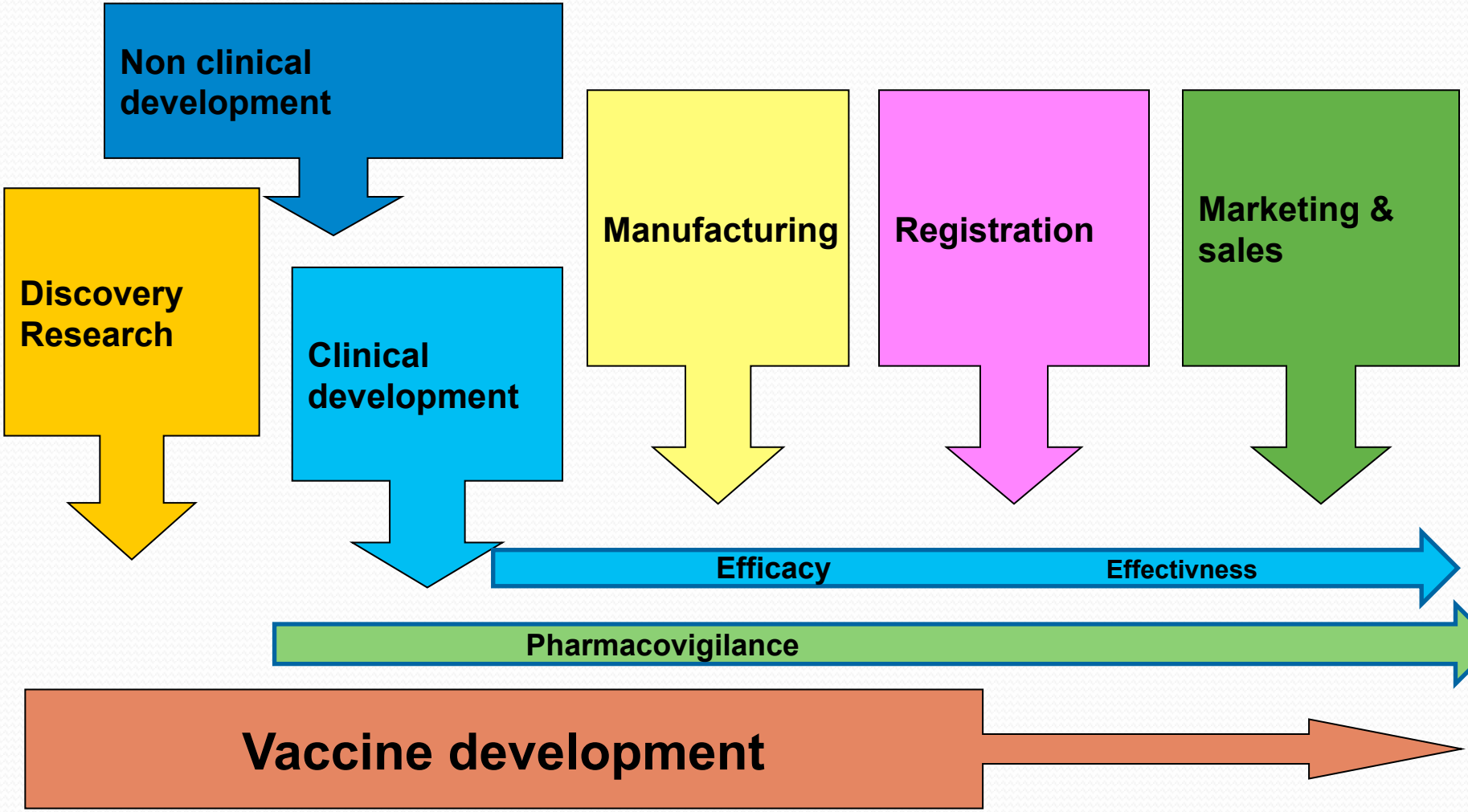
Vaccine Development is a Risky, Time Consuming and Expensive Process



Stages in vaccine development

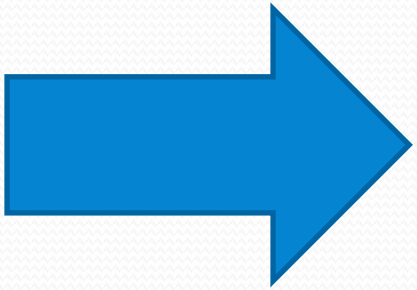


Vaccine development is an integrated process

Clinical Development Plan (CDP)

- CDP describes the clinical strategy and methodology to generate a clinical database that will support marketing authorization application (MAAR)

- requirement of regulatory guidelines (i.e. WHO, Asean CTD, EMEA)



CDP should be fully integrated with the other aspects aspects of vaccine development

CDP content: Introduction

- Disease Epidemiology
- Causative agent
- Mechanism of protection if known
- Other similar vaccines
- Scope of MY VACCINE development: brief outline of MY VACCINE preclincial development, justification of the adjuvant,if any, formulations used in the clincal phases

CDP content: Regulatory Strategy

- Indication
  - Age-group,population
  - Vaccine schedule, booster
  - Dose:vaccine composition, formulation
- Where MAA: country of origin, other countries of the Area (i.e Asian countries), WHO PQ, Europe, USA FDA)
- Regulatory guidelines for clinical development of vaccines are available from Asean,EMEA,WHO
- Some vaccines s guidelines issued by WHO are available always check at: http://www.who.int/biologicals/vaccines/en/

Assessing Safety

- Most vaccine trials are not aimed at testing specific hypotheses regarding adverse events.
- Consequently, safety assessment is generally characterized by exploratory data analysis.
- Descriptive statistics are presented and confidence intervals are often informative.
- *P*-values may be useful for detecting signals of possible vaccine-associated adverse events for further evaluation.
  - By individual clinical trials
  - By age-group analysis
  - All subjects included in the database

CDP content: Safety Key Parameters

- Deviations from normal laboratory values (Phase I)
- Local and systemic (solicited) post-immunization reactions (duration, age groups, etc)
- Adverse events, AEI
- Serious Adverse Events
- Ensure uniform definition as much as possible

Pharmacovigilance must be in place with quality system or outsourced to CRO

Data Safety Monitoring Board (independent experts,review SAEs,AEs, futility)

Vaccine Safety : sample size considerations for new vaccine

- **Unless an efficacy is performed, the clinical database is determined by the safety database**

Local & Systemic Reactions	Approximately 300 subjects Adverse reactions ≥ 1:100
AEs AEIs, Serious Adverse Events (SAE) and Medically Significant AEs necessitating a medical office or ER visit and/or resulting in premature withdrawal of subjects from the study	According the vaccine, approximately 5000 subjects may be appropriate to provide reasonable reassurance of pre-licensure safety in randomized controlled studies Adverse Events ≥ 1:1000

Annex 1 Guidelines on clinical evaluation of vaccines: regulatory expectations

World Health Organization WHO Technical Report, Series No. 924, 2004

Remember: Vaccine Safety is Paramount

- Unlike drugs which are given to sick people, vaccines are given to healthy people, so risk must be minimal
- Large numbers of people are exposed to vaccines, so rare and very rare adverse events can be detected
- The acceptance of the risk of rare or very rare adverse events is highest if the disease is highly endemic, epidemic or causes disability and mortality
- Risk-benefit changes overtime as an efficacious vaccine reduces the disease rate

A higher safety standard is required for vaccines than for other medical interventions

CDP Content: Immunogenicity

- The ability of the vaccine to induce an immune response (both at the serological and at the cellular level) is defined immunogenicity
- The quantitative and qualitative assessment of the vaccine's immunogenicity is a typical endpoint of a vaccine clinical trial
- Immunogenicity endpoints are included at each stage of vaccine clinical development (Phase I-III) and may or may not predict vaccine efficacy (immunological correlate of protection)

CDP Content: Immunogenicity aspects to consider further

- Primary response
- Persistence of response
- Booster response
- Memory response
- Consistency of response

CDP Content: Immunogenicity

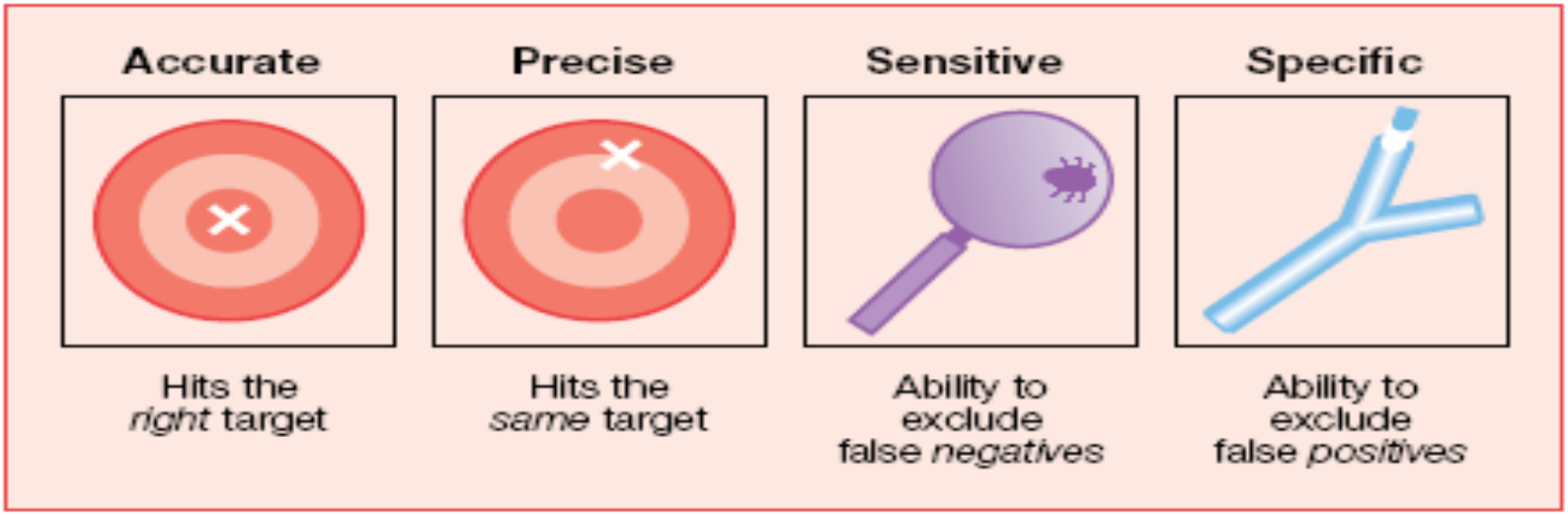
- Immunogenicity section should include description

  - of immunological assay used to evaluate the immuneresponse to the study vaccine
  - Case definition of responder (i.e. cut off value, X fold increase)
  - Criteria used to compare to other similar licensed vaccines (if this is the case)
  - Strategy to link immunogenicty to efficacy (correlates of protection) in case efficacy is required
  - Other exploratory or supportive immunological measurements (CMI, functional assay)

Vaccine Immunogenicity

Key features of a good serologic assay

A good serologic assay must be:



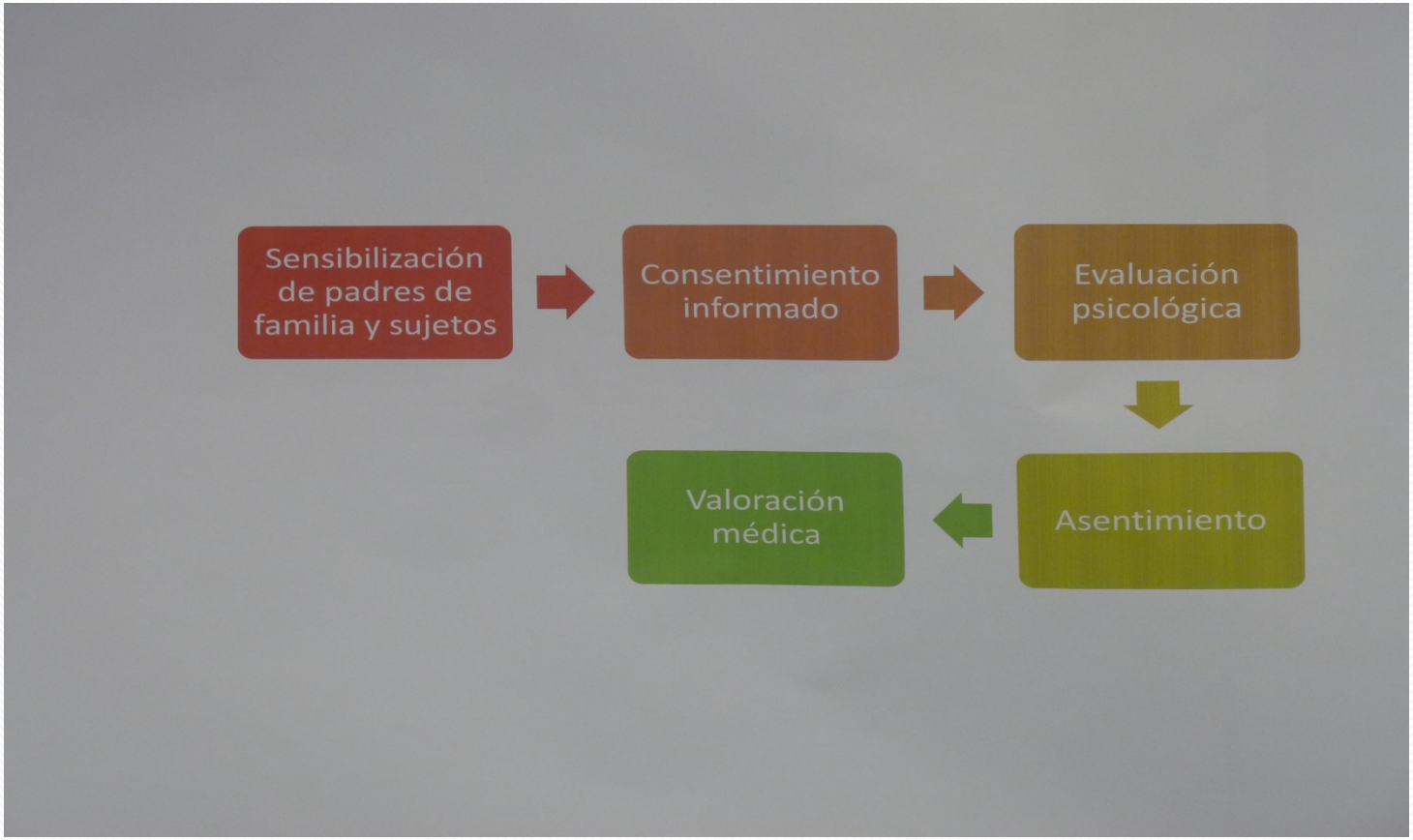
Assay validation is absolutely critical!

CDP Content: Ethics

- It should be described how ICH-GCP, DoH, local ethical guidelines will be complied with
- CTA process and approval
- Delivery of care to study participant issue
- Individual Consent, assent, community consent
- Countries pecularity: ethical acceptabilitites of placebo or control vaccine

Before CTAs: think of setting up a scientific and ethical review by recognized experts (Scientific Advisory Group-SAG? Scientific group of experts?)

Ethics



IC and assent process in an adolescents clinical trial in Colombia- 2010-

Ethics

Dr Jimenez , Bucaramanga, Colombia , explaining the process to participants and their families- Adolescents clinical trial-

CDP content: CDP strategy

- Overall description on how to prove that the vaccine is safe immunogenic (or efficacious)
- Whether demonstration of efficacy is needed
- If not a rationale has to be explained
  - Correlate of protection do exist (Pneumo,measles,rubella,hib,hepB,))
  - Correlate of protection do not exist but comparative licensed vaccine do (Meningo, Pertussis,
- If efficacy demonstration is needed in which target population and why

CDP Content: CDP strategy

- Indicate which studies will be considered pivotal (non-inferiority, large safety, long term follow-up, efficacy etc etc) to demonstrate safety, immunogenicty or efficacy

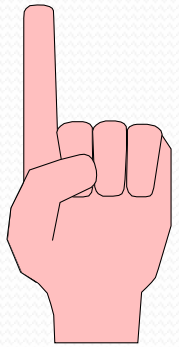
- Refer to existing guidelines, scientific publications, vaccine candidate or similar data in the public domain
  - always check at: http://www.who.int/biologicals/vaccines/en/

Clinical Development Plan

- For each study the following will be addressed:
  - Objective of conducting the study
  - Study population (age group, number of evaluable subjects)
  - Study design, duration, study vaccine dose
  - Criteria for assessment and GO or NO GO decision points

CDP : Clinical trials description -Phase I

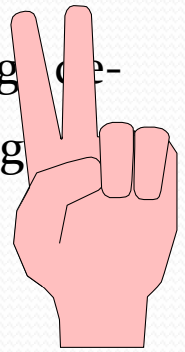
- Sample size
  - 20-50 small number of subjects
- Subjects characteristics
  - Healthy adult volunteers



- Aims
  - First use in human, closely monitored trials
  - Clinical laboratory data
  - Exclude frequent and serious adverse events, and first information on reactogenicity (local and systemic)
  - Obtain preliminary information on immunogenicity, for live vaccine viral shedding, viremia etc
  - Formulation-finding, dose-finding

CDP : Clinical trials description -Phase II

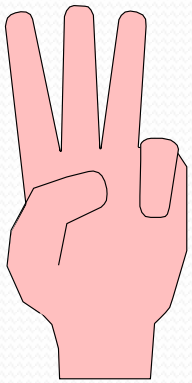
- Sample size
  - Several hundreds (appropriate sample size)
- Subjects characteristics
  - Target population (age de-escalation approach)
  - Stepwise testing of adults, adolescents, children, infants (age de-escalation approach)
  - Include study participants representative of those to be targeted in phase 3 trials



- Aims
  - Formulation/dose/schedule-finding
  - Definition of immunoresponse, (type, quality, kinetics etc)
  - Definition of safety profile
  - Comparison with licensed vaccines (non-inferiority), interference with concomitant vaccines (co-administration)
  - Typically randomized & controlled
  - Determine dose and schedule to be used in phase 3

CDP : Clinical trials description -Phase III

- Sample size
  - From several hundreds to thousands (appropriate sample size)
- Subjects characteristics
  - Target population
- Aims
  - Clinical efficacy
  - Confirmation of safety
  - Clinical demonstration of production consistency (lot-to-lot-)
  - “Bridging” studies



Phase III Clinical Efficacy Trials

- Aimed to define vaccine induced clinical protection (primary end point is prevention of disease)
- Typically double-blind, randomized, controlled
- Background epidemiology essential for sample size calculation (may be very large trials)
- Case definition
  - Well-defined clinical criteria and validated assays for laboratory diagnosis (culture, serology, etc.)
  - Clinical relevance
  - Case surveillance
- Primary and secondary endpoints
- Data Safety Monitoring Committee

Phase III Clinical Trials

- **Routine vaccines co-administration studies**
  - Obtain safety and immunogenicity data in pre-licensure studies to support simultaneous administration of routine vaccines
- **Bridging studies**
  - Support manufacturing changes
  - Extrapolate efficacy and safety data to a different population
  - Support a new dose or a new schedule
- **Clinical lot consistency studies**
  - Support physicochemical assessment of manufacturing consistency

Routine vaccines co-administration studies (1)

Potential issues

- Safety: potential for additive or synergistic effects
- Immunogenicity: potential for interference from multiple live or inactivated vaccines
- Similar conjugate carriers (e.g., diphtheria and tetanus toxoids) in multiple products:
  - Potential for protein carrier suppression
  - Exuberant responses to carrier
- Uncertainty about novel products, e.g., live virus or bacterial vectors; novel adjuvants
- Co-administration studies are needed for a label claim-indication- of immune non-interference and safety

Surprises

Vaccines co-administration studies

Enhanced immuneresponse response due to concomitant administration

COMPARISON OF ANTIBODY RESPONSES FOR Td AND MENACTRA VACCINES FOR PARTICIPANTS AGED 11–17 YEARS ON DAY 28 FOLLOWING RESPECTIVE VACCINATIONS

	Td + Menactra at Day 0, Placebo at Day 28			Td + Placebo at Day 0, Menactra at Day 28		
Antigen	N	GMT	(95% CI)	N	GMT	(95%CI)
Diphtheria	465	**120.9**	(105, 140)	473	**8.4**	(7.6, 9.2)

Adapted from Menactra Package Insert

Vaccines co-administration studies

Diminished response due to Hib co-formulated with other vaccines

THE LANCET

Randomised trial of the effect of co-administration with acellular pertussis DTP vaccine on immunogenicity of *Haemophilus influenzae* type b conjugate vaccine

Juhani Eskola, Rose-Marie Olander, Tapani Hovi, Leila Litmanen, Sara Peltola, Helena Käyhty

Hemophilus influenza type B polysaccharide antibody responses

	All separate	Hib separate	Hib combination	All mixed
At 7 months	DTaP+IPV+Hib	[DTaP/IPV]+ Hib	[DTaP/Hib] + IPV	[DTaP/IPV/Hib]
GMC (ug/mL) 95%CI	3.94 (12.08–7.44)	3.10 (1.78–5.39)	0.38 (0.19–0.78)	0.56 (0.34–0.92)
>0-15 ug/mL	93%	93%	78%	79%
>1-0 ug/mL	87%	77%	19%	48%

GMC=geometric mean concentration.
$p=4x10^{-8}$ (ANOVA)

Adapted from The Lancet 1996 Dec 21-28;348(9043):1688-92.

Co-administration study

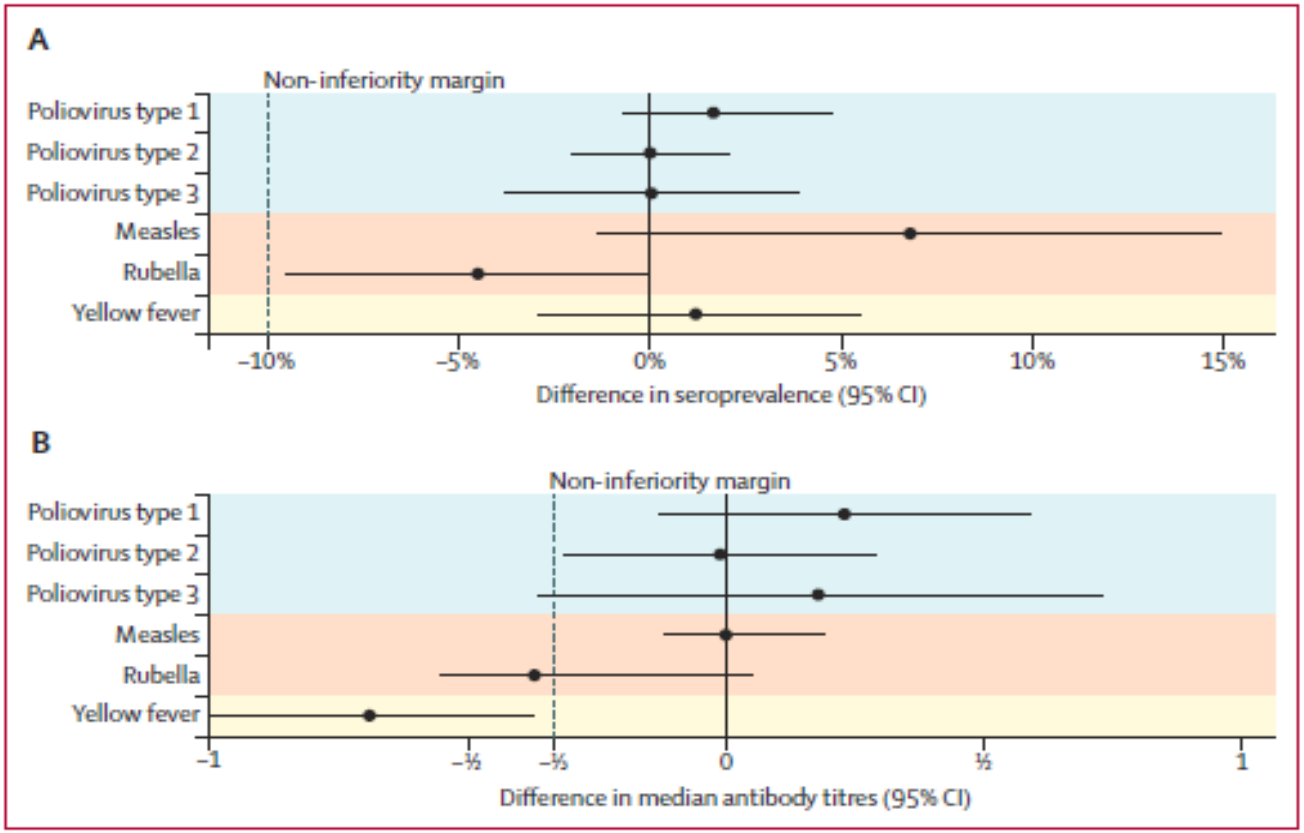


Figure 2: **Vaccine co-administration (objective one)**
(A) Differences in the seroprevalence for poliovirus types 1, 2, and 3 seroconversion for measles, rubella, andyellow fever, comparing each of the vaccines administered on its own with the combination of all three vaccines administered together. Circles represent the point estimate, lines are 95% CIs. (B) Difference in the antibody titres comparing each of the vaccines administered on its own with the combination of all three vaccines administered together. Circles represent the point estimate, lines are 95% CIs.

Clarke E. et al. Safety and immunogenicity of inactivated poliovirus vaccine when given with measles-rubella combined vaccine and yellow fever vaccine and when given via different administration routes: a phase 4, randomised, non-inferiority trial in The Gambia. Lancet Global Health 2016 Jun 27.

Bridging studies (1)

- **Bridging studies** are commonly performed in vaccine clinical research to define acceptability of the safety and immunogenicity of a new vaccine/immunization regimen, based on comparison with previous ones already accepted by a regulatory agency

- **Bridging studies may evaluate**:
  - Effect of manufacturing change
  - Effect of formulation change
  - Effect of dose/schedule change
  - Effect of other vaccines given concomitantly

- **Population bridging studies** are a special type of bridging studies which are aimed to evaluate the possibility to extrapolate an effect observed in one population (e.g., clinical efficacy) to other populations
- Given that evaluation of clinical efficacy in different populations may be unpractical or even impossible, the comparison of immune responses is the fundamental objective of these trials

Bridging studies (2)

- Bridging studies are generally randomized and well powered non inferiority studies
- They are designed to rule out clinically important differences in parameters of immune response (i.e., not less immunogenic than the control vaccine) or in parameters of safety (i.e., not more reactogenic than the control vaccine) such as:
  - Ratio of geometric mean concentration of post immunization antibodies
  - Per cent "responders" (immune response above a certain threshold)
  - Rate of serious adverse events

Clinical lot consistency studies

- Unlike drugs, which are chemical compounds and therefore the various lots of the same substance induce the same pharmacological effect, vaccines are biological substances and may induce variable biological responses

- Therefore these peculiar vaccine studies, which are aimed to evaluate the reproducibility of response (both safety and immunogenicity) induced by different production lots of the same vaccine, are a necessary pre-requisite for vaccine registration

- Clinical non-inferior immunogenicity amongst three consecutive production lot (final scale, final formulation) need to be produced (USA FDA)

Torresi J et al. Lot-to-lot consistency of a tetravalent dengue vaccine in healthy adusIts in Australia: A randomized study. **Vaccine**. 2015 Sep 22;33(39):5127-34

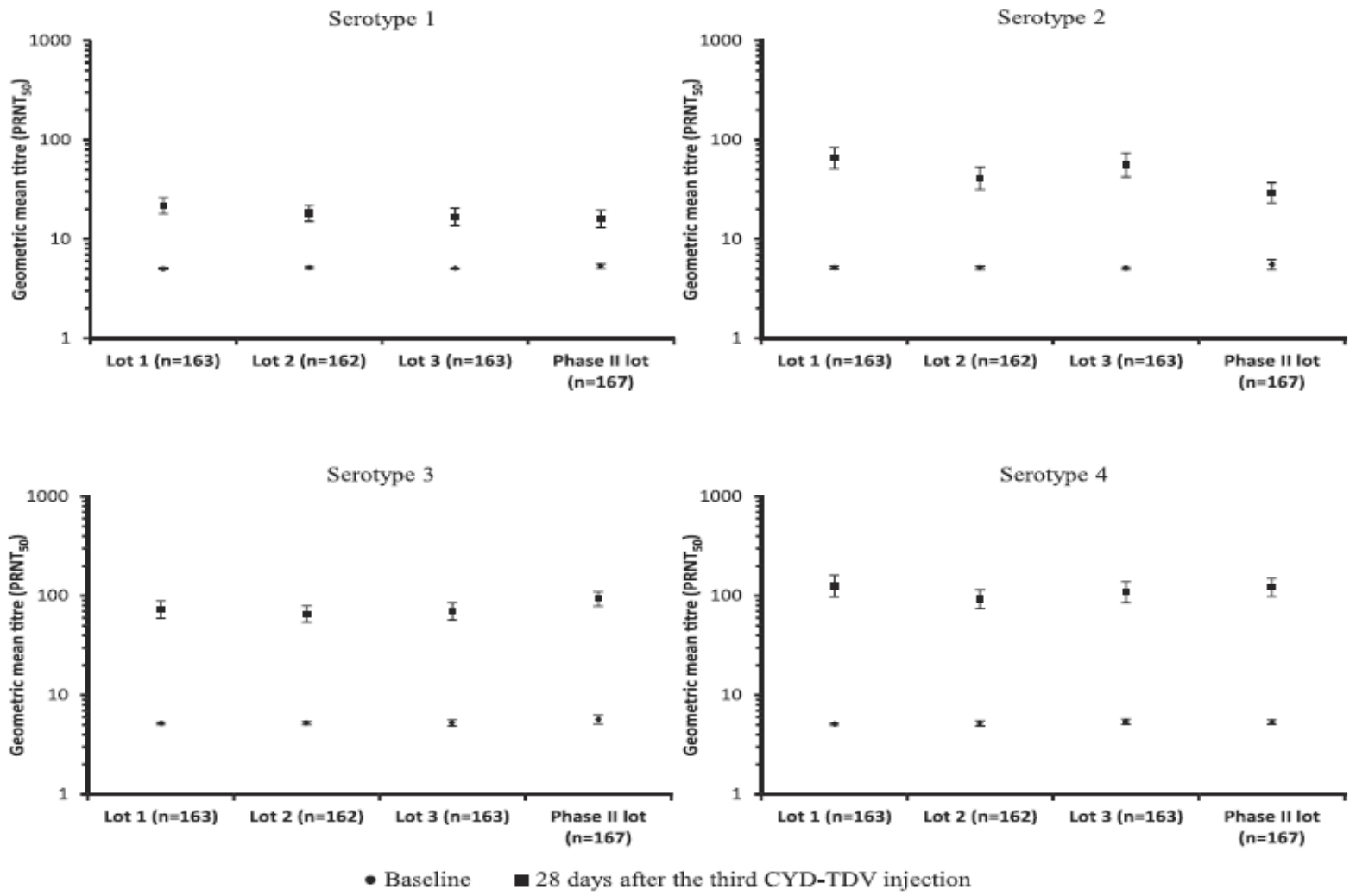
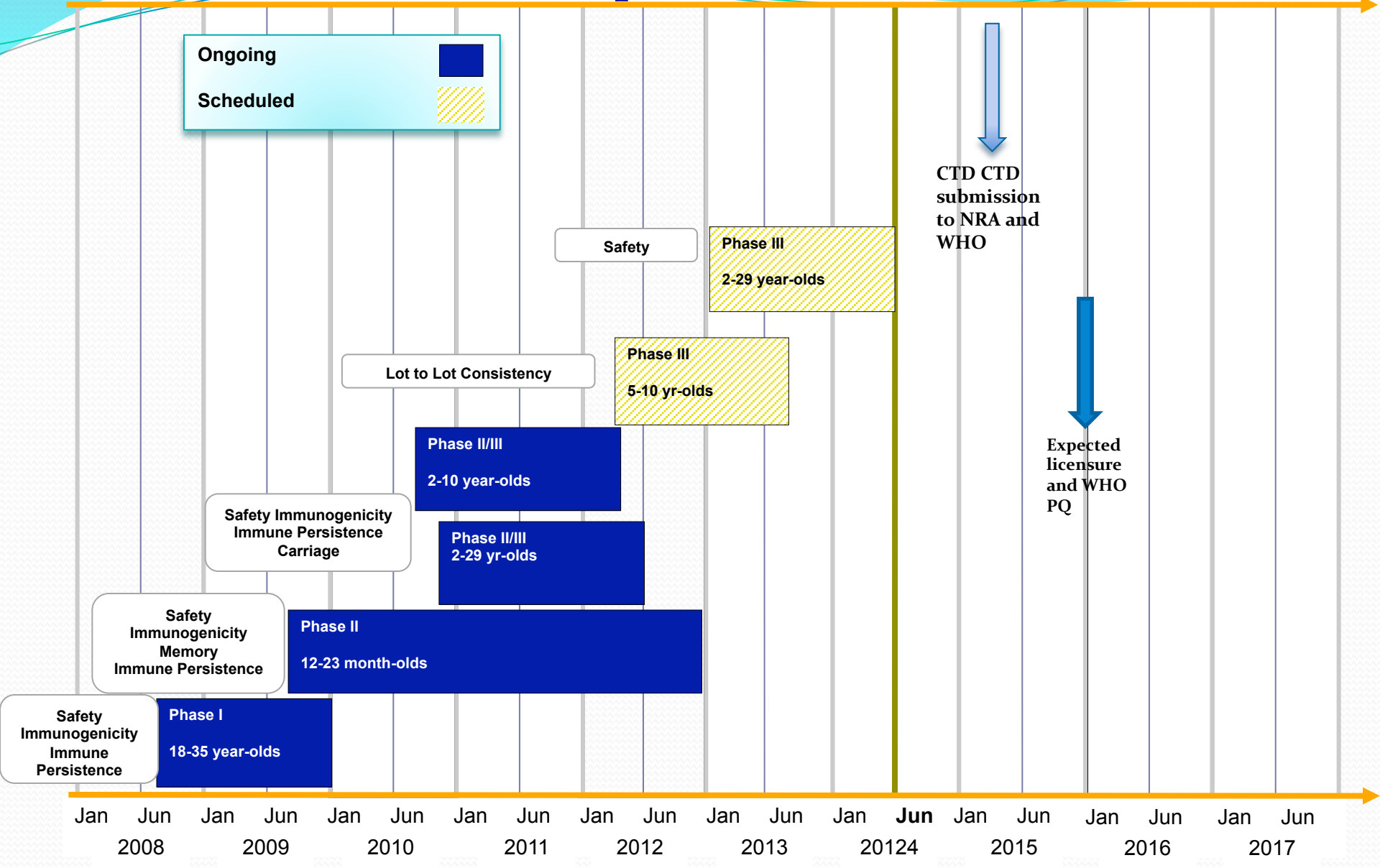


Fig. 2. Geometric mean titres (GMTs) and 95% CIs for each dengue serotype at baseline and 28 days following the third injection according to vaccine lot. Data shown for the full analysis set.

CDP for a vaccine against meningitis prequalified by WHO. Indication: one injection at the age 1-29 years

Study	Phase	Total Subjects	VAC vaccine	Control/ Reference vaccine	age-group	Study Design
VAC-001	I	60	20	40	18-35 y	Safety and immunogenicity of one dose -10 µg of VAC vaccine in healthy adult volunteer.
VAC-002	II	600	200	400	12-23 mo	Safety and immunogenicity of one dose of VAC vaccine in comparison to a control (Hib vaccine) or to MenPsACYW vaccine
VAC-002 B*	III	600	200	400	24-35 mo	Safety and immunogenicity of one booster dose of either PsA (memory) or VAC or Hib vaccine in subjects included in VAC-002
VAC-003	II	700	350	350	2-29 y	Safety and immunogenicity of one dose of VAC in comparison to MenPsACYW vaccine (non inferiority).
VAC-004	III	520	390	130	2-5 y	Safety and immunogenicity of one dose of 3 consecutive production lots of VAC vaccine (lot-to-lot consistency). For safety comparison MenPsACYW vaccine group.
VAC-005 And VAC-006	III	4.500	2.250	2.250	1-29 y	Safety of one dose of VAC vaccine and immunogenicity in a subset of subjects, in 1-29 years old in comparison to MenPsACYW vaccine.
Total		**6.980**	**3.410**	**3.570**		

Clinical Development Plan – VAC-



CDP GO/NO GO decision points

- Results will determine and define Go/NO GO decision points:
  - Phase I
  - Phase II
  - Phase III

Finally the Reference List

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CDPlan: think ahead and integrate with other company functions

- Overall planning and coordination:
  - Product characterization & manufacturing (cGMP)
  - Anticipate needs of future trials, e.g., critical assays
  - Accumulate sufficient safety, immunogenicity & efficacy data during development
  - Clinical bridging studies, e.g., population; product scale-up
  - Continuos and Prospective application of Good Clinical Practices

Thank You