

# **Immunization and Vaccine related Implementation Research (IVIR) Advisory Committee**

**1-2 February 2017 Meeting, Veyrier du Lac,  
France**

# IVIR Advisory Committee 2017

Advises WHO on implementation research related to vaccines and immunization programs  
Provides guidance on quantitative methods useful to vaccine research

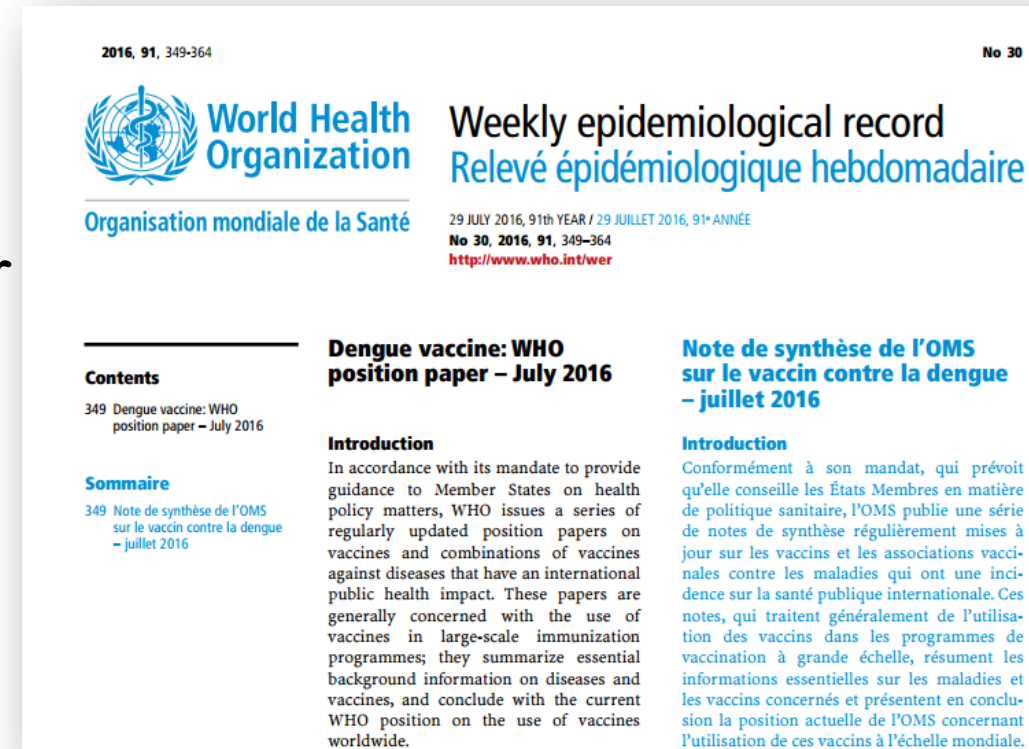


# WHO Implementation Research Themes

1	Minimize <b>barriers</b> and improve coverage of vaccines currently in use
2	Conduct <b>impact evaluation</b> of vaccines in use
3	Improve methods for <b>monitoring</b> of immunization programmes

# WHO recommendations on licensed dengue vaccines

- Countries should consider introduction of CYD-TDV only in geographic settings where epidemiological data indicate a high burden of disease.
- Seroprevalence should be approximately 70% or greater in the age group targeted for vaccination.
- The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination.
- Dengue vaccine introduction should be a part of a comprehensive dengue control strategy.



VPP published 29 July 2016

<http://www.who.int/wer/2016/wer9130.pdf>

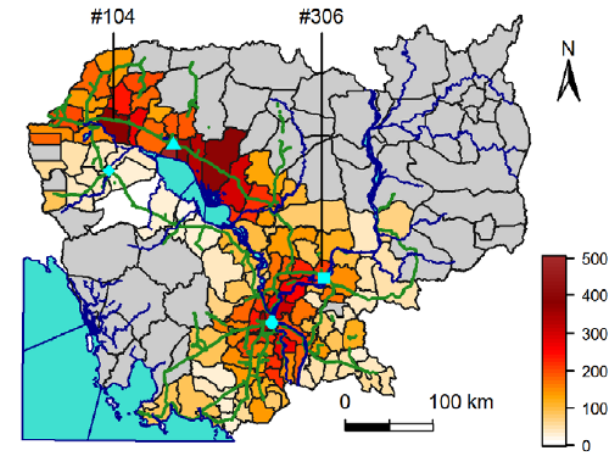
*How to translate these recommendations into practise in settings where representative seroprevalence data on high spatial resolution that is needed are generally not available?*



# Tools to operationalize WHO recommendations on licensed dengue vaccines

IVIR-AC requested to assess two tools:

1. Generic guidance on dengue seroprevalence surveys: vaccination
2. Global Dengue Transmission Map



Teurlai M, et al. Can human movements explain heterogeneous propagation of dengue fever in Cambodia? PLoS Negl Trop Dis. 2012;6(12):e1957.

IVIR-AC recommended both tools are useful.

1. Specific proposals were made to modify or expand the survey and to improve efficiency
  - consider salivary samples, opportunistic collection of residual blood samples from labs or to address questions for other pathogens.
2. Minimize the risk of misinterpretation of the map predictions
  - Maps should show more specific explanation on methods, source of information of estimates, data limitations and showing potential vaccine impact

# Measles mortality model (1)

- **Measles model to estimate global and country-specific measles cases and mortality used for measure:**
  - **Progress towards MDG4**
  - **Progress towards Regional Measles Elimination**
- **Since last IVIR-AC review in 2011 some methodological innovations were incorporated**

## Measles mortality model (2)

- **IVIR-AC welcomes innovations but cautioned for**
  - Biases in input data used to fit models
  - Validation of herd effects should be done with full dynamic epidemic model (SIR)
  - CFR changes over time; hence updated information need to be incorporated
  - Need to take into account additional coverage variables including the association between MCV1, MCV2, SIA coverage as well as the duration of high MCV coverage
  - For differences between estimates of global measles burden by WHO and other groups. A systematic model comparison would be helpful.

# Comparison of existing Hepatitis B impact models through systematic review and meta-analysis

## Objectives

- Identify & describe existing Hep B model characteristics and parameters
- Compare model predictions of strategies to prevent Hep B infection in neonates & young children
- Understand variabilities in model predictions

## IVIR-AC agreed on plan presented

- Inclusion criteria of models – systematic review and open call including HICs
- Model harmonisation – “explaining dissonance” rather than to converge to single point estimate
- Model uncertainty vs uncertainty from generalising to other settings
- Open source code such as CRAN initiative and clinical trials.gov may be useful
- Weighing models on quality



# Typhoid vaccine impact and cost-effectiveness model models

- Updated since SAGE recommendations in October 2017
  - Dynamic SIR model with compartments for primary and secondary infections as well as chronic carriers
  - CEA model to evaluate vaccination in 5 settings in India, Vietnam and Kenya
- IVIR-AC noted that:
  - Model findings should be considered in the context of available typhoid vaccines and non-vaccine interventions such as WASH
  - Data limitations could be improved i.e. granularity and sources of hospitalization cost data and age-specific CFR
  - Vaccine price assumption of 1\$/dose is not realistic
  - The role of chronic carriers and asymptomatic/mild infections on disease infection should be further investigated

# Reporting guide for observational influenza vaccine effectiveness studies

## Issues considered

- By design RCTs favour relatively frequent endpoints to avoid unfeasible large sample size requirements.
- As a result licensure of influenza vaccines focus on prevention of lower respiratory illness rather than on severe illness and mortality
- IVIR-AC recognizes the value and supports the aim of this guide.
- It will guide reporting from observational studies so that they may help may fill evidence gaps.
- For further development Guide should consider:
  - How to address potential sources of bias e.g health seeking and confounding for both risk of ILI and likelihood of vaccination
  - Adapt the influenza vaccine Guide and recommendations for vaccines against other diseases and seek collaboration with other groups developing guidelines ( e.g. STROBE)

# Non-specific effects of vaccines (NSE): SAGE recommendations, April 2014

NSEs on all-cause mortality warrant further research

- IVIR-AC should
  - Advise on **priority research questions to inform policy decisions** and on study designs to answer them
  - Assess use of **high quality randomized controlled trials** where feasible, with sufficient power to explore sex differences and a priori defined and standardized immunological endpoints

# SAGE recommendations on NSE, April 2014 (cont.)

- Future research should draw on a broad investigator pool and from a wide range of geographic locations **using standardized protocols**
- **Additional observational studies are unlikely to contribute to policy decision-making and therefore should not be encouraged**

**BMJ 2016;355:i5170**

## **Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review**

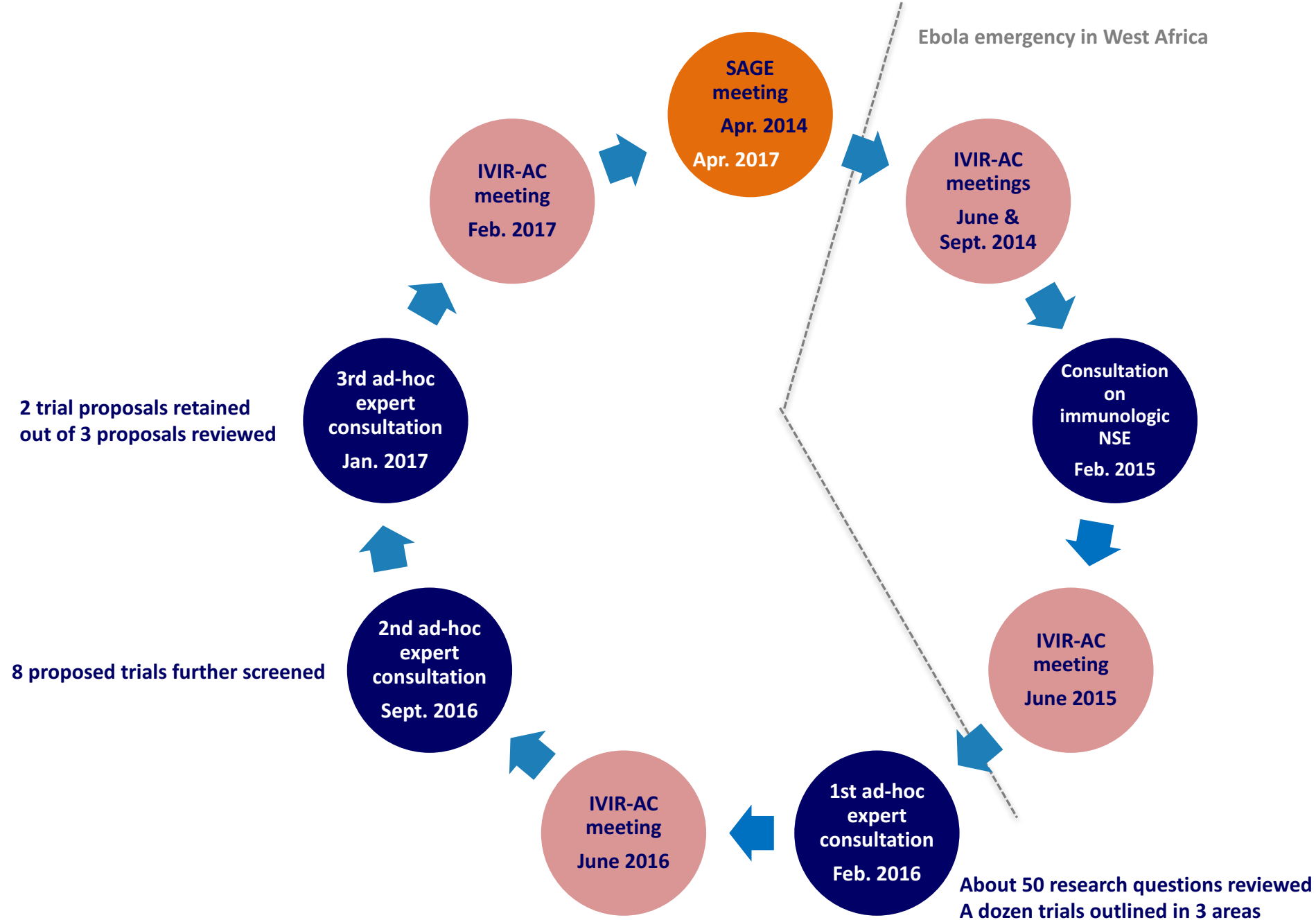
Julian P T Higgins,<sup>1</sup> Karla Soares-Weiser,<sup>2</sup> José A López-López,<sup>1</sup> Artemisia Kakourou,<sup>3</sup> Katherine Chaplin,<sup>1</sup> Hannah Christensen,<sup>1</sup> Natasha K Martin,<sup>1,4</sup> Jonathan A C Sterne,<sup>1</sup> Arthur L Reingold<sup>5</sup>

**BMJ 2016;355:i5225**

## **Non-specific immunological effects of selected routine childhood immunisations: systematic review**

Rama Kandasamy,<sup>1,2</sup> Merryn Voysey,<sup>1,2,3</sup> Fiona McQuaid,<sup>1,2</sup> Karlijn de Nie,<sup>1,2</sup> Rebecca Ryan,<sup>1,2</sup> Olivia Orr,<sup>1,2</sup> Ulrike Uhlig,<sup>4</sup> Charles Sande,<sup>1,2</sup> Daniel O'Connor,<sup>1,2</sup> Andrew J Pollard<sup>1,2</sup>





**Note:** Reports of the last IVIR-AC meeting (February 2017) and of the three ad-hoc expert consultations (February 2016 to January 2017) are among the background documents.

# Experts contributing to the consultation on immunologic NSE, February 2015

- Matthew L. Albert
- Matthias Egger
- Paul Fine
- Beate Kampmann
- Rama Kandasamy
- Chris Karp (Co-Chair)
- Tobias R. Kollmann
- Dominic F Kelly
- David B. Lewis
- Arnaud Marchant
- Joseph Mike McCune
- Helene McShane
- Mihai G. Netea
- Andrew J Pollard (Co-Chair)
- Bali Pulendran
- Octavio Ramilo
- Lynda Stuart
- J.J.M. van Dongen
- SingSing Way
- Morven Wilkie
- Chris Wilson
- Merryn Voysey

# Experts contributing to three consultations on NSE clinical trials, February 2016–January 2017

- Pedro Aide
- John Aponte
- Robert Breiman
- Marc Brisson
- John Clemens
- Frank Destefano
- Paul Fine
- Lourdes Garcia
- Brad Gessner
- Julian Higgins
- Fernando de la Hoz
- Momodou Jasseh
- Rama Kandasamy
- Chris Karp
- Ira Longini
- Elizabeth Miller
- John Modlin
- Victoria Nankabirwa
- Frank Odhiambo
- Walter Orenstein
- Richard Peto
- Andrew Pollard (Chair)
- Colin Sanderson
- Halvor Sommerfelt
- Dipika Sur
- Yot Teerawattananon
- Merryn Voysey

# Review & screening of potential research questions

## BCG (8 questions)

### Example

Does an immunization schedule with a bOPV dose at birth in addition to BCG reduce mortality by age 1 year compared to a schedule with only a BCG dose?

## Measles (10 questions)

### Example

Does an immunization schedule with an additional MCV dose at 18 weeks of age (4 weeks after DTP3) reduce child mortality by age 5 years compared to a schedule with only the currently recommended doses?

## DTP and order of vaccines (9 questions)

### Examples

- Does an immunization schedule with DTP doses increase child mortality by age 5 years compared to a schedule without DTP?
- Does an immunization schedule with bOPV at ages 6, 10 and 14 weeks reduce mortality by age 5 years compared to a schedule with IPV at the same ages?

## Multiple & new vaccines (19 questions)

### Example

Does an immunization schedule with a malaria vaccine at age 18 months administered 4 weeks after a measles-containing vaccine increase child mortality by age 5 years compared to a schedule with an inverted administration of those two vaccines?

# Priority research questions to inform policy decisions

- Questions and designs to address **one or more of the main hypotheses on NSEs**
- Designing the trial in a way that, if NSEs are not documented evidence can still **inform future policy**, e.g. childhood immunization schedule
- **Feasibility was a consideration**, e.g. sample size estimated for a trial leveraging introduction of a dengue vaccine among adolescents



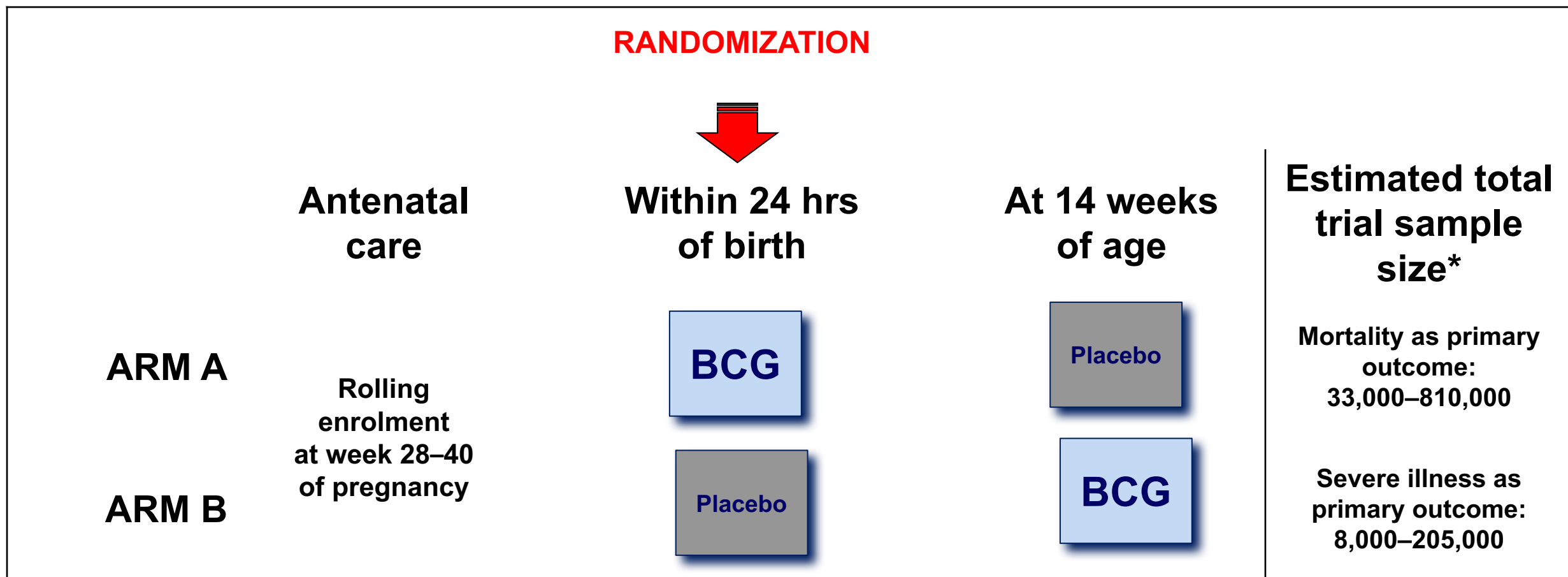


# Trial 1: NSE of BCG

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- Individually randomized placebo-controlled trial of early versus late vaccination with BCG to estimate its NSE in infancy
- Primary objectives
  - To compare the risk of death and severe illness in the first 14 weeks of life among infants who received BCG at birth with those who received BCG at 14 weeks of age

# Trial 1: NSE of BCG



\* Estimated sample sizes varies by different assumptions on key parameters.

# Trial 1: NSE of BCG

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## Anticipated methodological challenges

- Extent to which blinding can be implemented
- Independent outcome adjudication committee to classify objectively causes of death and severe illness
- Required sample size and recruitment procedure
- Properly conducted trials will reduce mortality for both arms

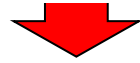
## **Trial 2: NSE of MCV (additional dose)**






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- **2x2 factorial double blind randomised placebo-controlled trial to assess NSE of an additional dose of measles-containing vaccine at 12–16 weeks of age**
- **Primary objective**
  - **To determine the effect on mortality <2 years of an infant schedule with an additional early dose of measles vaccine given with DTwP-HBV/Hib at 14 weeks of age**

# Trial 2: NSE of MCV (additional dose)

## Randomization



	Schedule	At 10 wks of age	At 14 wks of age	At 9 months of age	Estimated total trial sample size*
ARM A (current EPI)	3p+0 schedule		 	 	87,000–147,000
ARM B					
ARM C					
ARM D					



Standard EPI vaccination schedule containing: DTwP-HBV/Hib: Diphtheria, tetanus, pertussis (whole cell formulation), hepatitis B, and *Haemophilus influenzae* type b; and pneumococcal conjugate vaccine.



Placebo version of DTwP-HBV/Hib



Measles and rubella vaccine



Placebo version of measles and rubella vaccine



# **Trial 2: NSE of MCV (additional dose)**

**2x2 factorial design**

At 14 weeks of age	DPT 3p+0	DTP 2p+1
	Placebo	Additional MCV dose
	Arm A	Arm C
	Arm B	Arm D

## **Trial 2: NSE of MCV (additional dose)**

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### **Anticipated methodological challenges**

- **Required sample size may not allow to identify if interactions between allocated arms occurred**
- **DTP randomization may not fully resolve key uncertainties in relation to detrimental NSE**
- **Sample size....**

# Next steps

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**May 2017** - Online publication of proposed protocols to receive comments from researchers community

**June–July 2017** - Review and finalization of generic protocols by experts who drafted them

**August–December 2017** - Consultation with existing networks of researchers (and sites) already active in countries that are more likely to be an adequate setting for the implementation of the proposed clinical trials

... and ongoing review of emerging evidence on NSE

Ministerio de Salud y Deportes  
Programa Ampliado de Inmunización

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*Este es un Documento Importante*

Thank you