Reports of three ad-hoc expert consultations on clinical trials of non-specific effects of vaccines

A. 16–17 February 2016
B. 08–09 September 2016
C. 30–31 January 2017

Initiative for Vaccine Research (IVR)
Immunization, Vaccines and Biologicals (IVB)
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Ad-hoc expert consultation on epidemiological studies for non-specific effects of vaccines

16–17 February 2016

Summary of discussion and conclusions

Geneva, 2 October 2016

Ad-hoc expert consultation on epidemiological studies for non-specific effects of vaccines
Geneva, 16–17 February 2016

Summary of discussion and conclusions

1. Introduction

- Based on systematic reviews of non-specific effects of vaccines (NSE), WHO Strategic Advisory Group on Immunization (SAGE) did not consider in April 2014 changes to recommended immunization schedules necessary. However, the Group considered further research on all-cause mortality NSE warranted.
- The Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) took over the tasked to provide advice on priority research questions and study designs.
- SAGE and IVIR-AC concurred that implementation of high quality prospective studies, including randomized controlled trials where feasible, is needed to provide conclusive evidence on NSE.
- Consequently, the present wanted to advance toward the implementation of NSE clinical trials.

2. Objectives and organization

- Three objectives: To reach a consensus on priority questions for NSE clinical trials; to propose trial designs for each of the priority questions and to characterize the strengths and limitations of these designs; and to plan the work toward the finalization of possible trial protocols.
- The consultation was organized in three sessions: background and previous recommendations, priority questions, and outline of potential trial designs (see Agenda, **Appendix 1**). Seventeen experts from four Regions contributed (see List of participants, **Appendix 2**).

3. Summary of the presentation and discussion

Background

- Evidence submitted to SAGE in April 2014 was presented, included the assessment of the risk of bias done for epidemiological studies. Recommendations from both SAGE and IVIR-AC were also reviewed.
- Several experts cautioned against sweeping statements on class effects based on killed versus live vaccines. Within the same class, killed and live vaccines are in fact very different biologicals. Another comment was whether it is at all possible to measure NSE linked to a specific vaccine once this vaccines has been in use for several years. A third remark was that clinical trials ought to transform non-specific effects into specific effects through characterization of cause-specific morbidity/mortality rather than all-cause morbidity/mortality.

Priority research questions

- The WHO Secretariat presented an approach for prioritizing NSE research questions. **Table 1** reports the five possible primary questions related to beneficial effects and the question related to deleterious effects.
- To elicit and provide context to the debate among participants, two possible randomized clinical trials of NSE trials were presented and some general comments presented.

- Overall, the experts agreed on the need to evaluate equally deleterious and beneficial questions, although deleterious effects may have a greater role in terms of policy-making.

Table 1. Possible primary questions for NSE trials

Effect type	Questions
Beneficial	1. 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? 2. Does an immunization schedule with a MCV booster dose at 4 weeks after DTP4 (at approx. 18 months of age) reduce mortality by age 5 years compared to a schedule with concurrent doses? 3. Does an immunization schedule with an additional BCG dose at 6 weeks of age (concurrent with DTP1) reduce mortality by age 1 year compared to a schedule in children with only the currently recommended doses? 4. 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? 5. 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? (Where ≥1 IPV doses have been introduced in the national routine immunization schedule, the number of bOPV doses is reduced accordingly.)
Deleterious	6. Does an immunization schedule with DTP doses increase child mortality by age 5 years compared to a schedule without DTP? Is there a difference in the effect between boys and girls?

- The discussion led to recognize three main sets of possible research questions: questions related to early and late BCG vaccination; questions on the order of vaccines; and questions linked to the general hypothesis that killed vaccine are deleterious and live vaccine beneficial.

Outline of potential trial designs

- Groups worked on defining priority questions and possible designs for the three sets of trials. **Appendix 3** reports the proposed questions and designs.

4. Conclusions and future steps

- Taking action on SAGE and IVIR-AC recommendations, the ad-hoc expert consultation focused on the selection of priority research questions and a preliminary outline of related clinical trials. In particular, the experts outlined 6 clinical trials.
- The experts agreed on the need to present the outlined trials to the IVIR-AC meeting scheduled in June 2016. IVIR-AC members will be asked for advice on whether additional priority research questions should be considered and for comments and suggestions on the outlined trials.
- Based on the feedback of IVIR-AC members, the trial outlines could be developed into generic protocols with sight toward implementing comparable trials at multiple sites with heterogeneous conditions. Eventually, SAGE should review the generic protocols at a future meeting.

Appendix 1. Agenda

AD-HOC CONSULTATION ON EPIDEMIOLOGICAL STUDIES FOR NON-SPECIFIC EFFECTS OF VACCINES

16–17 FEBRUARY 2016

Hotel Royal, 41 Rue de Lausanne, Geneva, Switzerland

Agenda

Background

Researchers have advanced that vaccines can have beneficial or detrimental effects on child mortality other than those on the target disease. These effects are similarly referred to as non-specific (NSE), heterologous or off-target.

After considering systematic reviews on epidemiologic and immunologic studies, WHO Strategic Advisory Group of Experts on Immunization (SAGE) concluded in April 2014 that no change to the recommended immunization schedules was necessary. However, SAGE also recommended to prioritize research questions and to propose the study designs that can answer those questions. SAGE asked to focus research on questions that can inform immunization policy.

In September 2014, this issue was considered by the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC), which is committed to guiding the development of standard protocols and the implementation of high quality prospective studies - including randomized control trials where feasible.

To this end, IVIR-AC proposed the creation of a subgroup and two members volunteered to follow up on these plans. This ad-hoc consultation will provide an opportunity to review and further develop work in this area.

Objectives

1. To reach a consensus on priority questions for NSE clinical trials.
2. To propose trial designs for each of the priority questions and to characterize the strengths and limitations of these designs.
3. To plan the work toward the finalization of possible trial protocols.

Expected outputs

1. Priority questions identified and their related trial designs characterized.
2. Work plan to develop trial protocols outlined.

Day 1

08:30	Registration	
09:00–09:15	Welcome	
Session 1: Background and previous recommendations		***Chair: M. Brisson***
09:15–09:45	2014 systematic review of observational studies and trials on NSE	J. Higgins
09:45–10:00	Recommendations from 2014 SAGE meeting and summary of 2014–2015 IVIR-AC discussions	AM Henao Restrepo
10:00–10:30	Summary and conclusions of a February 2015 meeting on immunologic NSE	A. Pollard
10:30–10:45	Questions for clarification	
10:45–11:15	***Coffee***	
11:15–11:45	Considerations on risk of bias in the reviewed literature	J. Higgins
11:45–12:15	Discussion	
12:15–13:30	***Lunch***	
Session 2: Priority research questions		***Chair: P. Fine***
13:30 – 13:45	What perspective should we use to frame the selection of research questions? Insight from SAGE deliberations	E. Miller
13:45 – 14:00	Possible approaches for prioritizing research questions	A. Vicari
14:00 – 14:30	Examples of priority questions	B. Gessner
14:30–15:15	Discussion on the presented examples and opportunities for the participants to propose other priority questions	Plenary
15:15 – 15:45	***Coffee***	
15:45–18:00	Discussion on research questions and how we should prioritize them Consensus on which questions we should address first	Plenary
18:00	***Cocktail***	

Day 2

08:30-09:00	Summary of the previous day	E. Miller
Session 3: Outline of potential trial designs		***E. Miller***
09:00 – 09:30	Methodological issues in design and analysis of NSE trials	P. Fine
09:30–10:30	Discussion on potential trial designs including considerations of feasibility and ethics	Plenary
10:30 – 10:50	***Coffee***	
	Working groups on selected trial components	
10:50 – 12:30	Each group would ideally discuss the following components for one or more of the identified priority questions • Investigational plan (general study design, objectives, outcome definition and enumeration, site criteria) • Study interventions (interventions, blinding procedures) • Study assessments (visit schedule, withdrawal assessment) • Randomization	Working groups
12:30 – 13:30	***Lunch***	
13:30–14:30	Working groups, continued Preparation of group presentations	
14:30–15:15	Matching priority questions and study designs: Proposals by the working groups	Group presentation
15:15 – 15:45	Discussion	Plenary
15:45–16:00	***Coffee***	
Next steps		***Chair. B. Gessner***
16:00–16:15	Outline of potential next steps	AM H-Restrepo
16:15 - 17:00	Consensus on next steps and timelines	Plenary
17:00	***End of Meeting***	

Appendix 2. List of participants

Ad hoc expert consultation on epidemiological studies for non-specific effects of vaccines

16–17 February 2016

Hotel Royal, Geneva, Switzerland

List of Participants

Invited Experts

Pedro Aide, Researcher, Epidemiology, Manhica Health Research Centre, Manhica, **Mozambique**

John J. Aponte, Associate Research Professor, ISGlobal, Barcelona Institute for Global Health Hospital Clínic - Universitat de Barcelona, Carrer Rosselló 132, E-08036 Barcelona, **Spain**

Marc Brisson, Associate Professor, Department of social and preventive medicine, Faculty of Medicine, Laval University**, Canada**

John Clemens, Executive Director, International Centre for Diarrhoeal Disease Research, Dhaka 1000, **Bangladesh**

Paul Fine, Professor of Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, **United Kingdom of Great Britain & Northern Ireland**

Lourdes Garcia, Deputy Director, Center for Research on Infectious Diseases, National Institute of Health, Cuernavaca, **Mexico**

Brad Gessner, Scientific Director, Association pour la Médicine Préventive (AMP), Paris, **France**

Julian Higgins, Professor of Evidence Synthesis, School of Social and Community Medicine, University of Bristol, Canynge Hall, Whatley Road 39, Bristol BS8 2PS, **United Kingdom of Great Britain & Northern Ireland**

Momodou Jasseh, Unit Demographer, Medical Research Council, The Gambia Unit, P. O. Box 273 Banjul, **The Gambia**

Rama Kandasamy, Paediatric Clinical Research Fellow, Department of Paediatrics, Oxford Vaccine Group, University of Oxford, Churchill Hospital, Oxford, OX3 7LE, **United Kingdom of Great Britain & Northern Ireland**

Elizabeth Miller, Epidemiologist**,** Immunization Hepatitis and Blood Safety Department, Public Health England, 61, Colindale Avenue NW9 5EQ, London, **United Kingdom of Great Britain & Northern Ireland**

Frank O. Odhiambo, KEMRI/CDC HDSS Branch Chief, KEMRI – Centre for Global Health Research, Kisumu, **Kenya**

Andrew J Pollard, Professor of Paediatric Infection and Immunity, Department of Paediatrics, University of Oxford, Children's Hospital, Oxford OX3 9DU, **United Kingdom of Great Britain & Northern Ireland**

Fernando Restrepo, Professor, Department of Public Health, National University of Colombia, **Colombia**

Halvor Sommerfelt, Director, Centre for International Health, University of Bergen, Bergen, **Norway**

Dipika Sur, Secretary General IPHA and Scientific Director, PATH India Office, New Delhi 110067, **India**

Yot Teerawattananon, Founding Leader of Health Intervention and Technology Assessment Program & Senior Researcher Scholar of Thailand's Research Fund, Health Intervention and Technology Assessment Program, Department of Health, Ministry of Public Health, Nonthaburi, 11000 **Thailand**

WHO Secretariat

Ana Maria Henao-Restrepo, Medical Officer**,** Initiative for Vaccine Research, Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland

Raymond Hutubessy, Technical Officer, Initiative for Vaccine Research, Immunization, Vaccines and Biologicals, World Health Organization, Switzerland

Ximena Riveros, Technical Officer, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Andrea Vicari, Scientist, Initiative for Vaccine Research, Immunization, Vaccines and Biologicals, World Health Organization, Switzerland

Appendix 3. Proposed trials and research questions *

Proposed trial	**Primary research question**	**Observations**
Individually randomised controlled trial to assess potential of various schedules to reduce overall morbidity	Compared to the currently recommended schedule (with MV/MR given at 9/12 months of age), i) is an extra dose of measles-containing vaccine at 18 weeks of age beneficial (all-cause mortality/morbidity), ii) what is the effect of pentavalent vaccines and PCV given at 14, 18 and 36 weeks of age, and iii) is an extra dose of IPV at 9/12 months of age deleterious?	This trial could be designed as a multi-arm comparative experiment (MACE). Appendices 4 and 5 detail the schematic diagram of the trial and preliminary estimates of sample sizes.
Randomised placebo-controlled trial to assess effect of BCG given within 24 hours of birth or later (e.g. at first immunization contact) against severe clinical infection and or death	Does BCG given within 24 hours of birth (early BCG) protect young infants against severe clinical infection (all-cause morbidity)?	Either as individually or as cluster randomized trial
"Opportunistic trials" with the aim of testing the potential effect on all-cause mortality and morbidity of the order of live vs. killed vaccine as last vaccine, leveraging introductions of new vaccine introduction		
Cluster-randomized trial to assess the effect on mortality and morbidity of different timing of a third dengue vaccine dose vis-à-vis a booster dT dose	Does a dose of the dengue vaccine affect all-cause morbidity/mortality in adolescents depending on the order with a dT vaccine booster?	Some countries in South-east Asia or Latin America may plan to introduce the live-attenuated TDV-CYD dengue vaccine to children aged ≥9 years with a school-based vaccination. These countries may also recommend a dT vaccine booster at 12 years of age.
Randomized trial to assess the effect on mortality and morbidity of different timing of a fourth malaria vaccine dose vis-à-vis a	Does a dose of the malaria vaccine affect all-cause morbidity/mortality in children depending on the order with a second dose of a measles-containing vaccine dose?	Demonstration projects may be carried out in Sub-Saharan Africa with the killed malaria RTS,S vaccine (4-dose immunization schedule, with a booster dose administered 18 months after the primary 3-dose series). The order of

Proposed trial	Primary research question	Observations
second dose of a measles-containing vaccine		the third RTS,S vaccine dose and a second dose of a measles-containing could be randomly switched with an interval between vaccines of one-month. Demonstration studies will involve heightened surveillance, which can be taken advantage to assess NSE.
Randomized trial of different timing of a third PCV dose vis-à-vis a second dose of a measles-containing vaccine	Does a PCV dose all-cause morbidity/mortality in children depending on the order with a second dose of a measles-containing vaccine dose?	In some countries, the immunization schedule of the killed vaccine PCV is based on 3 doses administered at ages 6 weeks, 10 weeks and 9 months. Endpoints evaluation could be based on an active surveillance for morbidity/mortality with 2 weekly visits.

**** Note:*** The consultation provided limited time for experts to debate on the feasibility of the proposed trials. When full proposals are developed, practical challenges may become apparent and require additional discussion.

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Ad-hoc expert consultation on clinical trials of non-specific effects of vaccines

8–9 September 2016

Summary of discussion and conclusions

Geneva, 5 January 2017

Ad-hoc expert consultation on clinical trials of non-specific effects of vaccines
University of Oxford, Oxford, UK, 8–9 September 2016

Summary of discussion and conclusions

Background

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) made in April 2014 recommendations on research on non-specific effects of vaccines (NSE).(1) Following up on those recommendations, the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) recommended in September 2014 and June 2015 to develop standard protocols for high-quality randomized controlled trials.(2, 3) Such trials are the only means to provide definitive evidence on the existence or absence of NSE.

WHO Initiative for Vaccine Research implemented those recommendations and organized in February 2016 an ad-hoc expert consultation on NSE clinical trials.(4) Experts recognized three main groups of potential trials: administration of Bacillus Calmette-Guérin (BCG) at birth or delayed; order of vaccine administration during infancy; and opportunistic leveraging of new-vaccine introductions to test the general hypothesis that killed vaccines are deleterious and live vaccines are beneficial (specifically with regard to the order in which they are administered). Six different trials were outlined to test those questions (2 trials on BCG [individually and cluster-randomized trials], 1 on vaccine order, and 3 on new-vaccine introductions). IVIR-AC endorsed in June 2016 the process for designing one or more protocols and signalled its continued commitment to advise on the issue.(5)

Objective

The objective of the present consultation was to review and discuss draft protocols of clinical trials for non-specific effects of vaccines. To achieve that, the group of experts who met in February 2016 reconvened and considered the protocols outlined since then. An additional protocol under consideration for support by the Bill and Melinda Gates Foundation was also included.

Summary of the discussion

BCG administration at birth vs. delayed. An ongoing trial in Uganda will estimate the effect of deferring BCG vaccination from birth to age 14 weeks in 2,200 HIV-1 exposed infants.(6) The proposed modified protocol intends to generalize this trial in different settings and include the general infant population, i.e. also babies born to mothers who are not infected with HIV-1. In particular, the study is an individually randomized controlled trial. The use of a placebo should preferably protect randomisation. The primary proposed objective is to measure death in the first 14 weeks of life, but the trial should also allow measuring effects on severe illness, indicated by a hospitalization for non-injury reasons with symptoms and signs indicating sepsis. Infants are followed up to 52 weeks of life to assess secondary outcome measures (i.e., death/severe illness from 48 hours after randomization to 14 weeks of life; death/severe illness during week 14–52 weeks of life; diarrhoea/pneumonia during the last 38 weeks of infancy; growth up to 52 weeks of life; and BCG scar 12 weeks post vaccination). The protocol also proposes a functional immunology assessment. The production of Tumor Necrosis Factor, Interleukin (IL) 1b, IL-6 and Interferon-γ is measured at 1, 14, 15 and 28 weeks of age to evaluate the immune response to mycobacterial and

non-mycobacterial antigens. Selection of newborn infants would have occurred before their birth, when their expecting mothers attended antenatal care between 28 and 40 weeks of gestation. Their HIV-1 status should be recorded, wherever and whenever possible, thus enabling a sub-group analysis stratified on whether babies are HIV-1 exposed or not. Randomization would happen within 24 hours of birth using pre-prepared randomisation lists. Follow up visits at the study clinic are planned for day 7 and at predefined but not too frequent intervals during infancy (to avoid or limit observer effects). With death as the primary outcome, the required sample size ranges from 66,000 to 92,000 infants (assuming a 0.85 risk ratio and an estimated risk of death ranging from 3% to 1%. The sample size required for severe illness is smaller than that for death and follow-up for hospitalization could be restricted to a randomly selected subset of babies nested within the trial measuring mortality effects. To identify ≥15% relative reduction in risk of severe illness (≤0.85 risk ratio), the required sample size ranges from 36,000 to 98,000 infants (assuming a 0.85 risk ratio and an estimated risk of severe illness ranging from 5% to 2%). Although a proper sample size calculation for immunological readouts is pending, it is anticipated that 500 infants would be required to measure biologically relevant effects on cytokine responses to antigen stimulation.

In the discussion, the experts concluded that the proposed trial is explainable and realistic. Points considered included the need to enrol newborn at multiple sites and to respect the randomization by strictly adhering to concealment procedures, especially if placebo cannot be used. To counterbalance risk of tuberculosis, the trial should set up a system for early identification of and treatment of babies who contract tuberculosis and disseminated BCG disease. The experts also discussed whether to stratify the randomization on mothers' HIV-1 status. Such stratification would guarantee that randomization will effectively distribute confounders in each sub-group and thus enable specific analysis based on HIV-1 infection and disseminated BCG disease. A final determination decision on this point was postponed to a further consultation or during interaction with national authorities and ethics committees.

Trials based on administration sequence of infant vaccines. The proposed study is an individually randomised, placebo controlled trial that compares overall childhood morbidity following different administration order of vaccines traditionally given in the first 12 months of life. The considered vaccines are DTP (diphtheria-tetanus-pertussis, either alone or as combined pentavalent vaccine with *Haemophilus influenzae* type b and hepatitis B components [pentavalent vaccine]), oral and inactivated polio vaccines (OPV/IPV), and measles-containing vaccines (MCV).

This trial could have up to five arms (Figure 1), although the proposal is to select the most relevant arms. The first arm is the currently recommended standard immunization schedule (Arm 1, EPI schedule) and is considered the control arm. All other arms follow a "prime-boost principle," in which two doses of already indicated infant vaccines are administered at 6 and 14 weeks of age and a booster dose at 9 months of age ("2+1 schedules"). The difference between the two main experimental arms (Arms 2a and 2b) is in the administration of either the oral polio vaccine (OPV) or the inactivated polio vaccines (IPV). The two additional arms (Arms 3 and 4) include a dose of a measles-containing vaccine or of a DTP-containing vaccine, respectively, at 18 weeks of age.

This trial also aims at testing a widely generalizable schedule that already contemplates a switch from OPV to IPV as well as DTP as a combination vaccine (DTwP-HBV/Hib). With outcome being mortality up to 2 years of age, the primary research question related to Arm 2a/b is whether the 2+1 schedule (with either OPV or IPV) is non-inferior to the current EPI schedule. In particular, Arm 2b

could be seen as the preferable schedule in the polio post-eradication era. The primary intention of Arm 3/4 is to contrast concurrently within the same trial the effects of either a live or killed vaccine being respectively the last administered dose. Secondary questions may relate to effects on morbidity, sex-differential effects, effect modification by malaria or nutritional status, and programmatic and financial implications. From an immunological standpoint, possible questions are whether 2+1 schedules provide better immunogenicity and persistence of antibody and which immunological measures correlate with morbidity outcomes. To estimate sample size, Ghana, Bangladesh, Tanzania and Kenya were taken as example. In those countries, post-neonatal under-2 mortality ranges from 1.1% to 4.6% and post-neonatal under-5 mortality from 0.7% to 2.2%. Mortality clearly decreases over time and this fact will have to be taken into account when estimating sample size.

Figure 1. Study design of a trial on the infant vaccine order.

		RANDOMISATION				
	Birth	**6 weeks**	**10 weeks**	**14 weeks**	**18 weeks**	**9 months**
1. EPI arm	HBV, BCG, (OPV)	DTwP-HBV/Hib +PCV **+OPV** +Rota	DTwP-HBV/Hib +PCV **+OPV** +Rota	DTwP-HBV/Hib +PCV **+IPV +OPV** +Rota		MR
2a: 2+1 OPV arm	HBV, BCG, (OPV)	DTwP-HBV/Hib +PCV **+OPV** +Rota	PLACEBOS	DTwP-HBV/Hib +PCV **+IPV +OPV** +Rota		MR + DTwP-HBV/Hib + PCV **+OPV**
2b: 2+1 IPV arm	HBV, BCG, (OPV)	DTwP-HBV/Hib +PCV **+IPV** +Rota	PLACEBOS	DTwP-HBV/Hib +PCV **+IPV** +Rota + oral placebo		MR + DTwP-HBV/Hib + PCV **+IPV**
Additional optional arms						
3. Early MR arm	HBV, BCG, (OPV)	DTwP-HBV/Hib +PCV **+IPV** +Rota	PLACEBOS	DTwP-HBV/Hib +PCV **+IPV** +Rota + oral placebo	MR	MR + DTwP-HBV/Hib + PCV **+IPV**
4. Penta arm	HBV, BCG, (OPV)	DTwP-HBV/Hib +PCV **+IPV** +Rota	PLACEBOS	DTwP-HBV/Hib +PCV **+IPV** +Rota + oral placebo	DTwP-HBV/Hib	MR + DTwP-HBV/Hib + PCV **+IPV**

With a 0.025 alpha (one-sided) and 90% power, 82,000 children per arm should allow detection of a 0.25% non-inferiority difference margin when mortality in the control arm is 2.5%. Under the same statistical conditions and background mortality, 22,000 children per arm should allow detection of a 0.5% superiority mortality comparison. The latter should detect a 1.70 odds-ratio difference between sexes.

In the discussion, the experts sought clarification on the main intent of the trial, i.e. whether it is to test NSE or a new standard immunization schedule. The driver of any discussion on a 2+1 schedules is the pertussis component, as it is the only vaccine for infants without such an indication. Participants raised concerns that confounding of trial results would occur unless intervention arms were the same as the control arm in all respects except the additional NSE vaccines. Thus, the intervention arms would need to follow a 3+0 schedule in accordance with the EPI control arm. A further point of discussion was about the relevance to test OPV/IPV (Arm 2a vs. 2b). The current global plan is to achieve interruption of wild poliovirus transmission by September 2017 and that would lead to a switch from bivalent OPV to a 2-dose IPV schedule which would be maintained for

an additional 5–10 years at a minimum.(7) Considering that it will take 4–5 years to implement and conclude the proposed trial, the experts questioned the relevance of including an OPV/IPV comparison in this trial on the administration sequence of infant vaccines. Also, a specific trial on OPV/IPV is being planned under the sponsorship of the Bill and Melinda Gates Foundation (see below). In relation to methodology, discussion considered the pros and cons of individual and cluster randomizations, although the majority of experts ended favouring an individual randomization. Participants discussed at length different options of the possible sequence of vaccine administration in the different trial arms.

Opportunistic trials that leverage new vaccine introductions. A general hypothesis is that NSE depend on the length of time in which a killed or live vaccine is last in the administration order. To test such a hypothesis, experts proposed in February 2016 to leverage already planned new vaccine introductions and outlined three such "opportunistic trials." For the present consultation, the outline for a trial on dengue vaccine introduction was further developed for the Philippines, as this country had announced plans to start a nationwide campaign among adolescents aged 10 years. The cluster-randomized trial would assess the effect in the adolescents of the reversed order of the third dengue vaccine dose (the live vaccine) and a booster dT dose (the killed vaccine) with a 1-month interval between vaccines. The setting is elementary schools, where vaccination is also to take place. Classrooms of students are the cluster-level randomization unit and outcomes are all-cause mortality and morbidity (the later includes hospitalization and infection rates). In the Philippines, data on all-cause mortality could be collected from a vital registry using the identification numbers of study participants. All-cause hospitalizations are obtained from hospital databases and via active surveillance from parents of the students using self-directed questionnaires. Finally, infection rates are obtained with surveillance by asking the parents to take note of their children's illness. A follow-up at 3-month interval is proposed.

Compared to infants, the older age of the potential participants implies a markedly lower morbidity/mortality and thus requires a much larger sample size. With an estimated 0.12% background mortality and a 0.005 intraclass correlation coefficient, 1.75 million adolescents in 35,000 clusters would be needed in each arm to detect a 10% mortality difference. If mortality was twice as much, the required sample size is halved (864,000 adolescents in 18,000 clusters). The consultation participants considered these sample sizes prohibitive and thus discarded an opportunist trial based on the introduction of a new vaccine in adolescents. However, experts still suggested evaluating the opportunity to leverage proposed large-scale demonstration projects of the RTS,S/AS02 malaria vaccine—a killed vaccine administered as a 3-dose primary series to infants followed by a booster dose at 18 months of age. Specifically, 18-month-old children could be randomised so that a second dose of a measles-containing vaccine (the live vaccine) is administered one month before or after the RTS,S/AS02 booster.

Trials that compare OPV and IPV. In addition to the three sets of trials proposed at the February 2016's consultation, the group also considered a trial proposal sponsored by the Bill and Melinda Gates Foundation that would compare OPV to IPV. A beneficial NSE of OPV has been postulated since the mid-1950s, essentially on the principle that OPV would reduce the impact of diarrheal disease caused by other enteroviruses.(8) More recently and according to the overarching hypothesis that contrasts live and inactive vaccines, some researchers have postulated that OPV and IPV have beneficial and detrimental NSE, respectively.(9) The issue is relevant because

discontinuation of all OPV use with replacement by IPV is anticipated by 2021 following certification of global polio eradication.(7)

Researchers have focused on assessing a beneficial NSE of OPV. For instance, based on health registers of 137,000 children born in Denmark in 1997–1999, children who had received the prescribed OPV dose at 24 months of age had in the following year a lower rate of hospitalization due to any type of non-polio infection than children whose most recent vaccine was (incidence rate ratio = 0.85; 95% CI: 0.77–0.95).(10) An open-label, uncontrolled trial in Guinea-Bissau that randomized newborn babies at birth to receive either OPV and BCG or BCG alone and assessed mortality up to 12 months of age found a 0.83 hazard ratio in favour of the BCG/OPV combination (95% CI: 0.61–1.13).(11) Overall, the evidence on NSE of OPV and IPV comes mainly from observational studies. When reported, the beneficial NSE of OPV tends to increase with number of administered OPV doses, to be inversely proportional to the time from the last administration of OPV, and to be limited to male infants.

In a country with high infant mortality, it is proposed to randomise newborn babies to two OPV/IPV administration series: 4 doses of bivalent OPV at ≤2 days and 6, 10, and 14 weeks of age and 1 dose of IPV at 14 weeks of age; and 4 doses of IPV at 6, 10, 14 and 36 weeks of age. All infants would receive the remaining recommended vaccines on schedule and are followed up to 12 months of age or to the end of the study period. The proposed primary outcome is all-cause mortality; the sponsor, investigators and relevant regulatory authorities are further discussing potential secondary outcomes. Sample size ought to be sufficient to rule out a 20% difference in infant mortality between study arms using a non-inferiority analysis. In an exploratory calculation for 14 African and 2 Asian countries (infant mortality range: 3.4–9.5%), the samples size ranges from 7,500 to 22,000 children in total for both arms. (Sample size for an assumed 5% difference in mortality is 120,000–350,000 children in total.) The number of deaths drives the sample size. If OPV had a measurable positive or negative effect, an adaptive design could achieve up to a 40% reduction in sample size. For the implementation of this proposed trial, the sponsor has advanced negotiations with potential sites and principal investigators in South Asia and Africa.

Experts asked clarifications on the reliability of the assumed effect size (≥20% difference in mortality incidences), sampling for immunological studies, and site or sex stratification. However, two issues provoked most of the discussion. The first issue was on the policy implications of conclusive or non-conclusive trial results (e.g., would demonstration of a beneficial OPV effect halt the switch to IPV? would inconclusive results modify NSE policies?). The second issue was on whether, if an effect existed, it wouldn't already have manifested in national infant mortality trends in countries which have already switched to IPV or in settings that combine high child mortality, low vaccination coverage, and timely limited pulse vaccination with OPV. On the latter, it was proposed to contrast infant mortality data from England and India to the use of OPV and IPV, respectively.

Conclusions

- By consensus, experts consider that the protocol on BCG vaccination at birth versus delayed should be finalized.
- On the protocol on the order of infant vaccines, experts asked to clarify further how it will address assessment of NSE and of the 2+1 immunization schedule. Also, they concluded that the presented design may be too complex and suggested to simplify it.

- A trial that intended to leverage the introduction of dengue vaccine among South-east Asian adolescents was seen as unfeasible because the sample size would be very large. The principle of using new vaccine introduction is, however, useful and options to use vaccine introduction done in childhood (namely, a malaria vaccine at age 18 months) should be considered.
- Any trial that wants to test NSE of oral and inactivated polio vaccines must consider the potential implications on the decade-long, ongoing eradication initiative. No trial should be initiated on the general assumption that no NSE would be found.

Next steps

- Protocols are finalized in small groups (October–December 2016)
- Protocols are finalized during a face-to-face meeting (January 2017)
- Protocols are submitted to IVIR-AC for review (early February 2017)
- Protocols are published on WHO/IVB webpage for public comments (late February 2017)
- Public comments are used to correct protocols (February-March 2017)
- Finalized protocols are submitted to SAGE for review and possible endorsement (April 2017)

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Appendix 1: Agenda

AD-HOC CONSULTATION ON CLINICAL TRIALS OF NON-SPECIFIC EFFECTS OF VACCINES

8–9 SEPTEMBER 2016

University of Oxford, Andrew Wiles Building

Radcliffe Observatory Quarter, Woodstock Rd, Oxford

Agenda

Background

Researchers have advanced that vaccines can have non-specific effects (NSE), i.e. beneficial or detrimental effects on child mortality and morbidity other than those on the target disease. While concluding that no changes in immunization schedules were necessary, WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommended in April 2014 further research of NSE on all-cause mortality. SAGE thus suggested that the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) be tasked with providing advice on priority research questions and adequate studies.

IVIR-AC considered NSE in September 2014 and in June 2015. The Committee agreed with SAGE that additional observational studies are unlikely to provide conclusive evidence on NSE. IVIR-AC thus committed to guiding the development of standard protocols and implementation of high quality prospective studies, including randomized controlled trials where feasible.

The WHO Secretariat followed up on those recommendations and organized in February 2016 an ad-hoc expert consultation on NSE clinical trials. The specific objectives of this consultation were to reach a consensus on priority questions for NSE clinical trials and to propose trial designs for each of the priority questions. Experts recognized three main groups of possible research questions and outlined six different trial designs to address them.

In June 2016, IVIR-AC reviewed these advances and endorsed the process for designing one or more protocols to assess prospectively beneficial and detrimental NSE effects on mortality. IVIR-AC also considered that IVR needs to complete the preparation of generic protocols for the identified questions and outlined trial designs, as long as each trial has its own rationale. Consequently, this second ad-hoc expert consultation intends to progress further toward the design of robust and feasible NSE trials.

Objectives

1. To agree on the primary and secondary research questions for the clinical trials proposed in February 2016
2. To make final recommendations on the relative trial designs
3. To outline criteria for selection of sites and research groups for these trials

Expected outputs

- Protocol synopses for the proposed clinical trials reviewed and completed
- Preliminary criteria for selection of sites outlined

Day 1 — Thursday, 8 September

Chair: Andrew Pollard

From 08:30	Registration	
	Session 1: Background and previous recommendations	
09:00–09:15	Welcome	WHO/HQ
09:15–09:45	Previous SAGE and IVIR-AC recommendations and outcomes of the February 2016's consultation	A.M. Henao-Restrepo
	Session 2: Review of proposed trial questions and designs	
09:45–10:30	Trials based on administration sequence of infant vaccines	A. Pollard M. Voysey
10:30–10:45	Coffee	
10:45–12:00	Discussion	Plenary
12:00–13:00	Lunch	
13:00–13:45	Trials based on BCG administration at birth or delayed	V. Nankabirwa H. Sommerfelt
13:45–14:45	Discussion	Plenary
14:45–15:30	Opportunistic trials that leverage new vaccine introductions	Y. Teerawattananon
15:30–15:45	Coffee	
15:45–16:30	Discussion	Plenary
16:30–17:00	Considerations on studies for OPV/IPV with all-cause mortality as endpoint	J. Modlin
17:00–18:00	Discussion	Plenary
18:00	Closure of day 1	
18:30	Organizers-hosted dinner at Browns (5-11 Woodstock Rd)	

Day 2 — Friday, 9 September

08:30	Continuation	
08:30–09:00	Summary of the previous day	Fernando de la Hoz
	Session 3: Group work on key trial components	
09:00–10:30	Groups revise key trial synopses components based on plenary discussions	
10:30–11:00	Coffee	
11:00–12:30	Group work, continued	
12:30–13:30	Lunch	
	Session 4: Preliminary criteria for selection of sites	
13:30–13:45	Generic selection criteria	Andrea Vicari
13:45–15:00	Discussion	Plenary
15:00–15:15	Coffee	
	Next steps	
15:15–15:45	Outline of potential next steps	A.M. Henao-Restrepo
15:45–17:00	Consensus on next steps and timelines	Plenary
17:00	Meeting closure	

Appendix 2: List of Participants

Ad hoc expert consultation on epidemiological studies for non-specific effects of vaccines
8-9 September 2016
University of Oxford, Andrew Wiles Building
Radcliffe Observatory Quarter, Woodstock Rd, Oxford, UK

List of Participants

Invited Experts

John Clemens, Executive Director, International Centre for Diarrhoeal Disease Research, Dhaka 1000, **Bangladesh**

Frank Destefano, Director, Immunization Safety Office, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, **United States of America**

Paul Fine, Professor of Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London WC1E 7HT, **United Kingdom of Great Britain & Northern Ireland**

Lourdes Garcia, Deputy Director, Center for Research on Infectious Diseases, National Institute of Health, Cuernavaca, **Mexico**

Brad Gessner, Scientific Director, Association pour la Médicine Préventive (AMP), Paris, **France**

Fernando de la Hoz Restrepo, Universidad Nacional de Colombia, Bogotá, **Colombia**

Momodou Jasseh, Unit Demographer, Medical Research Council, Banjul, **The Gambia**

Ira Longini, Professor of Biostatistics, Department of Biostatistics, College of Public Health and Health Professions, and College of Medicine**,** University of Florida, Gainesville, FL, **United States of America**

Elizabeth Miller, Epidemiologist**,** Immunization Hepatitis and Blood Safety Department, Public Health England, London, **United Kingdom of Great Britain & Northern Ireland**

John Modlin, Deputy Director, Polio, Bill & Melinda Gates Foundation, Seattle, **United States of America**

Victoria Nankabirwa, School of Public Health, College of Health Sciences, Makerere University, Kampala, **Uganda**

Frank O. Odhiambo, KEMRI/CDC HDSS Branch Chief, KEMRI – Centre for Global Health Research, Kisumu, **Kenya**

Richard Peto, Professor, Nuffield Department of Population Health, University of Oxford, Oxford, Professor, Oxford, **United Kingdom of Great Britain & Northern Ireland**

Andrew J. Pollard, Professor of Paediatric Infection and Immunity, Department of Paediatrics,

University of Oxford, Children's Hospital, Oxford, **United Kingdom of Great Britain & Northern Ireland**

Halvor Sommerfelt, Professor, Department of Global Public Health and Primary Care, University of Bergen, Bergen, **Norway**

Yot Teerawattananon, Director, Health Intervention and Technology Assessment Program, Bangkok, **Thailand**

Merryn Voysey, Oxford Vaccine Group, University of Oxford, Oxford, **United Kingdom of Great Britain & Northern Ireland**

WHO Secretariat

Ana Maria Henao-Restrepo, Medical Officer**,** Initiative for Vaccine Research, Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland

Neddy Mafunga, Assistant, Initiative for Vaccine Research, Immunization, Vaccines and Biologicals, World Health Organization, Switzerland

Ximena Riveros, Technical Officer, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Andrea Vicari, Scientist, Initiative for Vaccine Research, Immunization, Vaccines and Biologicals, World Health Organization, Switzerland

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Ad-hoc expert consultation on clinical trials of non-specific effects of vaccines

30–31 January 2017

Summary of discussion and conclusions

Geneva, 27 March 2017

Ad-hoc expert consultation on clinical trials of non-specific effects of vaccines
Conference Centre Les Pensières, Veyrier-du-Lac, France, 30–31 January 2017

Summary of discussion and conclusions

Introduction

In April 2014, WHO Strategic Advisory Group on Immunization (SAGE) considered that non-specific effects of vaccines (NSE) on all-cause mortality warrant further research.(1) SAGE recommended that the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) be tasked with providing advice on which priority research questions need to be addressed to inform policy decisions, and what kinds of studies and study designs would provide answers to these questions. SAGE outlined some considerations for IVIR-AC to include in their deliberations—namely, the assessment of the use of high quality randomized controlled trials where feasible (noting the substantial ethical and methodological challenges involved), with sufficient power to explore sex differences, and a priori defined and standardized immunological endpoints designed to answer particular NSE questions.

The WHO Secretariat convened in February and September 2016 two consultations of the same group of experts to review NSE hypotheses that researchers have advanced, research questions that are related to these hypotheses, and trial designs that could effectively address such questions. Reports for each consultation are available.(2, 3)

IVIR-AC reviewed the ongoing work in June 2016.(4) The Committee acknowledged the progress made towards the refinement of priority research questions and trial designs resulting from the ad-hoc expert consultation. IVIR-AC endorsed the designing of one or more protocols to assess prospectively any non-specific effects of immunization on mortality.

At the present consultation, the same group of experts who met in February and September 2016 was presented with the advances on three trial designs developed during the deliberations at the two previous consultations and subsequent work.

Objectives and organization

The three objectives were:

- to review and propose suggestions on the trial protocols outlined and discussed in September 2016
- to discuss criteria for selection of sites for these trials, and
- to revisit the initial set of important research questions, and to consider if other questions need to be considered further.

The consultation was organized in three sessions: progress of ongoing work; group work on key trial components; and next steps (see Agenda, **Appendix 1**). Twenty-one experts from four Regions contributed (see List of participants, **Appendix 2**).

Summary of the presentation and related discussion

Overview of NSE hypotheses

An initial presentation reviewed some of the leading NSE hypotheses being proposed and how they have evolved over the last three decades. Additional peer-reviewed articles were published in 2016, notably two systematic reviews on epidemiology and immunology of NSE commissioned by WHO for the April 2014's SAGE deliberations.(5, 6) Taking into account that most identified studies were observational and thus prone to bias, the epidemiological review suggests a reduction in all-cause mortality linked to receipt of Bacillus Calmette-Guérin (BCG) and measles-containing vaccines (MCV) in excess of that caused by the diseases they target.(5) The studies identified for the immunological review had heterogeneous designs, could not be conventionally meta-analysed, and overall provided a low level of evidence quality.(6) Some studies related in particular to BCG and measles vaccine showed effects suggestive of immunological NSE, but the available evidence does not permit robust conclusions as to the nature, magnitude, or timing of such effects. The clinical interpretation of any differences observed is unclear. Also, NSE can possibly differ among countries because of heterogeneities among populations and as a function of the pattern of infections experienced by children in different circumstances.

A point of discussion was how, as long as they were definable, *a priori* immunological hypotheses can direct the design of the protocols. In fact, multiple plausible hypotheses exist and the suitable approach is to collect and store biological specimens from as many participants as possible for potential later testing if a clinical outcome occurred.

Another discussion point was about focusing not only on all-cause mortality but also about exploring cause-specific mortality. It was highlighted that demographic and health surveys rely on verbal autopsies and thus reliable data on specific death causes is seldom available.

The overall conclusion was that proposed trials don't need to try to address all the various hypotheses advanced about potential NSE, but rather that they would address those hypotheses that have immediate relevance from the public health perspective.

Age and order of administration of childhood vaccines

An ongoing systematic review and meta-analysis of up to 72 national immunization surveys, originally carried out for the SAGE meeting of April 2014, tracks at what ages and in what order children have received scheduled vaccines doses. The surveys provide estimates of the ages at which children receive BCG, third-dose diphtheria-tetanus-pertussis vaccine (DTP, alone or in combination with hepatitis B virus and *Haemophilus influenzae* type b [pentavalent vaccine]) and MCV, the percentage of children given a first DTP dose before or simultaneously with BCG, and the percentage of children given a last DTP dose with or after MCV.

In different subregions, BCG coverage ranged between 17–85% by the first week of life and 89–98% by age 14 weeks. In the surveys showing the greatest frequency of deviation from best practices (10^{th} percentile of all considered surveys), 5–7% of children received the first DTP dose before BCG, 20–21% received the BCG and the first DTP dose on the same day, and 0–8% received the third DTP dose and a measles-containing vaccine on the same day.

Overall, the analysis suggests substantial variation between countries. Adherence to vaccine order and timeliness of vaccine administration are similar in boys and girls, are worse in rural populations

compared to urban populations, and improve gradually from the lowest to the highest wealth quintiles. However, trends in the "out-of-order" administration of childhood vaccines are declining over time.

Trial proposal A — BCG administration at birth or deferred until 14 weeks of age

This proposed trial was described in details in the report of the September 2016's consultation. In short, the individually randomized trial would assign newborns to BCG administration within 24 hours of birth or at 14 weeks of age. To protect randomisation, the trial should preferably be placebo-controlled. Primary objectives are to measure mortality and severe morbidity in the first 14 weeks of life. Enrolment would occur at birth in institutions, although the pool of potential participants would have been identified previously when expecting mothers attend antenatal care visits. With mortality in the first 14 weeks of life as the primary outcome, the indicative sample size of the trial is 49,000 infants (when 90% power, a 0.80 risk ratio between two arms, and 2% mortality in the delayed BCG arm are assumed).

In the group work, the study rationale was strengthened by adding how demonstration of NSE could enhance efforts for greater BCG coverage at birth and would make consideration of these effects necessary in the clinical development of new tuberculosis vaccines. In addition, the inclusion of pre-term babies was addressed as well as other details.

The inclusion of a third arm with two BCG doses (at birth and at 14 weeks of life) was a main topic of discussion. Although it was recognized that a three-arm study could be adapted into a 2x2 factorial design, additional challenges of scale and complexity would remain compared to the two-arm trial. Also, it was questioned what would be expected with the two-dose schedule and whether such a schedule would be a policy option. Evidence suggests that repeated BCG administration may cause bigger ulcers at site of administration. Whether an adequate placebo will be available may ultimately determine the inclusion of the third arm.

Experts strongly suggested including mortality and severe morbidity up to age 12 months as co-primary endpoints, together with measurements in the first 14 weeks of life. Sample size will be re-calculated accordingly and experts advised to consider a low-end mortality (i.e., 1%) and a risk ratio chosen for its policy relevance. To increase the science and policy focus, a long-term follow-up beyond infancy for all-cause mortality among all participants and for cause-specific mortality among a subset of participants was also proposed.

The experts also noted that enrolment would require a well-developed and robust system of maternal and child health surveillance. Piloting the study may be beneficial for both characterizing the pool of eligible babies as well as understanding how to enrol them. Another discussion topic was whether institution enrolment would preclude generalizability to babies born at home—given that mortality may be different among babies born in the two different settings. Some experts thought that, as BCG is a biological intervention, an effect measure modification on birth place is unlikely, but others thought that effects may well change depending on background situation. Inclusion of babies born at home may significantly increase the trial costs.

The lowering of birth-weight exclusion cut-off (set at <2,000 grams) was suggested, as the factor seems important and not always considered. Still, a birth weight threshold is considered important as it is a proxy for prematurity and thus increased risk for some death causes (e.g., sepsis). Experts also suggested deleting a reference to scarring (originally included to assess adequacy of

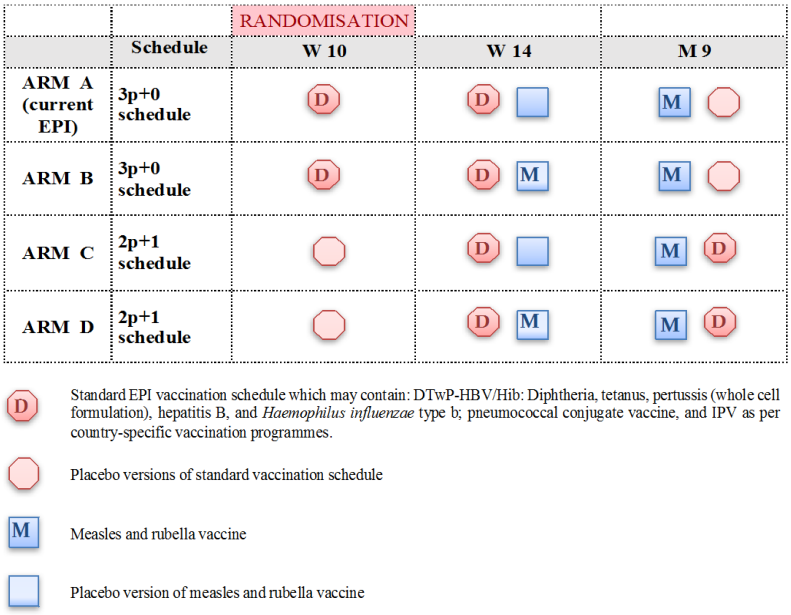
intervention) as mortality and severe morbidity are the key endpoints of the trial. Concomitant administration of other vaccines should be carefully recorded and, if feasible and affordable, stool specimens should be collected from a subset of participants for testing of enteric pathogens (e.g., rotavirus) and description of microbiota.

Trial proposals B/C — Order of administration of childhood vaccines

In September 2016, an individually randomized, controlled trial with up to five arms was presented. That design aimed at comparing a 2+1 schedule, the administration of an additional MCV dose at age 18 weeks, and the administration of either oral or inactivated polio vaccines (OPV and IPV) to a currently recommended immunization schedule (in brief, a 3+0 schedule with MCV at age 9 months). The trial is described in detail in the report of that consultation. Experts eventually questioned the relevance of including an OPV/IPV comparison, also noting that the multipronged design would make the trial conceptually unclear and logistically unfeasible.

Consequently, two separate trials were proposed at the current consultation. The first study is 2x2 factorial, randomised, placebo-controlled trial that focuses on testing the potential NSE of an additional MCV dose at 12–16 weeks of age. The factorial design results from the crossing of the 3+0 and 2+1 infant immunization schedule (pentavalent vaccine, pneumococcal conjugate vaccine, IPV) with the administration of an additional MCV dose at 14 weeks of age (Figure 1). The second study is a 3-arm, randomised, placebo-controlled trial to assess the effect of MCV given at 9 months of age before, simultaneously, or after a pentavalent vaccine dose (Figure 2).

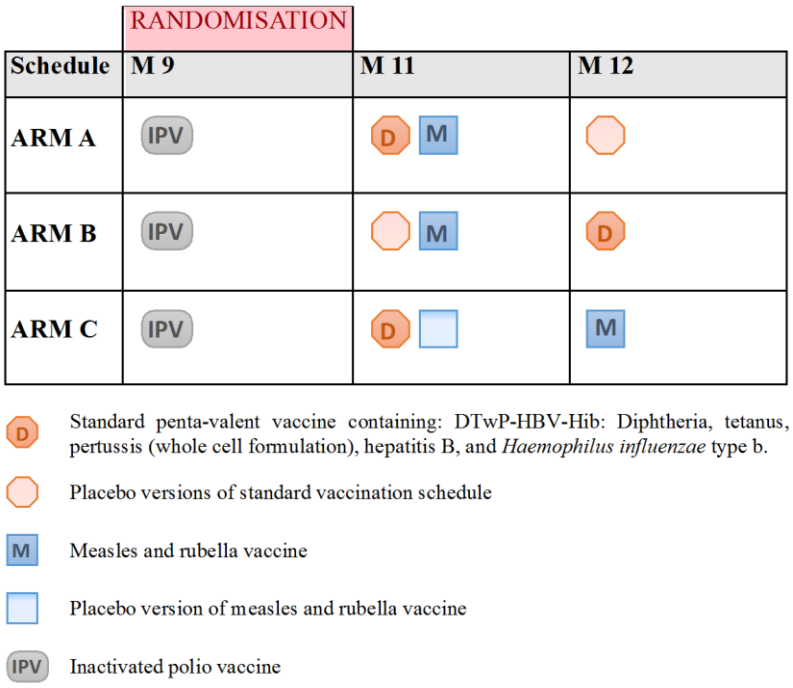
Figure 1. Design of 2x2 factorial trial with additional MCV dose at 12–16 weeks of age.



For the 2x2 factorial trial, discussion during the plenary and in groups left the design unchanged and focused on reviewing primary and secondary objectives as well as other elements. *Primary objectives* should be: impact of early MCV administered jointly with DTP at age 14 weeks on mortality and severe morbidity up to age 2 years (arms B+D vs. A+C); impact of moving DTP from age 10 weeks to 9 months (from 3+0 to 2+1 schedule) on mortality up to age 2 years (arms A+B vs. C+D). *Secondary objectives* should be: impact of 2+1 schedule vs. 3+0 on pertussis disease (arms A+B vs.

C+D); impact of early MV at 14wks on measles (arms B+D vs. A+C). For the assessment of the impact of early MCV+DTP at 14 weeks of age, the primary outcome is non-injury related all-cause mortality between 14 weeks and 2 years of age. For the comparison of 2+1 vs. 3+0 schedules, the primary outcome is unchanged but its assessment timeframe is between 10 weeks and 2 years of age. Secondary outcomes include cause-specific mortality, all-cause morbidity (defined as health seeking behaviour such as hospitalisation, ambulatory consultation, or access to other professional health care services), all-cause and cause-specific hospitalizations, and—in a subset of participants—mortality/morbidity to 5 years of age. Immunological objectives and outcomes were also outlined. With mortality as the primary outcome, the indicative sample size of the trial is 110,000 infants (when 90% power, a 0.80 risk ratio between two arms, and 2% mortality are assumed [same sample size assumptions as for the BCG trial]). Additional recruitment due to expected losses to follow-up would need to be factored into these estimates.

Figure 2. Design of a 3-arm trial with MCV dose before, simultaneously or after a pentavalent vaccine dose at 9 months of age.



Other elements of the 2x2 factorial trial were also debated. An implicit assumption of the 2x2 factorial design is the absence of interaction between the two factors (3+0/2+1; MCV at 14 weeks). Testing during the trial analysis whether such an interaction has occurred would require a greater sample size. Considering the large expected sample size, block randomization is not necessary. A potential programmatic advantage of the 2+1 schedule that merits great emphasis is the savings associated with the cancellation of the visit at 10 weeks of age, in addition to an expected longer duration of protection. Overall, a majority of experts considered that the design, objectives and outcomes that eventually resulted after the 2-day discussion represent an optimal trade-off to test the two effects, which are very important in informing policy-making.

The second trial was more thoroughly changed during the discussions. In particular, Figure 3 shows that the design was greatly simplified compared to the design proposed originally (Figure 2).

However, experts were unable to agree on how to formulate objectives. Also, as all-cause mortality would be measured over the period of 11–24 months of age, it was noted that an effect could only be observed in the highest mortality settings. Overall, this trial was perceived of being of lower priority and only rational if policy-makers felt strongly about testing whether moving the third pentavalent vaccine dose to age 9 months would blunt the potential beneficial NSE of the MCV.

Figure 3. Revised design of a 3-arm trial testing order of MCV and pentavalent vaccine at 9 months of age.

	RANDOMISATION	
Schedule	**M 9**	**M 10**
ARM 1	(p)	(p) **M**
ARM 2	(p)	**D** **M**
ARM 3	**D**	(p) **M**

M, measles containing vaccine; D, DTP-containing vaccines; (p) placebo

Trial proposal D — Use of bOPV or IPV

An update was provided on a potential randomized controlled trial that would compare in two arms immunization with bivalent oral polio vaccine (bOPV) and inactivated polio vaccine administered in a fractional dose with an intradermal injection (fIPV). The first arm contemplates 4 OPV doses (at ages 0, 6, 10 and 14 weeks) plus a fIPV dose (at age 14 weeks), while the second arm 4 fIPV doses (at ages 6, 10, 14 and 36 weeks). A 3-dose fIPV schedule is also under discussion as an alternative for the second arm.

Echoing the discussion held at the September 2016's consultation, experts questioned the evidence base for postulating detrimental NSE linked to the replacement of OPV with IPV (that was agreed internationally under the Global Polio Eradication Initiative [GPEI]) and thus doubted the rationale to carry out such a trial. Moreover, they pointed out that several issues limit the conception and design of the suggested trial. An IPV dose at age 14 weeks is needed in the OPV arm to manage an exposure risk to vaccine-derived poliovirus 2. However, the inclusion of the inactivated vaccine might alter the putative NSE of the live OPV. Also, the use of a fractional IPV dose given by intradermal injection is neither the route nor dose employed in previous NSE studies. The evidence on fIPV efficacy is limited. If the trial resulted in mortality differences between the arms, it would be unclear whether the results are due to beneficial and/or detrimental NSE of OPV, IPV, or both.

An overarching question is what policy implications finding a significant effect would have. Given the issues with results interpretation and experimental power, the experts highlighted that the proposed trial does not offer an obvious path from trial results to immunization policy changes. It may thus lead to more complications rather than a resolution in terms of absence or existence of NSE. The group debated on the opportunity and extent to which calls for halting GPEI plans because of hypothetical NSEs, such as a letter published in *Lancet* in March 2016 (7), should be challenged.

Overall, the group recommended that the issue of NSE associated with an OPV/IPV switch (and generally any change in immunization schedules) is better addressed by monitoring trends in child mortality at national level. Such monitoring could already be done in some countries based on historical data (e.g. United Kingdom, USA, Israel), while surveillance systems and the analyses would need to be strengthened for other countries. Statistical criteria need to be defined, also to deal with the potential for false-positive results.

Trial proposal E — Opportunist trial leveraging new vaccine introductions

In the previous consultations, it was advanced that the introduction of malaria vaccine may be leveraged to test NSE opportunistically by randomizing at age 18 months the fourth RTS,S/AS01 dose and a measles-containing vaccine given a month apart.

SAGE and the Malaria Policy Advisory Committee (MPAC) jointly reviewed in October 2015 evidence on the candidate malaria vaccine RTS,S/AS01.(8) They recommended staged pilot implementations with the 4-dose schedule in 3–5 distinct epidemiological settings in Sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings. The related WHO position paper also highlighted that, among the questions addressed in pilot implementations, the extent to which RTS,S/AS01 vaccination impacts all-cause mortality (including gender-specific mortality) should be included.(9)

At the present consultation, sex-specific efficacy and safety data from the Phase 3 RTS,S/AS01 vaccine trial carried out in 2007–2013 among 15,500 children of 7 African countries were presented.(10) The same data had been prepared for the SAGE/MPAC deliberations of October 2015. Against a backdrop of very low mortality (generally related to the high standard of care implemented in the trial), these data show in particular an excess of deaths from all causes combined among vaccinated girls compared to unvaccinated girls, but not in vaccinated boys compared to unvaccinated boys.(9) The WHO position paper concludes that these findings could be due to chance.

In their discussion, the experts reached three conclusions. First, they noted that other advisory groups have already reviewed the presented data in depth and their evaluation has been published. Second, the pilot implementation can only assess potential NSE if the study was randomized (e.g., random designation of clusters slated for vaccination). Finally, the excess mortality observed in the RTS,S/AS01 trial is of concern to the scientific community also because of the impact on the development of future malaria vaccines. A real risk exists that—if the pilot implementation is not properly designed and powered—it may result in results suggestive of NSE only by chance. This circumstance may hamper the development of malaria vaccines on the long term.

Criteria for site selection

Generic site selection criteria were presented. These criteria cover aspects related to staff and facilities, study population and epidemiology, ethics and local regulatory requirements, management

of investigational product, cold chain and laboratory facilities/issues, communications, and transportation. These criteria should preferably be documented based on the realization of trials similar to the one envisioned.

Considering that the proposed trials will likely require a sample size ranging into the tens of thousands of children, an operational consideration is how many sites need to be included to aggregate a cohort of children large enough to conclude a trial within a reasonable timeframe. To illustrate this aspect, data from a few INDEPTH Network sites with ongoing demographic and health surveys in Africa and South-East Asia were considered (Table 1). With those five sites, approximately 50,000 children could be enrolled over two years. As many as 15–20 similar sites would thus be needed to carry out a trial.

Table 1. Characteristics of some INDEPTH Network sites with ongoing demographic and health surveys in Africa and South-East Asia.

Location	Total population	Crude birth rate per 1,000 population	Births per year	Neonatal deaths per year	Eligible for screening at age 6 weeks (over 2 yrs)	Cumulative total (over 2 yrs)
Navrongo, Ghana	151,955	25.4	3,860	48	7,624	7,624
Matlab, Bangladesh	225,000	21.5	4,838	105	9,465	17,089
Dodowa, Ghana	111,976	23.5	2,631	23	5,217	22,305
Ifakara, Tanzania	161,000	33.5	5,394	180	10,428	32,733
Kilifi, Kenya	261,919	34.7	9,089	155	17,866	50,599

Conclusions and next steps

Among the proposals discussed during the three consultations held between February 2016 and January 2017, the ad-hoc expert group agreed that, in spite of the discussed challenges, the trial on the BCG administration at birth or delayed and the 2x2 factorial trial of an additional MCV at age 14 weeks and the 3+0/2+1 schedules offer the greatest likelihood to generate evidence valuable to the policy debate on NSE and generally to inform immunization policies. The group agreed that those two protocols could be presented to both IVIR-AC and SAGE for further guidance.

The proposed next steps are:

- Protocols are submitted to IVIR-AC for review (1–2 February 2017)
- Protocols are submitted for peer-review of an independent group of methodological experts (March 2017)
- Protocols are submitted to SAGE for information (25–27 April 2017)
- Protocols are published on WHO/IVB webpage for public comments (May 2017)
- Public comments are used to correct protocols (June 2017)

References

1. Meeting of the Strategic Advisory Group of Experts on immunization, April 2014 -- conclusions and recommendations. Wkly Epidemiol Rec. 2014;89(21):221-36.
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Appendix 1: Agenda

AD-HOC EXPERT CONSULTATION ON CLINICAL TRIALS OF NON-SPECIFIC EFFECTS OF VACCINES

30–31 JANUARY 2017

Conference Centre Les Pensières, Veyrier-du-Lac, France

Agenda

Background

Researchers have advanced that vaccines can have non-specific effects (NSE), i.e. beneficial or detrimental effects on child mortality and morbidity other than those on the target disease. While concluding that no changes in immunization schedules were then necessary, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommended in April 2014 further research of NSE on all-cause mortality. SAGE thus suggested that the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC) be tasked with providing advice on priority research questions and adequate studies.

IVIR-AC considered NSE in September 2014 and in June 2015. The Committee reiterated SAGE recommendation that clinical trials should be designed since additional observational studies are unlikely to provide conclusive evidence on NSE. IVIR-AC thus committed to guiding the development of standard protocols and implementation of high quality prospective studies, including randomized controlled trials where feasible.

The WHO Secretariat followed up on those recommendations and organized in February and September 2016 two ad-hoc expert consultations on NSE clinical trials. The same group of experts contributed to both consultations. During the first consultation, experts reached a consensus on priority questions for NSE clinical trials and outlined trial designs for each of the priority questions. During the second consultation, experts reviewed synopses of the proposed trials and made suggestions for the development of complete protocols.

In June 2016, IVIR-AC reviewed the advances and endorsed the process for designing one or more protocols and concluded that IVR needs to complete the preparation of generic protocols. Consequently, this third ad-hoc expert consultation intends to complete the revision of the proposed trial protocols.

Objectives

1. To review and propose suggestions on the trial protocols outlined and discussed in September 2016
2. To discuss criteria for selection of sites for these trials
3. To revisit the initial set of important research questions and to consider if other questions need to be considered further

Day 1 — Monday, 30 January

Chair: Andrew Pollard

From 08:45	Registration	
	Session 1: Progress of ongoing work	
09:00–09:15	Welcome	WHO/HQ
09:15–09:30	Summary of consultations held in February and September 2016	A.M. Henao-Restrepo
09:30–09:45	Overview of NSE hypotheses proposed to date	P. Fine
09:45–10:30	Discussion	Plenary
10:30–11:00	Coffee	
11:00–11:15	Update on BMGF-supported randomized trial on bOPV/IPV schedules	C. Karp
11:15–11:45	Discussion	Plenary
11:45–12:05	Randomized controlled trials of early versus late BCG vaccination	V. Nankabirwa H. Sommerfelt
12:05–12:30	Questions for clarification	Plenary
12:30–13:45	Lunch	
13:45–14:00	When do children receive their scheduled doses?	C. Sanderson
14:00–14:20	An optimal schedule for the post-polio eradication era: multicentre international randomised placebo-controlled trials to assess the effect of different vaccination schedules on childhood mortality and morbidity: • Option 1 – MR and DTP order • Option 2 – Extra MR dose in factorial design	R. Kandasamy M. Voysey A. Pollard
14:20–14:50	Questions for clarification	Plenary
	Session 2: Group work on key trial components	
14:50–15:05	Organization of group work Group work — Experts are split into three groups; each group reviews and edits all sections of one of the three proposed trial protocols • Are the objectives and primary questions adequately formulated? • Are the proposed methods and sample size sufficiently robust to reach a conclusion on NSE? • Are the proposed trials feasible?	
15:05–15:30	Group work	
15:30–15:45	Coffee	
15:45–18:00	Group work, cont.	
18:00	Closure of day 1	

Day 2 — Tuesday, 31 January

09:00	Continuation	
09:00–09:20	Summary of the previous day	E. Miller
09:20–10:20	Group work presentations and plenary discussion (30' each group, included plenary discussion)	
10:20–10:40	Coffee	
10:40–11:10	Group work presentation, cont.	
	Session 3: Next steps	
11:10–11:30	Review of evidence from malaria vaccine trials	J. Aponte
11:30–12:15	Discussion	Plenary
12:15–13:30	Lunch	
13:30–13:45	Generic criteria for site selection	A. Vicari
13:45–14:45	Discussion	Plenary
14:45–15:45	Potential policy questions for future consideration	Plenary discussion moderated by R. Breiman
15:45–16:30	Concluding remarks	A.M. Henao-Restrepo
16:30	Meeting closure	

Appendix 2: List of Participants

Ad hoc expert consultation on epidemiological studies for non-specific effects of vaccines
30–31 January 2017
Conference Centre Les Pensières, Veyrier-du-Lac, France
List of Participants

Invited Experts

Pedro Aide, Researcher, Epidemiology, Manhiça Health Research Centre, Manhiça, **Mozambique**

Robert Breiman, Professor, Emory Global Health Institute, Emory University, Atlanta, **United States of America** (IVIR-AC Chair)

Marc Brisson, Associate Professor, Department of social and preventive medicine, Faculty of Medicine, Laval University**, Canada** (IVIR-AC Member)

John Clemens, Executive Director, International Centre for Diarrhoeal Disease Research, Dhaka 1000, **Bangladesh**

Frank Destefano, Director, Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, **United States of America**

Paul Fine, Professor of Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, **United Kingdom of Great Britain & Northern Ireland**

Lourdes Garcia, Deputy Director, Center for Research on Infectious Diseases, National Institute of Health, Cuernavaca, **Mexico**

Leander Grode, Chief Scientific Officer, Vakzine Project Management GmbH, Hannover, **Germany**

Momodou Jasseh, Unit Demographer, Medical Research Council, The Gambia Unit, P. O. Box 273

Banjul, **The Gambia**

Rama Kandasamy, Paediatric Clinical Research Fellow, Department of Paediatrics, Oxford Vaccine Group, University of Oxford, Churchill Hospital, Oxford, **United Kingdom of Great Britain & Northern Ireland**

Chris Karp, Deputy Director, Discovery & Translational Sciences, Bill & Melinda Gates Foundation, Seattle, **United States of America**

Ira Longini, Professor, University of Florida, Gainesville, FL, **United States of America**

Elizabeth Miller, Epidemiologist**,** Immunization Hepatitis and Blood Safety Department, Public Health England, London, **United Kingdom of Great Britain & Northern Ireland**

Victoria Nankabirwa, Professor, Department of Epidemiology and Biostatics, School of Public Health, College of Health Sciences, Makerere University, Kampala, **Uganda**

Frank O. Odhiambo, Research Coordinator, KEMRI/CDC HDSS Branch Chief, KEMRI – Centre for Global Health Research, Kisumu, **Kenya**

Walter Orenstein, Professor and Associate Director, Emory Vaccine Center, Emory University School of Medicine, Atlanta, **United States of America**

Richard Peto, Professor, Nuffield Department of population Health, Medical Sciences Divisions, University of Oxford, **United Kingdom of Great Britain & Northern Ireland**

Andrew J. Pollard, Professor of Paediatric Infection and Immunity, Department of Paediatrics, University of Oxford, Children's Hospital, Oxford OX3 9DU, **United Kingdom of Great Britain & Northern Ireland**

Colin Sanderson, Professor, Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, **United Kingdom of Great Britain & Northern Ireland**

Halvor Sommerfelt, Department of Global Public Health and Primary Care, University of Bergen, Bergen, **Norway**

Merryn Voysey, Senior Statistician, Oxford Vaccine Group, University of Oxford, Oxford, **United Kingdom of Great Britain & Northern Ireland**

WHO Secretariat

John Aponte, Consultant, Global Malaria Programme, World Health Organization, Geneva, Swizterland

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Neddy Mafunga, Assistant, Initiative for Vaccine Research, Immunization, Vaccines and Biologicals, World Health Organization, Switzerland

Hiromasa Okayasu, Team Leader, Research, Policy & Product Development, Polio Eradication, WHO, Geneva, Switzerland

Ximena Riveros, Technical Officer, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Andrea Vicari, Scientist, Initiative for Vaccine Research, Immunization, Vaccines and Biologicals, World Health Organization, Switzerland