Agenda

#	Time (BST)		Subject	Responsible
1	2:00	2:05	Welcome [5 min]	Melanie Saville, CEPI
2	2:05	2:10	Background [5 min]	Peter Dull, BMGF
3	2:10	2:20	Fractional dosing – A perspective on vaccine supply [10 min]	Michael Kremer, Becker Friedman Institute, University of Chicago
4	2:20	2:30	Learnings from the UK trial on full / fractional booster doses: CoV-BOOST [10 min]	Saul Faust, Southampton NIHR Wellcome Trust Clinical Research Facility
5	2:30	2:40	Outline of the CEPI/COVAX platform trial concept [10 min]	Robbert van der Most, CEPI
6	2:40	2:50	Additional fractional versus full dose in primed populations: Core trial elements [10 min]	Amol Chaudhari, CEPI
7	2:50	3:00	Governance / Coordination / Support strategy [10 min]	Kerim Chitour, PATH
8	3:00	3:05	CEPI's Central Lab initiative [5 min]	Valentina Bernasconi, CEPI
9	3:05	3:10	Support options via CEPI/SPEAC incl. DSMB [5 min]	Robert Chen, BC/SPEAC
10	3:10	3:50	Discussion [40 min]	ALL
11	3:50	3:55	Timelines / next steps / EOIs [5 min]	Jakob Cramer, CEPI
12	3:55	4:00	Wrap-up / Closure [5 min]	Amol Chaudhari, Robbert van der Most, Jakob Cramer / CEPI

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COVID-19 Vaccines: Options for Dose-Sparing

A Platform Trial / Programme Approach

10th September 2021

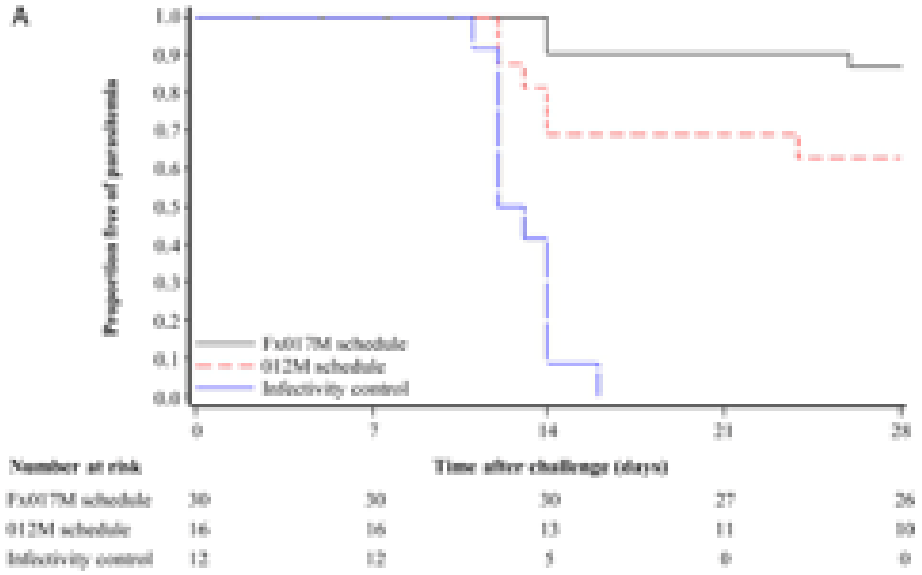
A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations

Reasons to believe

Examples of fractional dose vaccination indicate feasibility with different vaccine platforms:

- Inactivated: 1/5 dose id IPV (SCRs)
- Live-attenuated: 1/5 dose YFV-17D (SCRs)
- Non-adjuvanted protein: ¼ dose HBs Ag (antibody titers)
- Adjuvanted protein: 1/5 dose RTS,S malaria vaccine (protection against challenge)
- mRNA: dose ranging studies

Reduced reactogenicity expected
Positive benefit/risk anticipated
RCT data needed



A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations

→ Platform approach: to define core elements and design features

→ Individual trials addressing targeted needs / gaps with the following **scope**:

- **Improve immune response** (and vaccine effectiveness) against SARS-CoV-infection / transmission and COVID-19 illness **in the context of increasing numbers of VOCs in selected / special populations**
- **Positive effect on vaccine supply:** accelerate vaccination coverage (without compromising VE / public health impact)
- **Improve reactogenicity (and safety?) profile**

A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations

Aim: Data are primarily expected to support pragmatic recommendation by e.g. NITAGs / WHO SAGE (but may also serve to support regulatory approval of additional label claims)

- Focus on needs in LMICs
- It is not the intention to duplicate other programmes / trials generating similar evidence (e.g. on the general need for a booster dose in fully vaccinated healthy populations)

Terminology

- Priming:
  - 1 or 2 doses [given 3 weeks – 3 months apart (= dose 1 and 2)]

- Additional dose:
  - 1 dose given months (>6 months) or years after priming (= depending on scenarios above: dose 2, 3 or 4 ff.)
  - 2+1 scheme requiring a 3rd dose to complete primary immunization
    - for vaccines with a rapid initial decline in Ab-levels / with insufficient vaccine effectiveness post 2 doses
    - in special populations (e.g. elderly, immunocompromised)

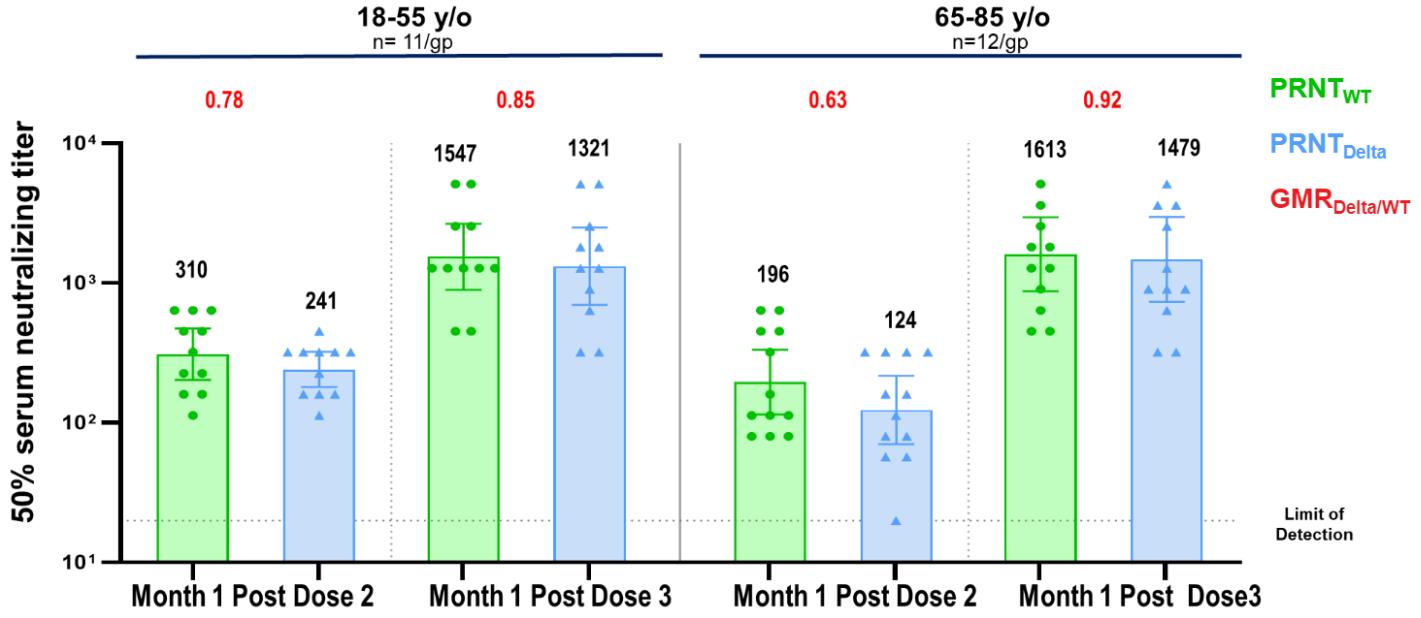
- Booster dose:
  - To maintain / broaden immune response over time in the general healthy population

Additional dosing: Existing Evidence

- Recent data indicate good immune memory and boostability of **WVI vaccines** (Sinopharm, Sinovac) after a third dose 6 months after primary immunisation
- On Aug 5th, **Moderna** presented data on reactogenicity and (cross-reactive) immunogenicity of a reduced dose (50µg) formulation
    - monovalent original (D614G) strain [mRNA-1273]
    - Monovalent Beta (B.1.351) VOC [mRNA-1273-351]
    - Bivalent original / Beta variant (25µg each) [mRNA-1273-211]
- **Pfizer / BNT:** early stage clinical data indicate room for antigen-saving considerations
- **Pfizer / BNT** recently released data on 6 months booster showing boostability of immune responses => nAbs
- Included cross-reactive responses against new VOCs (including Delta)

BNT162b2 3rd dose immune responses

COVID-19 Vaccine: 3rd Dose Strongly Boosts Neutralizing Titers Against Delta Strain[1,2]



- Post dose 3 titers vs. the Delta variant are **>5-fold post dose 2 titers** in 18-55 y/o & **>11-fold post dose 2 titers** in 65-85 y/o
- Estimated potential for up to **100-fold increase in Delta neutralization post-dose three** compared to **pre-dose three**

Platform Trial Concept: Prospective randomised trial(s) to assess the immunogenicity of fractional *versus* full dose given as a single additional vaccination in previously primed subjects

Additional blood draw for long term immuno?

Study Arm	Study Population	Visit #1	Visit #2	… F/U
	'Primed' populations, as defined by individual project with hx of …	Day 1	Day 29 (week 4)	1, 2 years… ?
A	• One dose (single dose regimen / incomplete 2-dose regimen) or • 2 doses (any vaccine, different intervals) • Evidence of nat. infection	1		
B		½ b)		
(C) a)		1		

a) Should a different vaccine be tested for full versus fractional dose for 'booster' it is recommended to include one comparator arm assessing a full dose of the vaccine used for primary vaccination
b) Fractional dose (not necessarily half dose)

'Rescue strategy' → Offer full vaccination with locally registered / available vaccine to those with insufficient immune response

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Platform Trial Approach: Core and Flexible Elements

Defined trial populations, e.g.

- Immunocompromised / SOT
- Immunocompromised / HIV
- Elderly / immunosenescense
- Primed via natural infection
- Other chronic conditions / risk groups
- 2 → 3 dose regimen (2+1)
- Post single dose

Selected vaccines*

Immunocompromised / SOT → **Fractional single booster dose**

1:1

Immunocompromised / SOT → **Full single booster dose**

Day 1:

Day 29:

Immune response (core assay + additional assays defined by project (incl. e.g. CMI, cross-reactivity etc.):

Primary comparison:
→ Individual trial population

Secondary comparisons → in subgroups, e.g.
- Within each individual trial
- Across all trials

→ overall, across all trials

Follow-up

- At least 3 months for safety F/U
- May include an additional blood draw e.g. at 6 months to assess long-term immune response post booster

*) E.g., as available in the country. Vaccine developers may want to contribute to specific trials / projects.

Fractional ‘Booster’ Platform Trial: Core Elements

1. **Full versus fractional single dose** of a selected vaccine. If the ‘booster’ vaccine differs from vaccine given for priming, a control group including the same vaccine (full dose) given for primary vaccination should be considered
2. **4 week interval** between ‘booster’ dose and primary immunogenicity endpoint
3. Immune response for primary endpoint assessed based on **binding antibodies** (IgG ELISA)
4. **Reactogenicity / safety** assessment (as co-primary objective)
5. Follow-up (safety) for at least **3 months**

→ allow comparability / analyses on **core objective** across programmes (meta-analysis type rather than pooled data)

Fractional ‘Booster’ Platform Trial: Flexible Elements

Examples:

- Population: to be justified. Examples:
  - Selected age groups (e.g. elderly) or special populations (e.g. HIV-positives / immunocompromised) possibly requiring e.g. a three-dose-regimen (2+1)
  - Healthy general population post full primary immunization with weakly immunogenic vaccines
  - Incomplete primary immunization
  - Post natural infection
- Vaccine used
- Secondary objectives re immune response (nAbs, B-cell memory, CMI)
- Additional time points for immunogenicity assessment (e.g. long(er) term immune response post 6 months)
- Additional secondary and exploratory objectives
  - Including e.g. vaccine effectiveness (trials are unlikely to be sufficiently powered)
- Follow-up beyond 3 months

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Safety

- Post dose FU - Reactogenicity (7 days); unsolicited AEs (28 days) & SAEs (3 months)
- To ensure consistent assessment of reactogenicity and safety of fractional COVID-19 vaccines, procedures to harmonized across individual projects.
- Vaccine -specific AESIs to be defined for individual projects (We recommend SPEAC / the Brighton Collaboration definitions).
- SPEAC guidance for collection of safety data on COVID vaccines on the SPEAC Sharepoint: https://speacproject.sharepoint.com/:b:/r/sites/Start/SPEAC%20PRIVATE/00.%20Deliverables/SO2/WP2/SO2-D2.4/SO2-D2.4._FINAL%20VERSION_20200731.pdf?csf=1&web=1&e=2b2Npc
- An independent trial specific DSMB is encouraged; Alternatively consider participating in the meta DSMB scheme offered by SPEAC

Other considerations

- Primary immunogenicity endpoint: **Seroresponse rate (SRR)** in the fractional and full dose arms.
- SR to be defined as
  - XX-fold (TBD) rise in GMTs at 28 days post 'booster' dose from baseline among subjects with detectable Ab titers pre-booster
  - Post dose detectable Ab titers among subjects with no pre-booster detectable titers
- NI design not entirely fit for purpose related to absolute titres (e.g. GMTs) whereas objective may be **threshold-driven** in this setting (SRR) – TBD
- Samples size for individual trials will be justified on the basis of primary endpoint
- Subgroups for additional analyses should be defined and justified
- Cross-reactive immune response against selected VOCs (Delta variant and preferably other VOCs / VOIs as appropriate)

Timelines

Summary of project plan / GANTT

	2021					2022								2023		
	08	09	10	11	12	01	02	03	04	05	06	...	12	01	02	03
COVAX/CEPI review and approval																
Core protocol																
Develop programme structure (coordinator, PSC), contracts signed																
Onboard individual project																
First trial: FSI → 1st results																
Last trial: FSI → 1st results																
Total F/U period (1 year) after last trial started																
Final results, programme close																

Next Steps

Discussion / Proposals:

- Define core / flexible elements
- **Working group meeting with relevant stakeholders and interested groups: 10th September 2021**
  - ➢ **Obtain EOIs …**
- September / October onwards: Start individual projects

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Current state of play

- There are still many operational unknowns
- Time is of the essence
- The initial study will need to be an Investigator sponsored study
  - The site is the regulatory sponsor
  - The vaccine to be used in the study is already available in the country
  - External support needs are minimal
- The onboarding of additional countries/sites can then occur in a stepwise fashion
- This will allow more time to adapt the operational support to the site's needs

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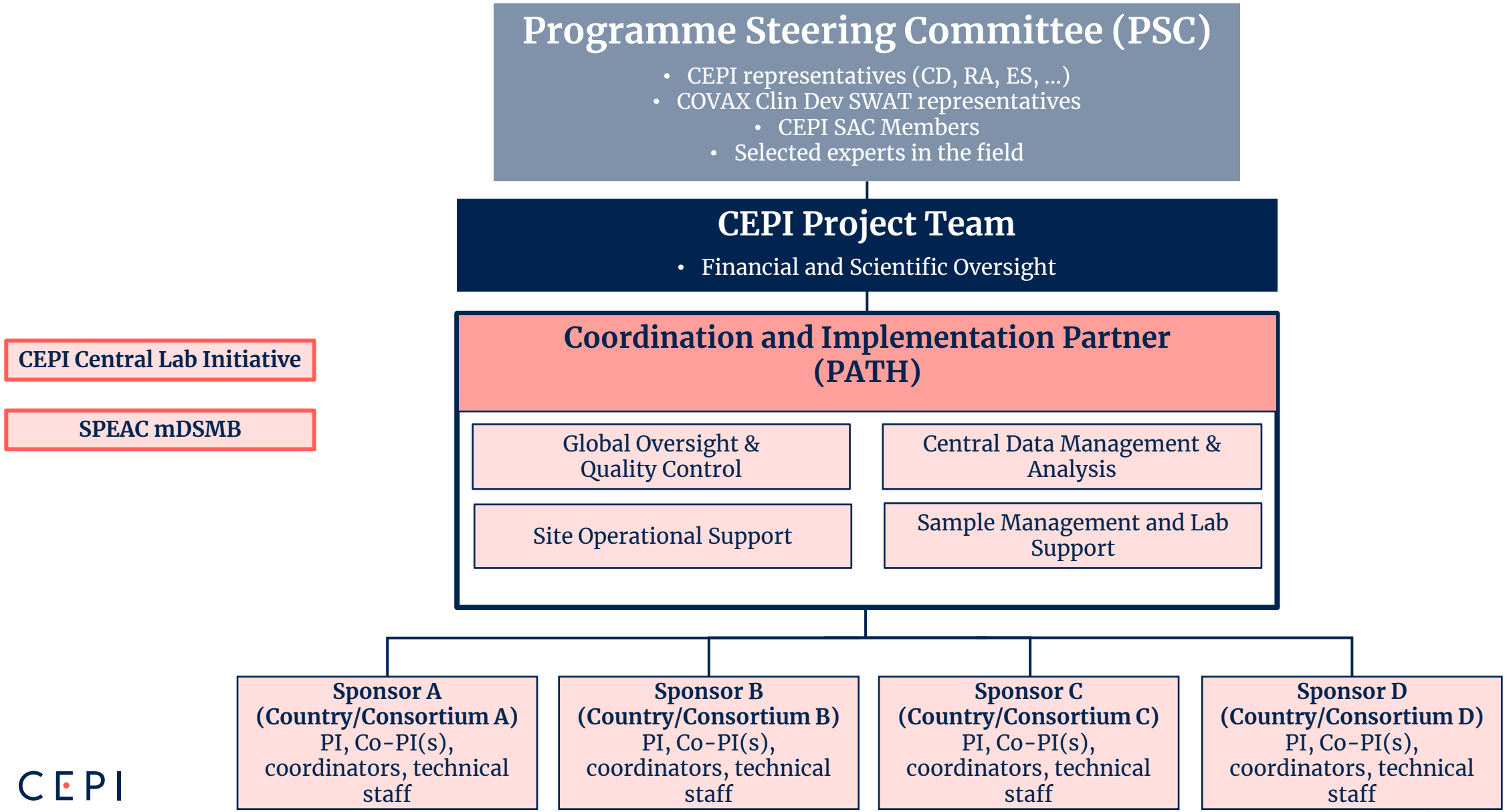
Programme Governance & Execution



COVID-19 Phase 3 Trial Preparation Project at PATH

Goal: To enhance capacity at low- and middle-income country clinical trial sites to prepare them for testing COVID-19 vaccine candidates alongside peer sites in high-income countries, including effectively sustaining and managing high-volume (participants & specimens) for rapid enrolling trials implemented in a pandemic setting while adhering to GCP guidelines and quality standards.

All 11 sites had prior relevant experience and demonstrated success in implementing clinical vaccine trials

- **<u>Standard capacity improvements</u>**
  - Hiring and training a core set of qualified trial management staff in GCP and HSR and site-specific procedures
  - Establishing a core set of SOPs, including COVID-19 specific SOPs promoting social distancing and infection prevention measures
  - Identifying a reliable source of COVID-19 surveillance data for country and local area, consistent monthly reporting
  - Consulting with National Regulatory Authorities and Ethics Committees to optimize timelines for review/approval
  - Conducting community/stakeholder consultation meetings to verify community readiness for a trial
  - Completing financial reviews to verify financial competency to manage trial finances

- **<u>Capacity improvements tailored by site</u>**
  - Improving infrastructure to allow for high-volume enrollment, social distancing, and preventing contact between suspected/confirmed patients and healthy study participants
  - Renovating/expanding storage and workspace in labs and pharmacies
  - Establishing satellite sites
  - Purchasing and/or maintaining refrigerators, freezers, and/or basic COVID-19 clinical care and assessment tools (e.g., oximeter, touchless thermometers, oxygen concentrators, etc.)

PATH

CEPI Centralized Laboratory Network: key features

Valentina Bernasconi Scientist at CEPI, Project Leader of CEPI Centralized Laboratory Network

Objectives of the Network

The CEPI Centralized Laboratory Network is open to **all** COVAX funded and non-funded vaccine developers:

- To test samples from pre-clinical to Phase III clinical studies for key immunogenicity and efficacy endpoint evaluation
- To support SARS-CoV-2 vaccine developers in the pathway towards licensure
- To help the identification of Immune Correlates of Protection
- To facilitate rapid evaluation, approval, and dissemination of the most effective vaccine candidates

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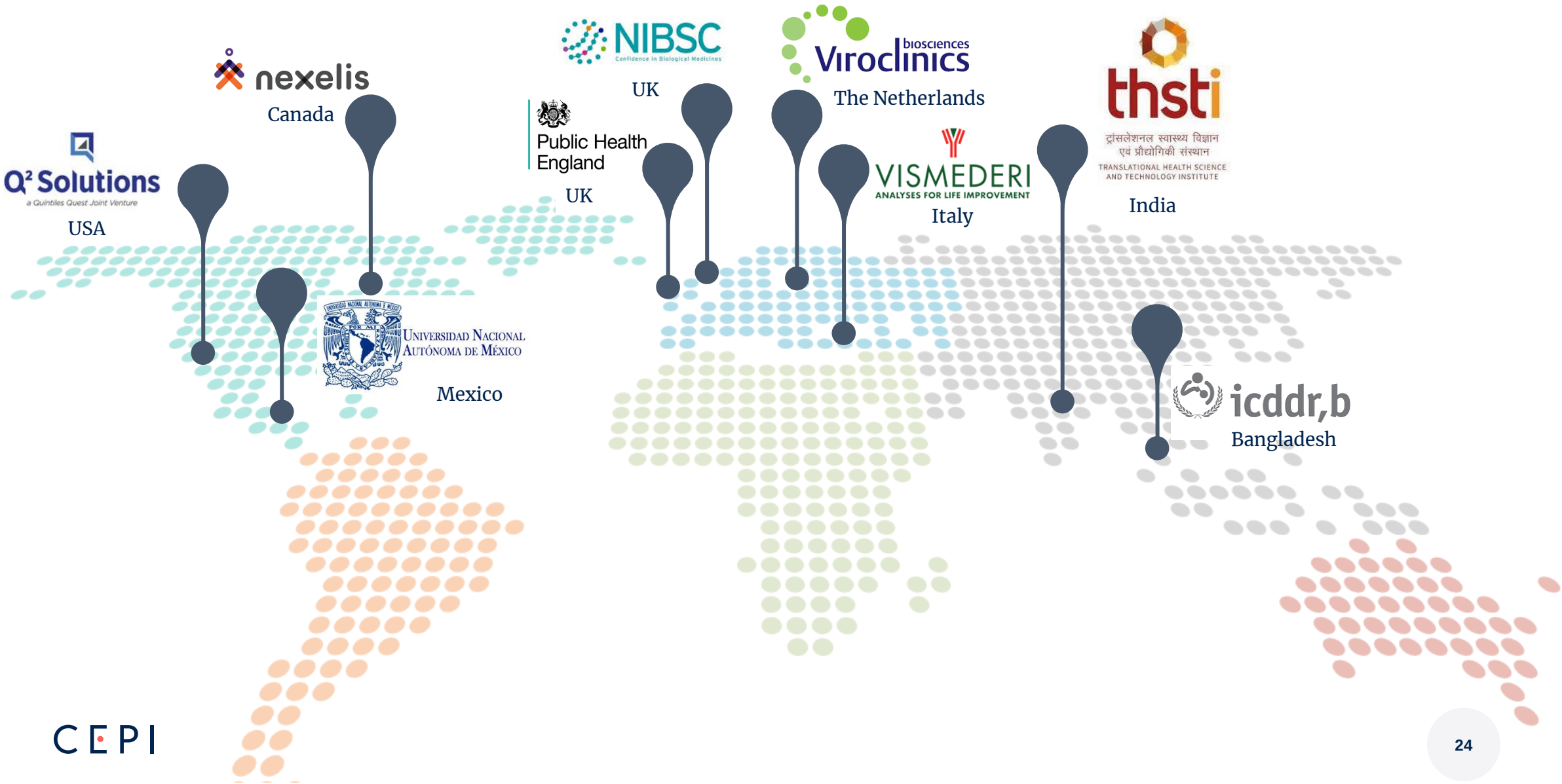
CEPI Centralized Laboratory Network



Assays available within the Network

	Binding antibodies	*Neutralizing antibodies*		*T cells*
	ELISA	**Pseudo typed virus neutralization**	**Wild type virus neutralization**	**ELISPOT**
	• Stabilized pre-fusion full length S, RBD, N • Total IgG in serum	• Pseudo particles with VSV backbone • Safer testing alternative (no BSL3 required)	• Colorimetric microneutralization assay • Victoria virus isolate	• Peptide pool of the whole S protein • Cytokines: IFNy (Th1), IL-5 (Th2)
Qualification (Nexelis/PHE)	Completed	Completed	Completed	Completed
Tech transfer (receiving labs)	In progress (completed for some labs)	In progress (completed for some labs)	In progress (completed for some labs)	In progress
Validation (Nexelis/PHE)	Completed	Completed	Completed	NA
Average current capacity (samples per week)	2500	1500	500	500

- *Common key reagents are provided to all the Labs in the Network*
- *Scalable throughput*

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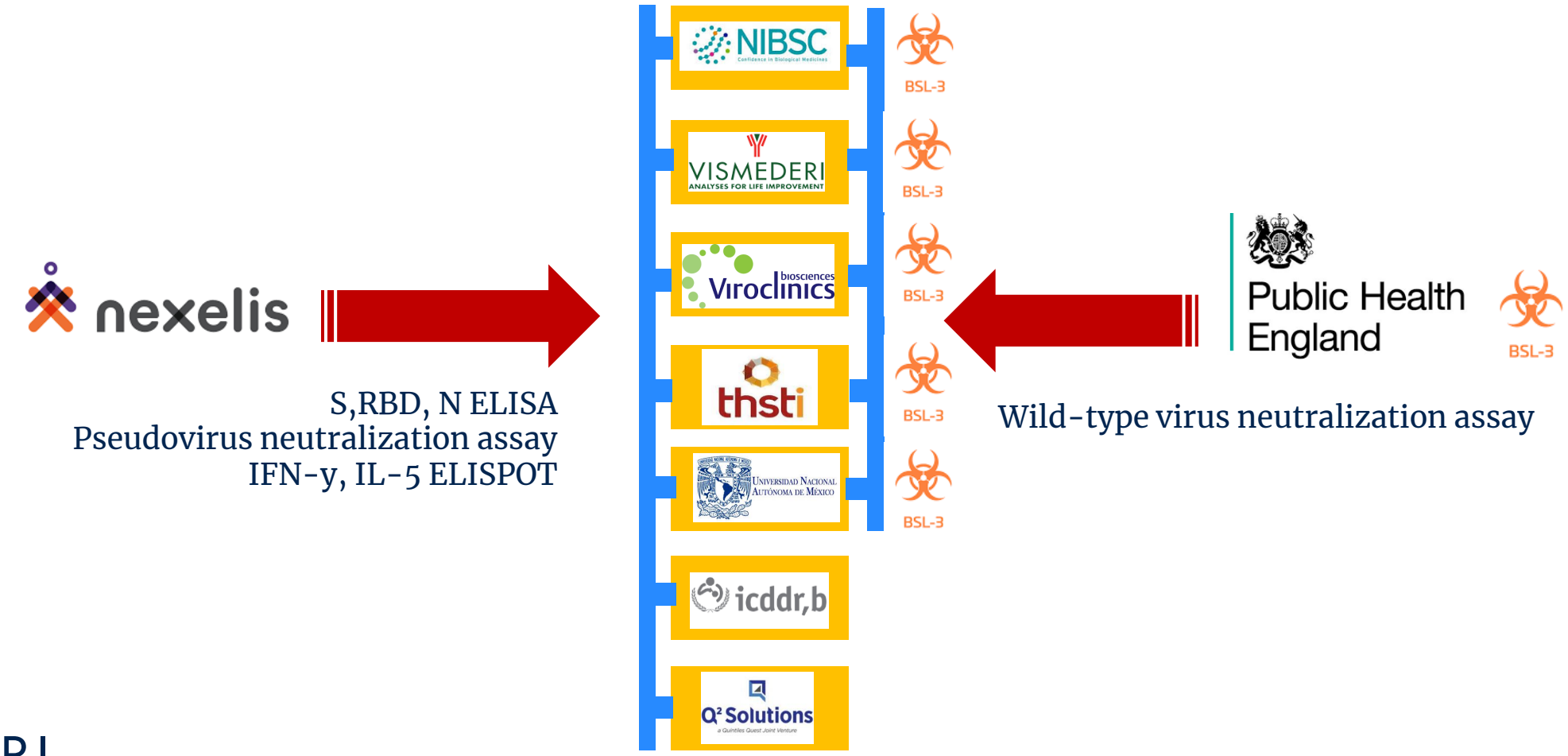
Assay harmonization and tech transfer

Common SOPs, Critical reagents, Controls and panels *



*Including bridging with WHO International Antibody Standard

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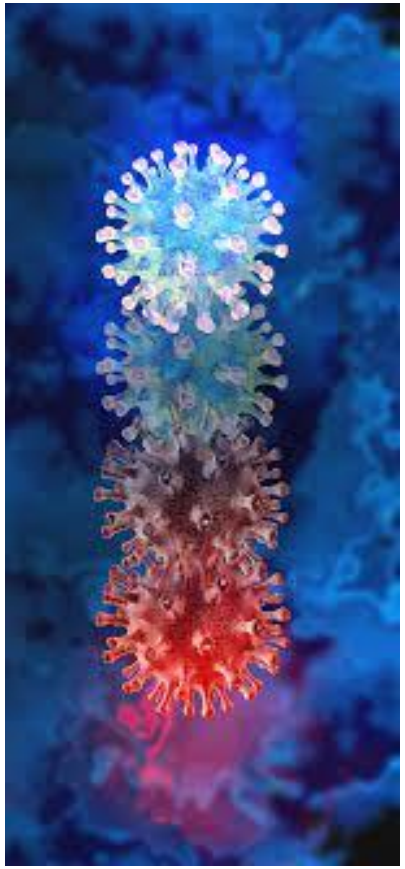
Tackling variants

- All viruses, including SARS-CoV-2, change over time
- CEPI Centralized Laboratory Network opens for testing of vaccines performance against SARS-CoV-2 variants:
  - Alpha, B.1.1.7, first identified in the UK
  - Beta, B.1.351, first identified in South Africa
  - Gamma, P.1, first identified in Brazil
  - Delta, B.1.617, first identified in India
- New circulating SARS-CoV-2 strains that might be tackled:
    - Lambda, C.37, first identified in Peru
    - Other variants that will potentially emerge in the future



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Apply for sample testing

- **All** COVID-19 vaccine developers are invited to apply to use the Centralized Laboratory Network

- **To apply for sample testing, please complete and submit the Sample Analysis Request Form**

More info:
https://epi.tghn.org/covax-overview/enabling-sciences/#ref1

Any further question? Reach out to centralizedlab@cepi.net

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Practical info

Step 1: Complete the Sample analysis request form.

Please note incomplete applications will not be considered.

Step 2: Your requests will be reviewed by a CEPI internal committee.

We commit to get back to each Vaccine Developer applicant within two weeks.

Step 3: If your request is approved, CEPI will connect you with one of our partner labs.

Note 1: CEPI will fund the approved sample testing. Sample shipment costs and documentation related to the shipment of the samples is the Vaccine Developer's responsibility.

Note 2: Each Vaccine Developer owns the data generated by the analysis of its samples and should commit to share results with the broader research community

Safety Platform for Emergency vACcines

Introduction to the Implementing partnership with the Brighton Collaboration program of the Task Force for Global Health

Robert (Bob) Chen MD MA
Scientific Director, Brighton Collaboration
Project Lead, SPEAC

CEPI Fx Dose Trial Platform

10 Sept 2021

CEPI-funded portfolio: multiple platforms for multiple pathogens

Risk:

- Each sponsor has own approach
- Safety signal may be missed in a single trial

Opportunity = SPEAC Goals:

- Enhance vaccine safety assessment across CEPI development programs.
- Harmonize vaccine safety monitoring during CEPI preclinical and clinical trials.
- Provide a continuous improvement framework

PLATFORM	DISEASE
Viral vector: Chimpanzee adenovirus	Lassa
	MERS
	Nipah
Viral vector: Measles	Chikungunya
	Lassa
	MERS
	Nipah
Viral vector: VSV	Nipah
Viral vector: VesiculoVax	Lassa
Viral vector: ChAdOx1	COVID-19
Viral vector: rVSVΔG-LASV-GPC	Lassa
Viral vector: MV	COVID-19
Viral vector: LAIV	COVID-19
Viral vector: MVA	MERS
DNA	Lassa
	COVID-19
	MERS
RNA	COVID-19
	Flu
	Disease X
	Yellow fever
Prefusion protein	COVID-19
Molecular clamp	COVID-19
	Disease X
Live attenuated / Inactivated	Chikungunya
	Rift Valley
Recombinant subunit	Nipah

SPEAC

Work Package 1: DSMB Pool and Meta-DSMB

- **SPEAC Pool of potential DSMB members**
- SPEAC will offer a list of persons by country with CV, and prior experience. There is currently a list of potential members.
- **SPEAC Meta-DSMB**
- Support CEPI by providing context regarding CEPI vaccines with similar constructs/platforms or target disease via liaison members to study DSMBs
- Support developers by providing expertise regarding CEPI vaccine and assessment of their safety

SPEAC

How is the Meta-DSMB different than a DSMB for an individual study?

- The study sponsor constitutes the individual DSMBs and the study DSMB has direct responsibility for oversight of that trial and reports to the sponsor.
- The goal of the Meta-DSMB is to provide overall oversight for all CEPI vaccine clinical trials to identify potential safety concerns:
  - Across trials using the same platform
  - Across platforms for the same disease target.
  - To encourage harmonization, when possible, regarding how safety data is collected and reported to facilitate data comparisons.
- Meta-DSMB members are **non-voting liaison members** to the individual study DSMBs. They are funded by SPEAC.
- The Meta-DSMB reports to SPEAC and through SPEAC to CEPI. Its role is advisory and supportive

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Current Status: The Meta-DSMB

SPEAC Meta-DSMB

- SPEAC is providing liaison observer members for each CEPI funded vaccine trial
- Can serve as a consulting resource for study DMSBs and sponsors.
- Aim: to support sponsors and their studies and to provide safety oversight of CEPI funded studies.

CURRENT STATUS

- Meta-DSMB members have been identified: Kathy Edwards (chair), Neal Halsey, Alex Dodoo, Ulrich Heininger, Cyndy Whitney, Walt Orenstein, Shabir Madhi, Juhani Eskola, Mathu Santosham, Najwa Kuhri, Seif Al-Abri, Jim Buttery and consulting statistician Stephen Evans.
  - A charter has been developed to be shared with all developers.

Work Package 2: Standards and Tools – Objectives & Outputs

2. To facilitate a harmonized approach to safety data collection and assessment

- **Key output:** online vaccine safety "toolbox" containing:
  - Landscape analysis results and publications used
  - Brighton Collaboration guidelines, safety templates
  - Existing and new Brighton AESI case definitions
  - **Companion Guides to AESI case definitions**
    - Risk factors
    - Background rates (systematic literature review)
    - ICD 9/10 CM / MedDRA Codes
    - Guidance for real time investigation and summary of Brighton guidance on data collection
    - Data abstraction and interpretation forms for Medical Chart review to assess AESI
    - Tabular and pictorial checklist and algorithms for assessing AESI level of certainty

Guides completed for: anaphylaxis, thrombocytopenia, generalized convulsion, GBS, facial palsy, ADEM, myelitis, encephalitis and aseptic meningitis

https://brightoncollaboration.us/category/pubs-tools/case-definitions/companion-guides/

Preliminary guidance on safety data collection for COVID-19 vaccine safety

August 31, 2021 - English / News / Relevant for COVID-19 / SPEAC Project

This deliverable provides guidance on the collection of safety data for COVID-19 vaccine candidates. This includes a brief discussion of the types of safety data to collect in trials, a sample memory aid template for collection of solicited local and systemic reactions with guidance re: data analysis and presentation, a literature search on enhanced disease and a report of the consensus conference on enhanced disease following immunization.

Click here to download SO2-D2.4_Preliminary guidance on safety data collection for COVID-19 vaccine safety_V1.0

Summary & Value Proposition

THE SPEAC PARTNERSHIP OFFERS NUMEROUS ADVANTAGES

- Expertise: Brighton Collaboration leverages global network of vaccine safety assessment and evaluation experts
  - For DSMBs and assessment of possible safety signals by Meta-DSMB
- Mitigates vaccine program risk by anticipating vaccine safety crises
- Develops tailored practical solutions for vaccine developers/sponsors
  - Safety landscape analysis for disease areas of interest
  - Case definitions for adverse events of special interest
- Improves data quality and comparability by harmonizing safety assessment

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a CEPI project

Questions?

Project Manager: angel.honrado@cepi.net

Project Lead: robert.chen@cepi.net

SPEAC Executive Board

WP	Key persons	Key relevant expertise
1. Meta-DSMB	1· Dr. Steven Black* (USA) 2· Dr.. Cornelia Dekker (USA)	DSMB experts, vaccinologists, pediatric infectious disease (ID) specialists
2. Toolbox	3· Dr. Barbara Law* (CA)	Former Chief Vaccine Safety Public Health Agency Canada, Chair BC SB, pediatric ID specialist
	4· Dr. Marc Gurwith (USA)	New vaccine technology lead, adult ID specialist
3. Evaluation	5· Dr. Wan-Ting Huang* (TW)	Medical Epidemiologist; Former Chief Medical Officer, Taiwan CDC
4. Coordination & project management	6· Dr. Robert Chen* (USA)	Project lead, former CDC
	7· Prof. dr. Miriam Sturkenboom* (NL)	Pharmaco-epidemiologist, scientific coordination
	8· Chantal Veira	Program management TFGH
	9· Ángel Honrado (ES) · Maria Pia Aristimuño (ES)	Project management, WeDo

** All with long-standing expertise in vaccine safety research & Brighton Collaboration Science Board. EB is supported by consultants and experts*

SPEAC

Founded in 2000

- **Goal:** to build trust in the safety of vaccines via rigorous science
- **Problem:**
  - Unlike efficacy, safety generally cannot be measured directly.
  - (Relative) safety inferred from relative absence of multiple adverse events following immunization (AEFI) studied given size of vaccinated population.
  - (Rare) AEFI easily missed unless standard case definition available.
- **Mission**: develop internationally accepted standards for monitoring vaccine safety throughout the vaccine life cycle
  - >750 volunteers from all stakeholders (academia, industry, government)
  - 20 years of enhancing vaccine safety research (by focusing on harmonization)

Work Package 2: Standards and Tools – Objectives & Outputs

1. To conduct landscape analyses for potential vaccine safety issues relevant to CEPI candidate vaccines.
   - **Key output:** list of possible adverse of events of special interest (AESI) for each target disease based on:
     1. Proven association with immunizations *(e.g. anaphylaxis)*
     2. Proven association with a vaccine platform and/or adjuvant *(e.g. MVA platform and myocarditis)*
     3. Theoretical concern based on immune-pathogenesis of wild type disease.
     4. Theoretical concern related to viral replication (for live-attenuated vaccines).
     5. Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccines *(e.g. enhanced disease in a MERS CoV vaccination/challenge mouse model)*

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Landscape Analyses to identify AESI related to wild type disease

- **Usual Process:** CEPI target diseases - Lassa Fever, MERS, Nipah, Rift Valley Fever, Chikungunya
  - Identify 8-10 recent review articles (primary references)
  - Articles reviewed, summarized and AESI list created independently by two experts
    - Secondary references of interest identified from those cited in primary references
    - Seek consensus on AESI list

- **COVID-19 – emerging disease with evolving understanding of clinical features**
  - Initial AESI list developed in early February based on first reports out of China
    - Hospitalized patients reported by Huang(n=41), Chen(n=99), Guan(n=1099), Wang(n=138)
    - 44,672 confirmed cases reported by China CDC
  - daily screening of published reports in PubMed and input from SPEAC EB members to update list (May 25th)
  - May 27th: updated AESI list presented to and adopted by WHO Global Advisory Committee on Vaccine Safety
  - Dec 2020: systematic literature review completed for May 16-Nov 9, 2020; identified 3 new AESI

COVID-19: AESI List (27 May 2020, adopted by WHO GACVS; updated Dec 2020)

	AESI (red font indicates existing case definition)	Rationale to include as an AESI[1]
1	**Vaccine Associated Enhanced Disease (in press)**	1 FI measles & RSV, HIV; 2 Chimeric YF Dengue; 5 SARS / MERS-CoVs
2	**Multisystem inflammatory syndrome in children and adults (in press)**	3, 4
3	**Acute respiratory distress syndrome (in press)**	3, 4
4	Acute cardiovascular injury (Microangiopathy, Heart failure, Stress cardiomyopathy, Coronary artery disease Arrhythmia, Myocarditis) CD for Myocarditis / pericarditis nearly ready	3, 4
5	Coagulation disorder (Thromboembolism, Hemorrhage). CD for thrombosis/thromboembolism nearly ready	3, 4
6	Acute kidney injury	3, 4
7	Generalized convulsion	1, 2
8	Guillain Barré Syndrome	3, 4
9	Acute liver injury	3, 4
10	Anosmia, ageusia	3, 4
11	Chilblain – like lesions	3, 4
12	Single Organ Cutaneous Vasculitis	3, 4
13	Erythema multiforme	3, 4
14	Anaphylaxis	1, 2
15	Acute aseptic arthritis	2 (r-VSV)
16	Meningoencephalitis	1
17	Acute disseminated encephalomyelitis	4
18	Thrombocytopenia	1, 2, 3, 4
NE W	Acute pancreatitis, rhabdomyolysis, Subacute pancreatitis	3, 4

1. Proven association with immunization
2. Proven association with specific vaccine platform
3. Theoretical concern based on immunopathogenesis
4. Theoretical concern related to viral replication during wild type disease
5. Theoretical concern based on demonstration in an animal model

Work Package 2: Standards and Tools – Objectives & Outputs (cont)

3. To develop *standardized templates* with key benefit/risk assessment considerations
   - Tool to facilitate discourse by increasing transparency/comparability of info on platform technology
   - Originally
     - Viral vector vaccines: (wild type virus of vector; vector itself; vaccine(s) constructed w/ vector)
   - More recently
     - Protein subunit (e.g., molecular clamp, VLP)
     - Nucleic acid (e.g., RNA, DNA)
     - Inactivated viral vaccines
     - Live attenuated viral vaccines

SPEAC

Vaccine: X 1 (2019) 100009

Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

rVSVΔG-ZEBOV-GP (also designated V920) recombinant vesicular stomatitis virus pseudotyped with Ebola Zaire Glycoprotein: Standardized template with key considerations for a risk/benefit assessment

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3. Characteristics of wild type agent	Information	Comments/Concerns	Reference(s)
3.1. Please list any disease(s) caused by wild type, the strength of evidence, severity, and duration of disease for the following categories:			
• In healthy people	Infection of humans with wild type VSV (wtVSV) New Jersey and Indiana serotypes can cause an influenza- like disease (usually without vesicle formation), incubation period 48 hrs, resolving in 3–5 days without complications. Mucosal ulceration and lymphadenopathy are reported. Rare cases are severe enough to warrant hospitalization Two published human cases of encephalitis caused by VSV have been reported, but are a rare complication of infection	Occupational exposure to wt or lab-adapted VSV strains (in veterinarians, farmers in livestock operations, laboratory workers) The reporting rate of naturally acquired overt disease with wtVSV in humans is very low, but in areas of Central and South America, infection appears to be common, with up to 94% of some populations being sero-positive. Surveys of individuals in close contact with VSV-infected livestock have shown high rates of seroconversion. Most infections may be asymptomatic or escape medical attention VSV *sensu stricto* is not present in Africa or in Europe Closely-related vesiculoviruses cause sporadic or epidemic encephalitis (Piry, Chandipura viruses in South America and India, respectively)	[50–59,65]
• In immunocompromised	Not known in humans	Immunosuppression with steroids did not potentiate wtVSV disease in experimentally infected swine Defects in innate immunity may underlie disease expression. VSV is exquisitely sensitive to IFN-α/β. Studies in mice lacking IFN receptors indicated that IFN response controls wtVSV and an intact innate immune response likely controls VSV replication	[60–62]
• In neonates, infants, children	Disease potential in children seems to be the same as that for adults	7–18% of children 0–5 years of age reported to be seropositive in areas surveyed in South and Central America	[57,63]
• During pregnancy and in the unborn	There is no evidence that wtVSV can cause abortions in livestock following natural infection. However, in ferrets experimentally infected with wtVSV-I during the second half of pregnancy transplacental infection, fetal resorption, abortion or neonatal death were observed		
• Are there any other susceptible human populations	Unknown		
• Animals	Wild-type VSV-NJ and Indiana cause disease in livestock.	The virus is biologically transmitted by biting insects such as	[51,60,64,65]

Agenda

#	Time (BST)		Subject	Responsible
1	2:00	2:05	Welcome [5 min]	Melanie Saville, CEPI
2	2:05	2:10	Background [5 min]	Peter Dull, BMGF
3	2:10	2:20	Fractional dosing – A perspective on vaccine supply [10 min]	Michael Kremer, Becker Friedman Institute, University of Chicago
4	2:20	2:30	Learnings from the UK trial on full / fractional booster doses: CoV-BOOST [10 min]	Saul Faust, Southampton NIHR Wellcome Trust Clinical Research Facility
5	2:30	2:40	Outline of the CEPI/COVAX platform trial concept [10 min]	Robbert van der Most, CEPI
6	2:40	2:50	Additional fractional versus full dose in primed populations: Core trial elements [10 min]	Amol Chaudhari, CEPI
7	2:50	3:00	Governance / Coordination / Support strategy [10 min]	Kerim Chitour, PATH
8	3:00	3:05	CEPI's Central Lab initiative [5 min]	Valentina Bernasconi, CEPI
9	3:05	3:10	Support options via CEPI/SPEAC incl. DSMB [5 min]	Robert Chen, BC/SPEAC
10	3:10	3:50	Discussion [40 min]	ALL
11	3:50	3:55	Timelines / next steps / EOIs [5 min]	Jakob Cramer, CEPI
12	3:55	4:00	Wrap-up / Closure [5 min]	Amol Chaudhari, Robbert van der Most, Jakob Cramer / CEPI

For Discussion

- **Do additional doses work?**
  - **Evidence from clinical trials (immunogenicity and safety/reactogenicity)**
- **Are primary immunization schedules incomplete?**
  - **Considerations for specific vaccines and special populations**
- Do we need additional doses?
  - Largely data from observational studies

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- **What?** → objectives
- **Which?** → vaccine(s) [info on procurement]?
- **Who?** → trial population
- **Where?** → country / region
- **When?** → timeline

Conclusion

- Slide deck to be published on: **https://epi.tghn.org/**
- Further questions on the approach: **Dr. Amol Chaudhari** [amol.chaudhari@cepi.net]
- Questions around fractional / booster / additional doses will also be addressed on an ongoing base by the COVAX Clin Dev SWAT team (next workshop planned for 30th September 2021 – TBC)

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