Brighton Collaboration Safety Platform for Emergency vACcines (SPEAC) Project

World Health Organization

Covid-19 Vaccine Safety Ecosystem Workshop

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Robert T Chen, MD MA

Scientific Director

Brighton Collaboration

Outline

- Background
  - Brighton Collaboration
  - CEPI/COVAX
- SPEAC
  - DSMB/mDSMB
  - AESI
  - Vaccine-Associated Enhanced Disease (VAED)
  - Vaccine Technology Safety Templates

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)

CEPI-funded portfolio: Multiple platforms for multiple pathogens

Risk:

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

Opportunity:

- Learn across all trials
- Harmonize across CEPI-funded trials
- 28 May 2019: Brighton Collaboration Safety Platform for Emergency vACcines (SPEAC) Project

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: rVSVΔG-LASV-GPC	Lassa
Viral vector: MVA	MERS
DNA	Lassa
	MERS
RNA	COVID-19
	Flu
	Disease X
	Lassa
	Marburg
	Rabies
	Yellow fever
Molecular clamp	COVID-19
	Disease X
	MERS
Live attenuated	Chikungunya
	Rift Valley
Recombinant subunit	Nipah

Data Safety Monitoring Board (DSMB) Pool & Meta-DSMB

- **SPEAC Pool of potential DSMB members**
  - SPEAC offers a list of persons by country with CV, and prior experience to serve on sponsor DSMBs. There is currently a list of potential members who are willing to serve.
- **SPEAC Meta-DSMB**
  - Support CEPI by reviewing safety data on CEPI vaccines with similar constructs/platforms or target diseases.
  - Support developers by providing their expertise on CEPI vaccines and assessment of their safety.

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.

SPEAC Standards and Tools

- **Goals/Objectives:**
  - facilitate harmonized approach to safety data collection & assessment
  - anticipate vaccine safety issues that could arise during clinical trials
- **Step 1: define 'adverse events of special interest' (AESI) for each target disease based on landscape analyses/literature review (*challenging for COVID19!!*):**
  - Events associated with immunization in general; e.g. **anaphylaxis**
  - Events associated with specific vaccine platforms; e.g. **live vaccines: encephalitis, aseptic meningitis**;
  - Events associated with wild type target disease; related to:
    - Viral replication
    - Immuno-pathogenesis
- **Step 2: prioritize AESI to make available:**
  - Brighton case definitions if not yet published
  - Tools to facilitate harmonized approach to AESI data collection, investigation and assessment
  - Risk factors and background rates
  - ICD / MedDRA codes for AESI as a whole and key case definition terms

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

	AESI (red font indicates existing case definition)	Rationale to include as an AESI[1]
1	Enhanced disease following immunization	1 FI measles & RSV, HIV; 2 Chimeric YF Dengue; 5 SARS / MERS-CoVs
2	Multisystem inflammatory syndrome in children	3, 4
3	Acute respiratory distress syndrome	3, 4
4	Acute cardiovascular injury (Microangiopathy, Heart failure, Stress cardiomyopathy, Coronary artery disease Arrhythmia, Myocarditis)	3, 4
5	Coagulation disorder (Thromboembolism, Hemorrhage)	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

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

COVID-19 AESI: Step 2 - Tool Development

A. New AESI Case Definitions

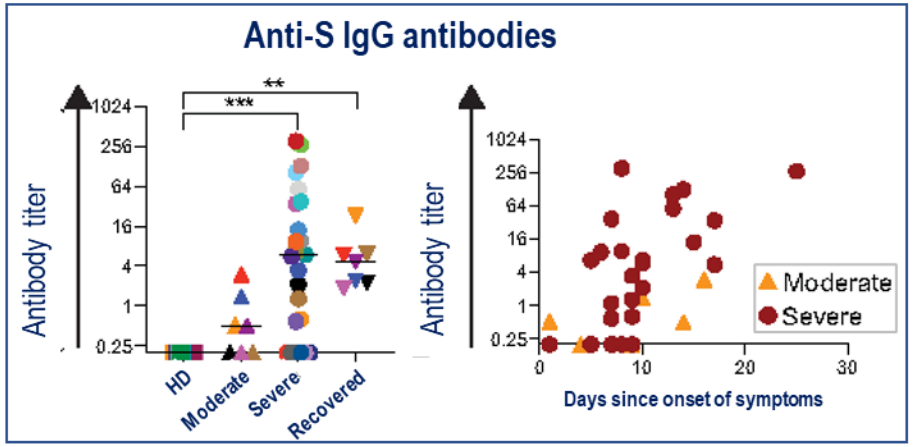
	AESI	Status of New Case Definition Development
1	**Enhanced disease following immunization**	Draft under expert/BC peer review; for submission by Sept. 15
2	**Multisystem inflammatory syndrome in children**	WGs established, CDs under development; target submission by Oct 15
3	**Acute respiratory distress syndrome**	
4	**Acute cardiovascular injury**	WGs established, 1st meeting held; target submission by Nov 15
5	**Coagulation disorder**	
6	**Acute kidney injury**	Call for WG volunteers posted Aug 10; target submission by Nov 30
9	**Acute liver injury**	
10	**Anosmia, ageusia**	
11	Chilblain – like lesions	
13	Erythema multiforme	

COVID-19 vaccines are at risk of vaccine-associated disease enhancement: Why??

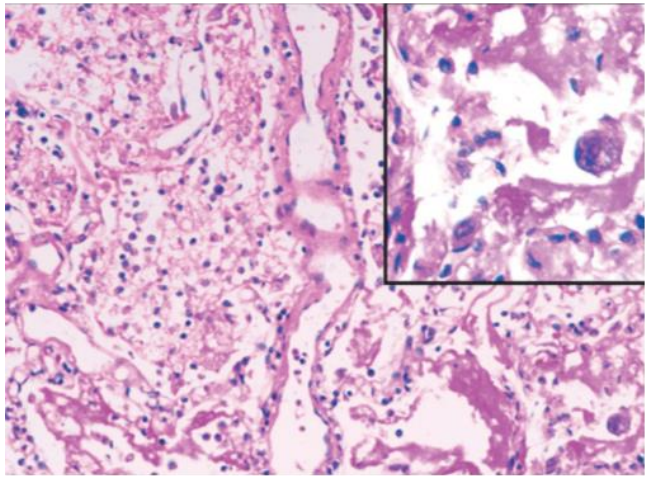
1. COVID-19 often appears as a two-stage disease-
   In the second phase , severe cases are associated with an active immune response: early and higher antibody levels than in mild cases.

2. Severe disease appears associated with immunopathology (inflammatory infiltrates dominated by activated monocytes and T-cells, cytokine storm)

3. In animal models, other coronavirus candidate vaccines (SARS, MERS, FIP) were associated, after challenge, with enhanced disease

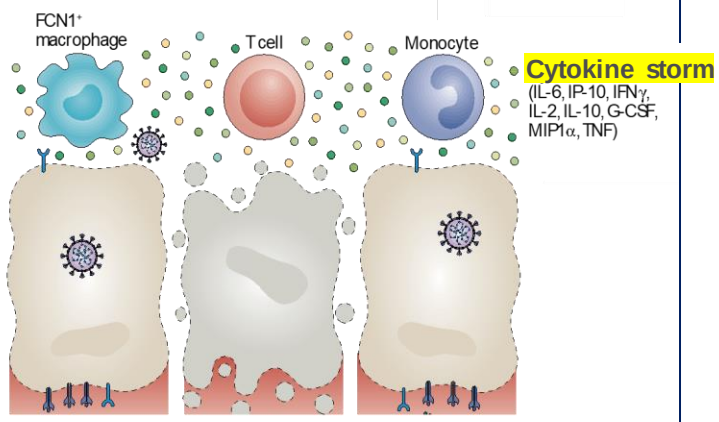


Kuri-Cervantes et al. Sci. Immunol. 2020



Lancet Respir Med 2020; 8: 420–22

Presence of highly activated monocytes/macrophages and T-cells is a hallmark of severe disease



Vzirui Tay, Nat Rev Immunol, 2020

Vaccine 38 (2020) 4783–4791

Contents lists available at ScienceDirect

Vaccine

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

Conference report

Consensus summary report for CEPI/BC March 12–13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines

Paul-Henri Lambert [a], Donna M. Ambrosino [b], Svein R. Andersen [c], Ralph S. Baric [d], Steven B. Black [e], Robert T. Chen [e], Cornelia L. Dekker [e,*], Arnaud M. Didierlaurent [a], Barney S. Graham [g], Samantha D. Martin [h], Deborah C. Molrine [i], Stanley Perlman [j], Philip A. Picard-Fraser [k], Andrew J. Pollard [l], Chuan Qin [f], Kanta Subbarao [m], Jakob P. Cramer [n]

COVID-19 vaccines

Consensus considerations on the assessment of the risk of VAED in animal models

- Animal models of COVID-19 imperfectly reproduce the human disease but are useful for assessing the risk of disease enhancement.
- Observations made in NHP are probably more significant. Vaccine responses are closer to human responses than in mice, ferrets or hamsters

- Attention to the risk of VAED should be raised if pre-clinical studies show:

  - High level of binding antibodies with low level of neutralizing antibodies & low affinity antibodies,
  - Dominant Th2 T-cell response profile
  - Increased post-challenge inflammatory response (CRP, Ferritin, cytokines)
  - Enhanced lung pathology (Histopathology or PET SCAN).
  - Unexpected extra-pulmonary lesions (e.g. vasculitis)

- Such markers of VAED may be monitored during Phase I-II clinical trials and in vaccine failures during Phase III trials

Risk Perceptions*

Less Risk		Greater Risk
voluntary	vs.	*involuntary*
individual control	vs.	*system control*
omission	vs.	*commission*
natural	vs.	*manmade*
not memorable	vs.	*memorable*
knowable	vs.	*unknowable*
not dreaded	vs.	*dreaded*
familiar	vs.	*Exotic*

(e.g., GMO)

*Hance BJ, Chess C, Sandman P; Industry risk communication manual,Chelsea, MI; Lewis Publishers1990

CDC™

Brighton Collaboration: Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group*

- Formed 2008 @ encouragement of WHO (M.P. Kieny) after unexpected stop STEP Ad5 HIV trial.
- Improve ability of key stakeholders (e.g., regulators, public health, general public) to anticipate potential safety issues, assess/interpret safety data, facilitate improved public acceptance when vaccines licensed
- Developed standardized templates as a tool to facilitate:
  - Effective communication of complex information among key stakeholders
  - Increase transparency, comparability, comprehension of essential information
  - Function as checklist for risk management of complicated activity (e.g., airplane pilot checklist)
  - Gaps in current data inevitable but can help prioritize future research
- Hope vaccine developers (especially those likely to be used in human in near future) will complete the relevant template, submit to WG + BC for peer review & publish + update

*ex- Viral Vector Vaccine Safety Working Group (V3SWG)

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

Thomas P. Monath [a,1], Patricia E. Fast [b], Kayvon Modjarrad [c], David K. Clarke [d], Brian K. Martin [a,2], Joan Fusco [a,1], Richard Nichols [a,1], D. Gray Heppner [a,1], Jakub K. Simon [e], Sheri Dubey [e], Sean P. Troth [e], Jayanthi Wolf [e], Vidisha Singh [f], Beth-Ann Coller [e], James S. Robertson [g,*], For the Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) [3]

[a] NewLink Genetics Corp, Ames, IA, United States
[b] International AIDS Vaccine Initiative, New York, NY 10004, United States
[c] Walter Reed Army Institute of Research, Silver Spring, MD 20910, United States
[d] Profectus Inc., Pearl River, NY 10965, United States
[e] Merck & Co., Inc., Kenilworth, NJ 07033, United States
[f] Immunology and Molecular Pathogenesis, Emory University, Atlanta, GA 30322, United States
[g] Independent Expert, United Kingdom

Vaccine Technology Platform Safety Templates

https://brightoncollaboration.us/bravato/

- Adapting original viral vector template suboptimal, BRAVATO developed new templates for:
  1. Nucleic Acid (RNA/DNA) vaccines - https://doi.org/10.1016/j.vaccine.2020.06.017
  2. Protein vaccines – https://doi.org/10.1016/j.vaccine.2020.06.044
  3. Inactivated viral vaccines – https://doi.org/10.1016/j.vaccine.2020.07.028
  4. Live attenuated viral vaccines – Vaccine (submission pending); draft on website
  5. Viral vector vaccines - Vaccine (in press); draft on website
  6. Maternal Immunization/Pregnancy module (to add to other templates) - Pending
- Key stakeholders can use templates to evaluate and communicate the benefit-risk of vaccines using these platforms

Summary

- Brighton Collaboration goal: build trust in safety of vaccines via rigorous science
- COVID19 presents many challenges and opportunities
- Safety Platform for Emergency vACcines (SPEAC) project progress to date on:
  - DSMB pool and meta-DSMB
  - Standards and Tools:
    - Adverse Events of Special Interest (AESI; e.g., VAED++)
    - Vaccine Technology Safety Templates
- Look forward to filling other gaps and needs

Executive Board

WP	Key persons	Key relevant expertise
1. META-DSMB	1· Dr. Steven Black* (USA) 2· Dr. Cornelia Dekker (USA)	DSMB expert, vaccinologist, pediatric infectious disease (ID) specialist
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 Epidemiolgist; Former Chief Medical Officer, Taiwan CDC
4. Coordination & project management	6· Dr. Robert Chen* (USA)	Project lead, former Chief Immunization Safety Branch, US CDC
	7· Prof. Dr. Miriam Sturkenboom* (NL)	Pharmaco-epidemiologist, scientific coordination
	8· Chantal Veira	IT specialist & 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*