Brighton Collaboration Webinar on Tools for COVID-19 Vaccine Safety Assessment

Thursday 27th August 2020

11:00am - 12:30pm EDT || 17:00pm - 18:30pm CEST

SPEAC
a CEPI project

Agenda

Session A (60 Minutes)

• Welcome/Intro to COVAX *(Jakob Cramer)*	3 minutes
• WHO/GACVS Perspective *(Madhava Balakrishnan)*	3 minutes
• Intro to Brighton Collaboration/SPEAC *(Robert Chen)*	4 minutes
• Adverse Events of Special Interest (AESI) List *(Barbara Law)*	10 minutes
• Vaccine Associated Enhanced Disease (VAED) *(Paul Henri Lambert)*	10 minutes
• Case Definitions for VAED + other AESI's *(Flor Munoz)*	10 minutes
• Q&A I *(Moderator: Robert Chen; Triage: Miriam Sturkenboom)*	20 minutes

Session B (30 Minutes)

• Vaccine Technology Safety Templates *(Robert Chen)*	10 minutes
• Meta-DSMB *(Corry Dekker)*	5 minutes
• Q&A II *(Moderator: Robert Chen; Triage: Miriam Sturkenboom)*	15 minutes

Welcome from COVAX

Jakob Cramer

Head of Clinical Development

CEPI

World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) Perspective

Dr. Madhav Ram Balakrishnan

WHO

The Global Advisory Committee on Vaccine Safety
Extraordinary meeting

28-29 May 2020

Update - progress

Background and mandate

GACVS

- **Risk Assessment** of vaccines and provides recommendations to the SAGE* that makes policy decisions
- Advice on **vaccine safety monitoring** systems, tools and studies
- Significant role in composing scientific messages for use by **risk communicators**

Established in 1999

Provides independent, authoritative, scientific advice to WHO on vaccine safety issues of *global* or *regional* concern with the potential to affect in the short- or long-term national immunization programmes:

*SAGE: Strategic Advisory Group of Experts on Immunization. SAGE is the principal advisory group to WHO for vaccines and immunization
https://www.who.int/immunization/policy/sage/en/

Update

The objectives

The outcomes

Recommendations

Available and newly generated Brighton Collaboration case definitions for AESI and tools to assess certainty of cases should be shared widely for countries to use and to be aligned

Progress

Working group 1: Coordinate with CEPI and review the Vaccine platforms

Working group 2: Global, Regional and National guidance for pharmacovigilance preparedness

Working group 3: COVID19 vaccine related AEFI Surveillance & Data Mx

Working group 4: Vaccine safety communications in the context of COVID 19

Guidance document to prepare countries for addressing safety of COVID 19 vaccines when introduced

GACVS Recommendations

What were the key outcomes?

COVID-19 vaccine safety surveillance infrastructure and capacity should ideally be in place and existing infrastructures reactivated and actively engaged prior to vaccine introduction.

A working group of experts should be established to provide guidance to countries and regions on prerequisites for vaccine introduction.

Basic adverse events of special interest (AESI) list should be created. Prioritization of AESI may be based on those identified in the COVID-19 clinical trials.

Available and newly generated Brighton Collaboration case definitions for AESI and tools to assess certainty of cases should be shared for countries to use and to be aligned.

A minimum institutional capacity should be in place in countries for AEFI identification & a working group established to incorporate specific case definitions when Brighton Collaboration definitions do not exist.

Countries should consider using a Delphi method in instances where case definitions are not available from the Brighton Collaboration.

GACVS Recommendations

What were the key outcomes?

WHO should work with national teams of Expanded Programme on Immunization to strengthen routine vaccine safety monitoring alongside COVID-19-related activities.

National regulators should review risk management plans obtained from vaccine developers and share with immunization programmes and other stakeholders in countries and incorporate them into their vaccine safety preparedness strategies at the time of vaccine introduction.

Developers should share available regional and international safety data including safety summaries with the reviewing regulatory authority.

Any review of the safety of new vaccines should be based on the appropriate Brighton Collaboration standardized templates for benefit-risk assessment of vaccines.

An ambitious, proactive vaccine safety communication plan is needed. Less visible social media such as WhatsApp should be monitored as closely as possible.

The Communication approaches should clearly explain the difference between AESI and AEFI to relevant stakeholders.

Introduction to Brighton Collaboration Safety Platform for Emergency vACcines (SPEAC) Project

Robert T. Chen, MD MA

Scientific Director

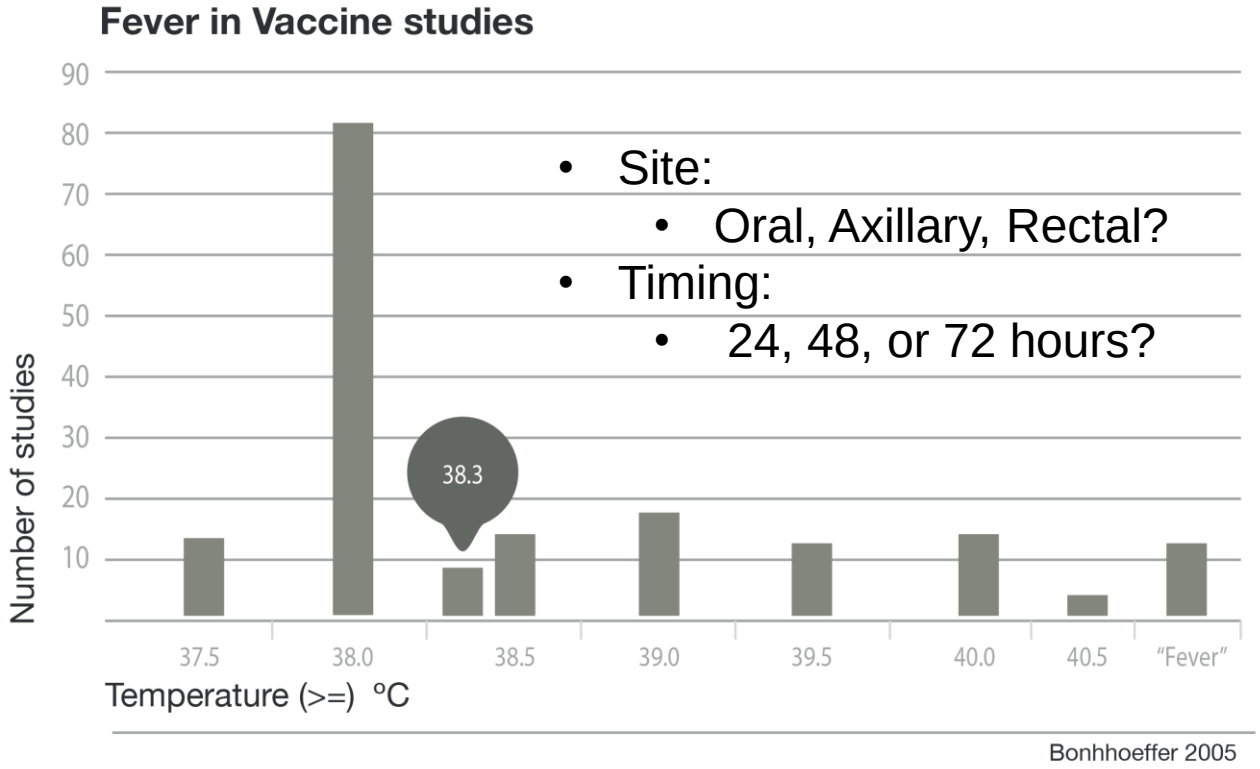
Brighton Collaboration

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)

Brighton Collaboration recognized the need for harmonization to advance science of vaccine safety

Lack of shared definitions hampers research



- Site:
  - Oral, Axillary, Rectal?
- Timing:
  - 24, 48, or 72 hours?

- Brighton Collaboration has delivered:
  - **>60 AEFI Case definitions (GAIA, GBS, seizures, intussusception etc.)**
  - **Tiered by 3 levels of evidence**
  - **Guidance for collection and reporting vaccine safety data**
- Endorsements from major stakeholders (FDA, EMA, WHO, ….
- 18 (72%)/25 2009 H1N1 Flu Vaccine & Guillain-Barre Syndrome (GBS) Studies used Brighton Case Definition

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

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*

Adverse Events of Special Interest (AESI)

Dr. Barbara Law

Standards and Tools

Overarching Goal: facilitate harmonized approach to safety data collection & assessment

Key objective: anticipate vaccine safety issues that could arise during clinical trials

- **Step 1:** define ‘adverse events of special interest’ for each target disease based on:
  - 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

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

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

Standards and Tools

Overarching Goal: facilitate harmonized approach to safety data collection & assessment

Key objective: to anticipate vaccine safety issues that could arise during clinical trials

- **Step 1:** AESI for each target disease

- **Step 2: prioritize AESI to make available:**
  A. Brighton case definitions if not yet published
  B. Tools to facilitate harmonized approach to AESI data collection, investigation and assessment
  C. Risk factors and background rates
  D. ICD / MedDRA codes for AESI as a whole and key case definition terms

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 Aug 31
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	

Standards and Tools

Overarching Goal: facilitate harmonized approach to safety data collection & assessment

Key objective: to anticipate vaccine safety issues that could arise during clinical trials

- **Step 1:** AESI for each target disease

- **Step 2: prioritize AESI to make available:**
  A. Brighton case definitions if not yet published
  B. Tools to facilitate harmonized approach to AESI data collection, investigation and assessment
  C. Risk factors and background rates
  D. ICD / MedDRA codes for AESI as a whole and key case definition terms

COVID-19 AESI: Tools to Facilitate AESI data collection & interpretation

Vaccine 29 (2011) 599–612

Contents lists available at ScienceDirect

Vaccine

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

Guillain–Barré syndrome and Fisher syndrome: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data☆

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2. Clinical case definitions: Guillain–Barré syndrome (GBS)[3,4,5]

Level 1 of diagnostic certainty
- Bilateral AND flaccid weakness of the limbs[6,7,8]
  AND
- Decreased or absent deep tendon reflexes in weak limbs[9]
  AND
- Monophasic illness pattern[10] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[11]
  AND
- Electrophysiologic findings consistent with GBS[12]
  AND
- Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μl)[13]
  AND
- Absence of an identified alternative diagnosis for weakness (see Appendix A.3)[3].

Level 2 of diagnostic certainty
- Bilateral AND flaccid weakness of the limbs[6,7,8]
  AND
- Decreased or absent deep tendon reflexes in weak limbs[9]
  AND
- Monophasic illness pattern[10] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[11]
  AND
- CSF total white cell count <50 cells/μl (with or without CSF protein elevation above laboratory normal value)[13]
  OR
- IF CSF not collected or results not available, electrophysiologic studies consistent with GBS[12]
  AND
- Absence of identified alternative diagnosis for weakness (see Appendix A.3)[3].

Level 3 of diagnostic certainty
- Bilateral AND flaccid weakness of the limbs[6,7,8]
  AND
- Decreased or absent deep tendon reflexes in weak limbs[9]
  AND
- Monophasic illness pattern[10] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[11]
  AND
- Absence of identified alternative diagnosis for weakness (see Appendix A.3)[3].

Clinical case definitions: Fisher syndrome (FS)[14]

Level 1 of diagnostic certainty
- Bilateral ophthalmoparesis AND bilateral reduced or absent tendon reflexes, AND ataxia[15]
  AND
- Absence of limb weakness[16]
  AND
- Monophasic illness pattern AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[17,18]
  AND
- Cytoalbuminologic dissociation (i.e., elevation of cerebrospinal protein above the laboratory normal AND total CSF white cell count <50 cells/μl])[19]
  AND
- Nerve conduction studies are normal, OR indicate involvement of sensory nerves only[20]
  AND

[3] If an *alternative diagnosis* explaining flaccid weakness/paralysis is present (Appendix A.3), a diagnosis of Guillain–Barré syndrome is *excluded*. However, in many, if not most cases, a comprehensive documentation of testing for various other etiologies will either be incomplete or unavailable. These case definitions are provided to give guidance in the absence of detailed information on investigations for alternative etiologies of flaccid paralysis.

[4] It is recognized that there are several clinical syndromes which are considered as part of the spectrum of Guillain–Barré syndrome that may not be captured under these case definitions. However, these are rare and comprise under 1% of overall GBS cases. Thus, the number of cases missed by these definitions is considered to be extremely low. An exception to this is the FS of ophthalmoplegia, ataxia, and loss of tendon reflexes which is generally considered to be a subtype of GBS (see FS case definition).

[5] The clinical and electrophysiologic criteria specified in this document were designed to be applicable to all ages. The Working Group recognizes that neurologic features in infants and young children are continually developing and that assessment of infants can be difficult. However, GBS in children under 6 months of age is a very uncommon occurrence [71]. When possible, infants and children under 2 years of age should preferably be evaluated by a clinician familiar with the neurologic evaluation of young children, and such evaluations should be performed in an age-appropriate fashion, taking into account the changing neurologic features in the developing infant.

[6] Weakness is usually, but not always, symmetric in nature, and usually has a pattern of progression from legs to arms (ascending). However, other patterns of progression may occur (e.g., beginning in the arms). The degree of weakness can range from mild to moderate to severe, i.e., complete paralysis.

[7] Respiratory or cranial nerve-innervated muscles may also be involved.

[8] It is important that strength be assessed in a manner that takes into account subject age, sex, and level of functioning.

[9] Decreased or absent tendon reflexes may also be seen in limbs without weakness. However, to meet case definition criteria, decreased or absent tendon reflexes must be observed in weak limbs.

[10] Fluctuations in level of weakness, before reaching nadir, or during the plateau or improvement phases, occur in some cases, usually associated with the use of disease-modifying therapies. Such fluctuations usually occur within the first 9 weeks after onset [66] and are followed by eventual improvement.

[11] The eventual outcome is either stabilization at nadir OR subsequent improvement OR death.

[12] Electrophysiologic patterns consistent with polyneuropathy of the types described for GBS [23]. Electrophysiologic studies performed sooner than 7 days after weakness onset may be normal and should thus be repeated at a later time if possible, and "normal" studies may occur in otherwise typical cases of GBS. However, cases with persistently "normal" studies will not meet Level 1 criteria.

[13] CSF (cerebrospinal fluid) protein concentrations should be elevated above what is considered normal reference values for the testing laboratory. CSF may be "normal" in otherwise typical cases of GBS; this is particularly true within the first week of illness. However, cases with persistently "normal" CSF, or CSF with ≥50 WBC, will not meet Level 1 criteria.

[14] If an *alternative diagnosis* explaining the triad, including (but not limited to) botulism, diphtheria, and Wernicke's encephalopathy, is present (Appendix A.3), a diagnosis of FS is *excluded*. However, in many, if not most cases, a comprehensive documentation of testing for various other etiologies will either be incomplete or unavailable. These case definitions are provided to give guidance in the absence of detailed information on investigations for alternative etiologies of this clinical triad.

[15] Ophthalmoparesis, tendon reflexes, and ataxia are relatively symmetric. Ptosis or pupillary abnormalities may be present in the setting of the ophthalmoplegia. The clinical severity of each component may vary from partial to complete. Hypo- or areflexia tends to be diffuse/global, and symmetric. However, selective involvement of upper or lower extremity reflexes may be seen. Facial and bulbar weakness may also be features.

[16] Presence of limb weakness would suggest a diagnosis of Guillain-Barré syndrome (GBS) (see case definition for GBS).

[17] Improvement of symptoms may occur with or without treatment.

[18] The eventual outcome is either stabilization of symptoms at nadir OR subsequent improvement OR death.

[19] CSF protein levels should be elevated above what is considered normal reference values for the testing laboratory. CSF may be "normal" in otherwise typical cases of FS; this is particularly true in the first week of illness. However, cases with persistently "normal" CSF will not meet Level 1 criteria.

[20] Motor nerve conduction abnormalities in this clinical setting likely indicate GBS/FS overlap.

COVID-19 AESI: Step 2 - Tool Development

B. Tools to facilitate AESI data collection, investigation and assessment

- Data abstraction and interpretation forms (Setting: medical chart review)

Example Guillain Barré Syndrome:

1. Case definition criteria, likely and actual sources of information

Criterion	Criterion category	Likely sources of information	Actual source of Information
A	Muscle weakness	• Outpatient clinic / emergency room record(s) • Neurology / Infectious Disease / other consultation notes • Hospital admitting history & physical exam; • Hospital discharge summary; • ICU admission notes • Follow-up clinic records	
B	Deep tendon reflexes		
C	Temporal illness pattern		
D	Ophthalmoparesis		
E	Ataxia		
F	Encephalopathy		
G	Corticospinal long tract signs		
H	Alternative causes for weakness	Differential diagnosis, investigations & results (see Appendix 1)	
I	Electrophysiologic testing	EMG, nerve conduction study reports	
J	Cerebrospinal fluid (CSF) testing	Laboratory reports – CSF analysis	

COVID-19 AESI: Step 2 - Tool Development

B. Tools to facilitate AESI data collection, investigation and assessment

- Data abstraction and interpretation forms (Setting: medical chart review)

Example Guillain Barré Syndrome:

2. Structured report form to record data for case definition criteria and rules to assign a value to each

<table>
<tr><th>1. Clinical Criteria</th><th>2. Results</th><th>3. BCCD Criteria Value Determination</th></tr>
<tr>
<td>Criteria A & B Flaccid (reduced tone) weakness (graded power of 4 or less – see Appendix 2, Table 1)</td>
<td>* wherever ‘yes’ is chosen, indicate the worst grade of muscle strength during course (See Appendix 1. Assessment of Muscle Strength)
<table>
<tr><th>R = right; L = left</th><th>1.
R Leg</th><th>2.
L Leg</th><th>3.
R Arm</th><th>4.
L Arm</th></tr>
<tr><td>A-i Qualitative Muscle Strength:
N=normal; W=weak; ND=not documented</td><td></td><td></td><td></td><td></td></tr>
<tr><td>A-ii. Quantitative Muscle Strength(0-5):
Lowest recorded score if available</td><td></td><td></td><td></td><td></td></tr>
<tr><td>B. Deep Tendon Reflexes:
A=absent; D=decreased; N=normal;
I=increased; ND=not documented
Leg: Kn=knee; Ank=Ankle
Arm: Bi=biceps; Tri=Triceps;</td><td></td><td></td><td></td><td></td></tr>
</table>
</td>
<td>A=A-1 (bilateral flaccid paralysis) IF:
Both legs and/or both arms are weak or have a quantitative muscle strength <5

A=A-2 (absence of weakness) IF:
Both legs and both arms have qualitatively normal muscle strength or graded strength = 5

B = B-1 IF Deep tendon reflexes are absent or decreased in weak limbs

B = B2 IF absent or reduced tendon reflexes in both legs and/or both arms despite absence of weakness</td>
</tr>
</table>

COVID-19 AESI: Step 2 - Tool Development

B. Tools to facilitate AESI data collection, investigation and assessment

- Data abstraction and interpretation forms (Setting: medical chart review)

Example Guillain Barré Syndrome:

3. Tabular summary of values for all case definition criteria

Case Definition Criteria	Criteria Values
A. Bilateral flaccid weakness	__A-1 (bilateral leg and/or arm weakness) __A-2 No limb weakness __neither A-1/nor A-2
B. Deep tendon reflexes (DTRs)	__B-1(DTRs absent/reduced in weak limbs) __B-2 DTRs absent/reduced but limb weakness __neither B-1/nor B-2
C. Monophasic illness pattern	__Yes __No __Unknown
D. Bilateral ophthalmoparesis	__Yes __No __Unknown
E. Ataxia	__Yes __No __Unknown
F. No altered level of consciousness	__True __Not true __Unknown
G. No corticospinal tract signs	__True __Not true __Unknown
H. No alternate etiology for weakness	__True __Not true __Unknown
I. Electrophysiology	__I-1 Typical for GBS __I-2 Normal or sensory abnormalities only __I-3 Not done, results unavailable/uninterpretable
J. CSF WBC and protein	__J-1 WBC <50/ul/CSF protein elevated __J-2 WBC <50/ul/CSF protein normal/unknown __J-3 LP not done, no results

COVID-19 AESI: Step 2 - Tool Development

B. Tools to facilitate AESI data collection, investigation and assessment

- Data abstraction and interpretation forms (Setting: medical chart review)

Example Guillain Barré Syndrome:

4. Logic to apply criteria values to reach level of certainty

Level of Certainty	4A. GBS	
Level 1	[A = A1] & [B = B1] & [C=YES] AND [H = TRUE] AND [I = I-1] AND [J = J-1]	
Level 2	[A = A1] & [B = B1] & [C=YES] AND [H = TRUE] AND	EITHER [I = I-1] AND [J = J-2 or J-3] OR [I = I-3] AND [J = J-2]
Level 3	[A = A1] & [B = B1] & [C=YES] AND [H = TRUE] AND [I = I-3] AND [J = J-3]	
Level 4	Reported as GBS but Insufficient information available to meet any level of case definition.	
Level 5 (Not a Case)	[NO to A1, B1 or C] AND/OR [H = Not true; i.e. alternative cause for weakness found]	

COVID-19 AESI: Step 2 - Tool Development

B. Tools to facilitate AESI data collection, investigation and assessment

- Data abstraction and interpretation forms (Setting: medical chart review)

Clinical Criteria	
A. Bilateral flaccid weakness	__A-1 (bilateral leg and/or arm weakness) __ A-2 (absence of limb weakness) __ Unable to choose either A-1 or A-2
B. Decreased or absent deep tendon reflexes	__B-1. Reflexes absent or reduced in weak limbs __B-2 Reflexes absent or reduced but absence of weakness __Unable to choose either B-1 or B0=-2
C. Monophasic illness pattern	__YES __ NO __ UNKNOWN
H. No alternative cause for weakness	__True __Not true __Not documented
I. Electrophysiology results	__I-1. Typical for GBS (AIDP, AMAN, AMSAN) __I-2. Normal or sensory abnormalities only __I-3. Not done, results unavailable, inexcitable or unknown pattern
J. Cerebrospinal fluid results	__J-1 WBC < 50/uL and CSF protein elevated __J-2 WBC< 50/uL and CSF protein normal or value unknown __J-3 LP not done OR results unavailable or unknown

Example Guillain Barré Syndrome:

4. Logic to apply criteria values to reach level of certainty

Level of Certainty		
Level 1	[A = A1] & [B = B1] & [C=YES] AND [H = TRUE] AND [I = I-1] AND [J = J-1]	
Level 2	[A = A1] & [B = B1] & [C=YES] AND [H = TRUE] AND	EITHER [I = I-1] AND [J = J-2 or J-3] OR [I = I-3] AND [J = J-2]
Level 3	[A = A1] & [B = B1] & [C=YES] AND [H = TRUE] AND [I = I-3] AND [J = J-3]	
Level 4	Reported as GBS but Insufficient information available to meet any level of case definition.	
Level 5 (Not a Case)	[NO to A1, B1 or C] AND/OR [H = Not true; i.e. alternative cause for weakness found]	

COVID-19 AESI: Step 2 - Tool Development

C. Risk factors and Background Rates

Example Guillain Barré Syndrome:

Risk Factor	Evidence
Age	• Incidence increases about 20% for every 10 years in age after 1st decade
Gender	• Relative to females relative risk in males is 1.78 (95% confidence interval 1.36-2.33)[1]
Comorbidity	• Malignancy, especially Hodgkin's and other lymphomas

Infection	• Antecedent diarrheal or respiratory illness reported in 2/3 of cases [1,3,4]
	  • Campylobacter jejuni the strongest association, and most notable in Asia
	  • Less frequent: influenza, Mycoplasma pneumoniae, HIV, EBV, CMV, enterovirus D68
	  • Hepatitis E associated noted in Netherlands, Bangladesh
	  • Zika and chikungunya infection

Medication / Vaccine	• Rabies vaccine cultured in mammalian brain tissues (e.g. Semple vaccine) • may induce Tcells reactive to myelin basic protein • Pandemic H1N1 vaccines: 1976 - about 1 / 100,000 vaccinated; 2009 – about 1.6 excess cases per million vaccinated • Some seasonal influenza inactivated vaccines - about 1.6 excess cases per million vaccinated • Tetanus toxoid: causality based on a case report of a man who developed GBS 3 times, each following a Tetanus booster
Procedure / Trauma	• Prior surgical procedure – reported following surgery for obesity[1]

COVID-19 AESI: Step 2 - Tool Development

C. Risk factors and Background Rates

Example Guillain Barré Syndrome: Background Rates – by country, stratified by age and sex

Age (years)	Prevots 1997[2] US (Relative Risk M:F)	Olivé 1997[5] Latin America (1989-1991)	Black 2009 Multiple Countries[11]				Sevjar Systematic Review And Meta-analysis[2]
			Brazil	Finland	UK	USA	(13 studies: 2 US, 1 Canada, 1 England, 4 Italy, 4 Spain, 1 Sweden)
<1	0.38 (0.87)						
1	1.3 (0.93)	0 to <15 years: 0.91/100,000		0-17 yrs	0-17 yrs		0-9 years: 0.62
2	1.9 (1.4)						
3	1.7 (0.9)			F: 1.68	F: 0.79		F: 0.45
4	1.9 (1.6)	(Range from low in Peru					
<5	1.4 (1.3)	[0.72]	0.56	M: 0.18	M: 0.70		M: 0.80
5-9	1.4 (1.0)	to high in El Salvador [1.83])	0.47				
10-14	1.7 (0.94)	M:F ratio 1.4 (range 1.2-1.8)	0.37			10-17yrs F: 1.8 M: 2.1	0.75 (F 0.55; M 0.97)
15-19	2.3 (0.67)						
20–29	1.7 (0.91)			18-44yrs F: 1.24 M: 3.02	18-44yrs F: 1.57 M: 1.63	18-25yrs F: 0.4 M: 0.8	0.90 (F 0.66; M 1.18)
30-39	1.9 (1.1)						1.07 (F 0.80; M 1.43)
40-49	2.6 (1.2)					26-62 yrs F: 2.3 M: 3.3	1.29 (F 0.97; M 1.73)
50-59	4.1 (1.2)			45-65yr F3.95 M 7.15	45-65 yrs F: 2.07 M: 2.50		1.54 (F 1.18; M 2.09)
60-69	6.1 (1.4)						1.85 (F 1.42; M 2.54)
70-79	8.6 (1.3)			≥65yrs F: 6.18 M: 10.13	>65yrs F: 2.52 M: 4.57		2.22 (F 1.72; M 3.07)
≥80	5.2 (1.9)						2.66 (F 2.09; M 3.72)
All	3.0 (1.1)						

Vaccine-associated enhanced disease (VAED)
Considerations for COVID-19 vaccine development

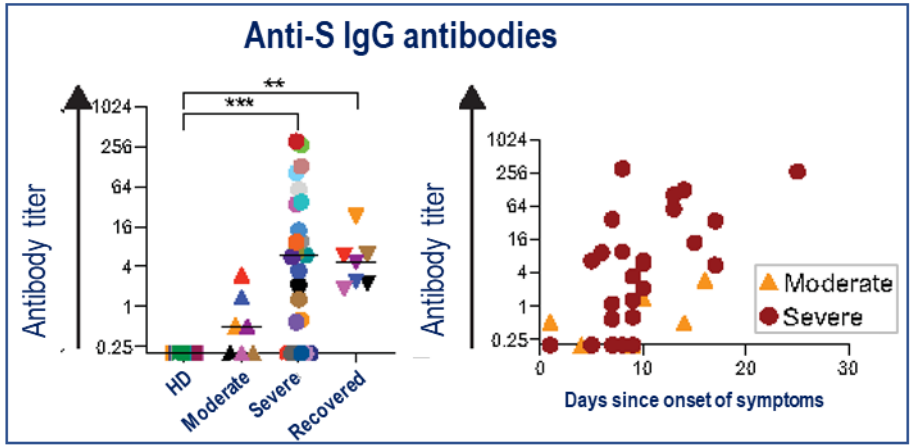
Paul-Henri Lambert
Centre of Vaccinology
University of Geneva

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

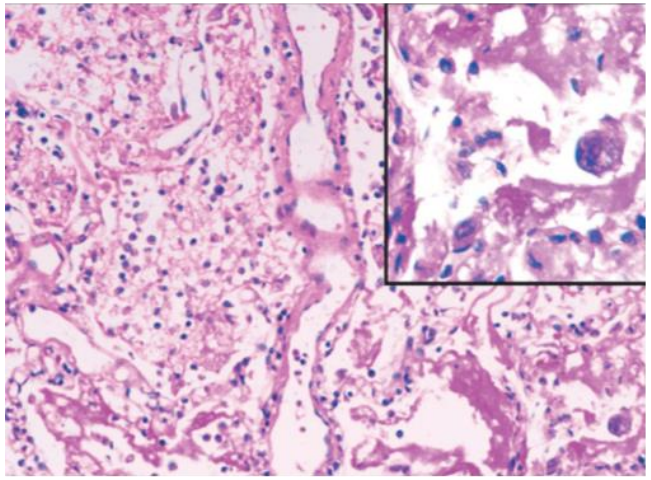
1. COVID-19 often appears as a two-stage disease-
   In the second phase , severe cases are associated with an active immune response: early and higher antibody levels than in mild cases.

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

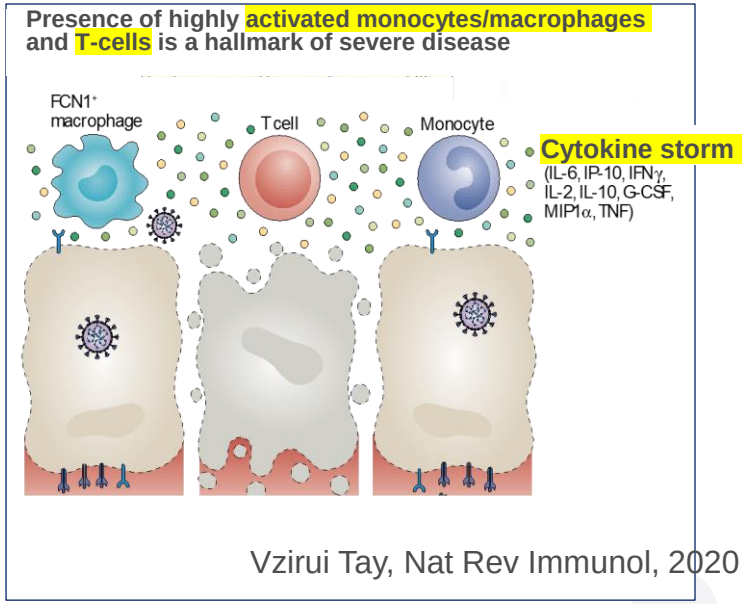
3. In animal models, other coronavirus candidate vaccines (SARS, MERS, FIP) were associated, after challenge, with enhanced disease



Kuri-Cervantes et al. Sci. Immunol. 2020



Lancet Respir Med 2020; 8: 420–22



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]

Can the risk of VAED can be assessed in small animal models?

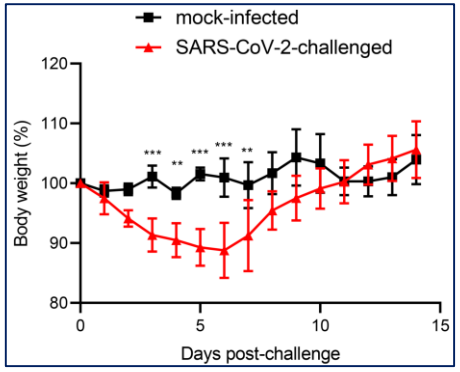
1. SARS vaccines

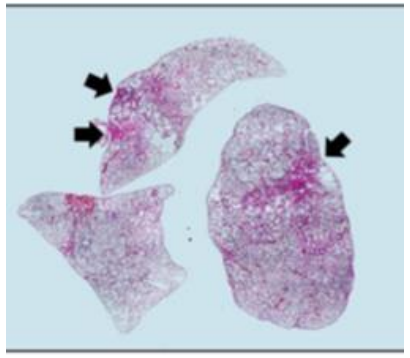
In mice, some vaccines (e.g. inactivated) were associated with post-challenge enhanced disease.
This was considered as a consequence of a dominant Th2 type immune response leading to a massive eosinophil infiltration and inflammation in lungs.
ED was not seen with other vaccines known to drive immune responses towards Th1, e.g. Inactivated vaccine + TLR agonists

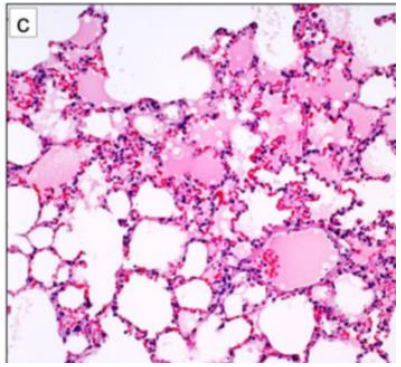
2. COVID-19 vaccines

Murine models require the use of hACE2 transgenic mice, preferably with a 'knocked-in' approach.
Mice are primarily used for immunogenicity and protection studies. No ED after antibody passive transfer.
Ferrets develop only mild COVID-19 disease. Primarily used for immunogenicity studies.

Golden Syrian Hamsters can be infected by SARS-CoV-2.
Now appears now as an excellent model to assess protective efficacy

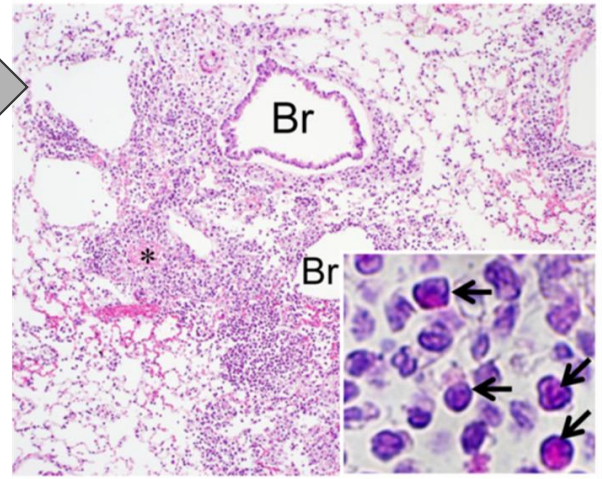






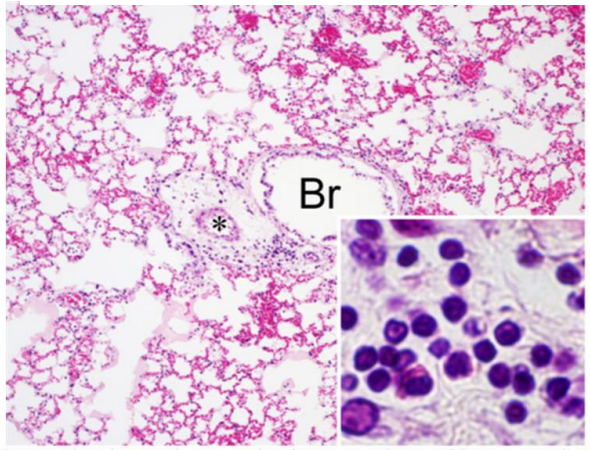
Chan JFW, 2020

UV Inactivat. + SARS Challenge



Highly inflammatory lesions, with dominance of eosinophil infiltration

Control + SARS Challenge



Congestion, hemorrhage, and pulmonary edema with mononuclear cell infiltration

J. Virol. 2014, 88(15):8597

Can the risk of VAED can be assessed in Non-Human Primates?

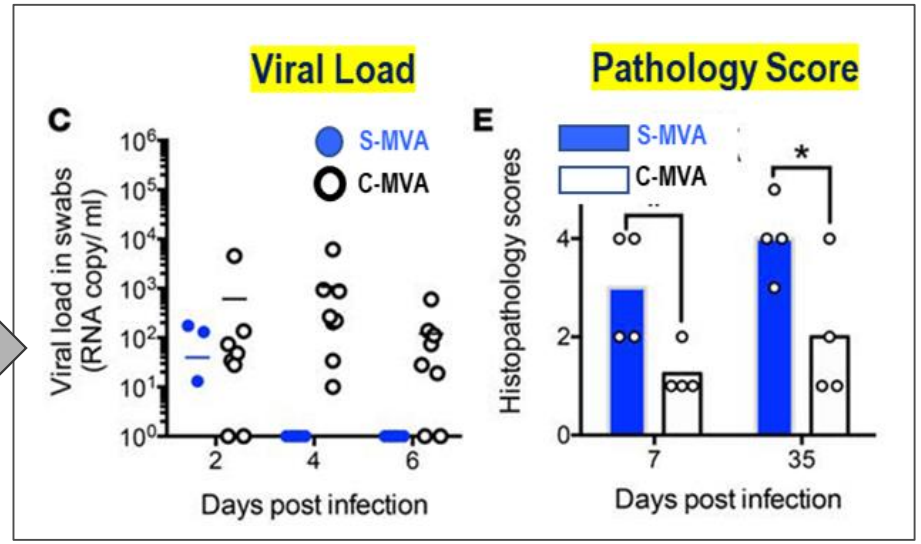
Non-human primates are of particular interest in view of (i) ACE2 homology with hACE2 and (ii) human-like immune responses.

1. SARS vaccines

- Some SARS candidate vaccines were associated with VAED after viral challenge. Massive lung inflammation but eosinophilic infiltrates were not prominent. VAED seen after Formaldehyde Inactivated vaccine and after S-MVA vaccine.
- VAED also seen after passive transfer of anti-S antibody (polyclonal or mabs)

- Mechanisms of VAED in NHP (SARS vaccines)?
  - Associated with partial protection: reduced viral load (no classical ADE)
  - Role of virus binding antibodies,
    - immune complex formation and complement activation
    - Fc-mediated viral capture in monocytes/macrophages
    - Monocyte and T-cell activation

S-MVA (SARS) + Challenge in Rhesus macaques



Liu et al., JCI Insight 2019

Are VAED observations with SARS vaccines relevant for COVID-19 vaccines?

SARS-CoV-2 challenge leads to some lung pathology, with mild clinical signs, including CT Scan visible lesions, in Rhesus macaques and African Green Monkeys.

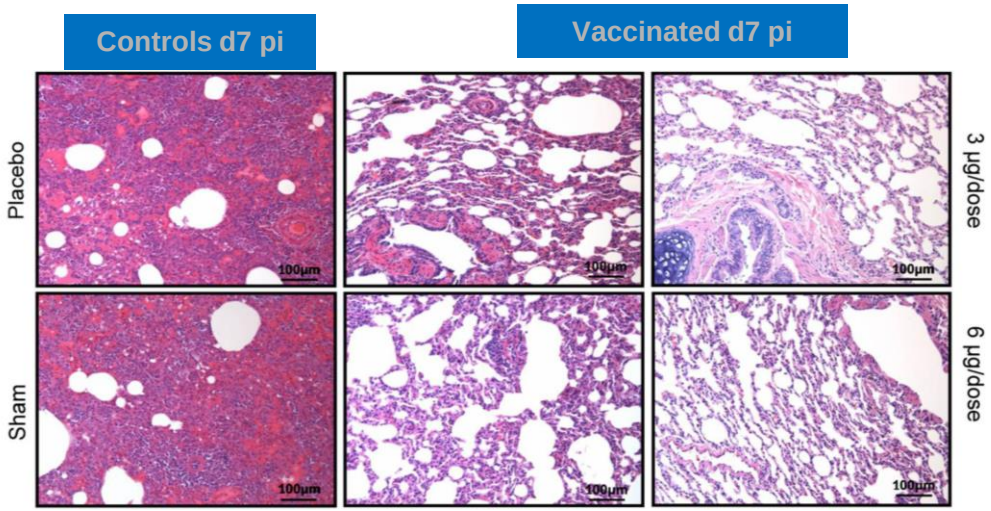
So far, VAED was not reported after challenge in NHP immunized with tested COVID-19 vaccines
e.g.

- **mRNA**
- **BPL Inactivated SARS-CoV2**
- **Adeno-5 or -26 vectors**
- **ChAdOx1 vector**
- **VSV vector**

but,

- **short interval between last dose and challenge**
- **short duration of follow-up post infection**
- **very limited number of animals**

Vaccine efficacy in Rhesus macaques of an Inactivated SARS-CoV-2 vaccine



No evidence of Enhanced Disease

Q. Gao et al., Science 2020

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

Concluding remarks

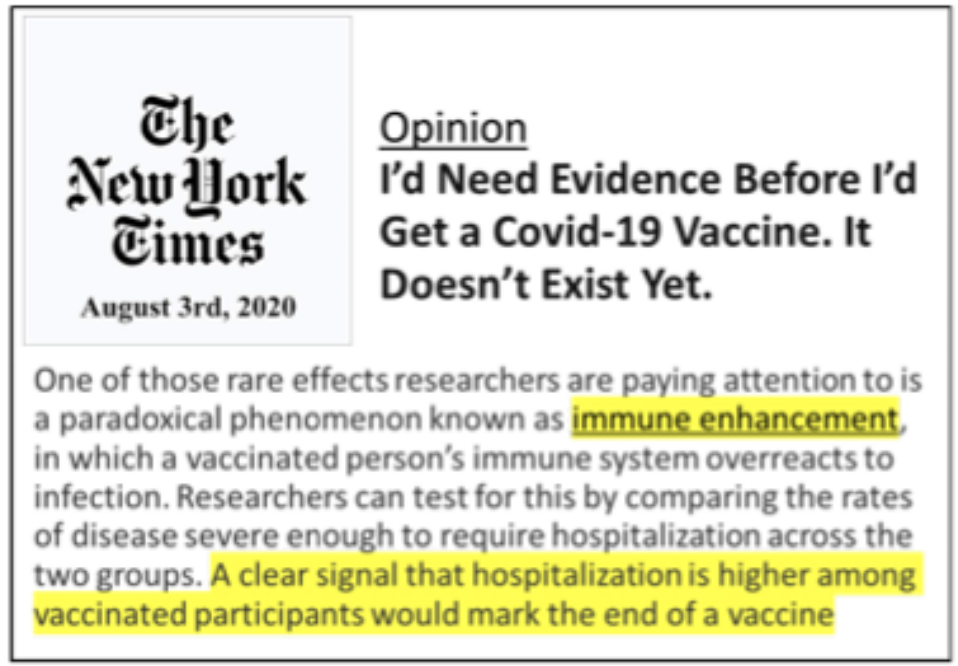
- the demonstration of disease enhancement with any candidate vaccine after viral challenge in animal models should raise attention during clinical development of a COVID-19 vaccine.
- So far, no V-MED was reported with COVID-19 candidate vaccines
- Increasing media attention to the risk of V-MED
- Public concerns regarding disease enhancement may affect the acceptance of COVID-19 vaccines, particularly for low risk individuals


TheScientist
EXPLORING LIFE, INSPIRING INNOVATION

COVID-19 Vaccine Researchers Mindful of Immune Enhancement

There is no evidence that any of the coronavirus vaccines in development worsen a coronavirus infection rather than confer immunity to it, but the phenomenon is something scientists are closely monitoring.

Katarina Zimmer


The New York Times

August 3rd, 2020

Opinion

I'd Need Evidence Before I'd Get a Covid-19 Vaccine. It Doesn't Exist Yet.

One of those rare effects researchers are paying attention to is a paradoxical phenomenon known as immune enhancement, in which a vaccinated person's immune system overreacts to infection. Researchers can test for this by comparing the rates of disease severe enough to require hospitalization across the two groups. A clear signal that hospitalization is higher among vaccinated participants would mark the end of a vaccine

Brighton Collaboration Case Definitions Vaccine-associated enhanced disease (VAED) & other Adverse Events of Special Interest (AESI)

Flor Munoz, MD

Associate Professor of Paediatrics, Infectious Diseases

Baylor College of Medicine

Houston, Texas, US

CASE DEFINITIONS IN DEVELOPMENT

Case Definition	Timeline
VAED / VAERD	March – August 2020
MIS-C	July – October 2020
ARDS	July – October 2020
ACUTE CARDIOVASCULAR INJURY	August – November 2020
COAGULOPATHY	August – November 2020
Calls out for: AKI, Acute Hepatic Injury, Anosmia	Plan to organize for September – December 2020

VAED Working Group Members

- Task lead/Coordinator: **Flor Munoz, MD** – Ped ID, Vaccine safety, Baylor College of Medicine, USA
- **Matthew Dudley** –Literature review support, Johns Hopkins School of Public Health, USA
- **Paul Henri Lambert** – Immunology, Geneva, Switzerland
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- **Fernando Polack** – Pediatric ID, RSV enhanced disease, Argentina and Vanderbilt University
- **Brian Ward** – Immunology Adult ID, McGill University, Canada
- **Barney Graham** – Vaccine development, NIAID, NIH, USA
- **Eva Van Braeckel –** Adult pulmonologist, Ghent University Hospital, Belgium
- **Jonathan Spergel** – Immunology, Children's Hospital of Philadelphia, PA, USA
- **Stanley Perlman** – Immunopathology, University of Iowa, USA
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- **Jacob Kramer –** CEPI scientist, UK

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- **Lorena Tapia**, MD, Pediatric ID, MISC clinical team, Chile

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- **WG Coordinator Nathan Serazin** – Pediatric Intensivist – Baylor College of Medicine, USA
- **WG Coordinator: Bassey Edem** – Vaccinology, epidemiology, clinical trials, LSHTM, The Gambia
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- **Sarah Williams** – Internal Medicine, pulmonary critical care, U. Maryland, USA
- **Kathy Edwards** – Pediatric ID, vaccinology, Science Board BC, Vanderbilt University, USA
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- **Manoj Das** – Pediatrics, vaccine safety, INCLEN, India
- **Maja Subej** – Epidemiology, GAIA definitions, Slovenia
- **Shreemanta Parida** – ID, Immunology, Vaccinology, TB, Germany
- **Anh Wartel** – Vaccine research and development, Seoul, South Korea
- **Paula Ortiz** – Pediatric Intensivist, Chile
- **Helen Maltezou** – Pediatric ID, epidemiology, vaccinology, Greece

VAED Timeline

Task	Anticipated	Status
Selection of WG members, Logistics of WG, Invitation to participate in the WG	March 2nd	Completed
Confirm WG membership, participate in introductory TC, participate in ED Consensus Meeting (March 12-13) by videoconference	March 15th	Completed
WG TC to agree on scope of work, outline, assignments and timelines	March 20th	Completed
First draft of manuscript	April 30th	Completed July 2020
Manuscript draft for Expert and BC Peer review (Neal Halsey, Kanta Subbarao, Kathy Edwards)	July 1st, 2020	Completed August 2020
Final manuscript for submission for publication	August 31st, 2020	Plan to finalize early September after discussion with authors

Conference calls Completed to date (7): March 10th, March 17th, March 31st, April 14th , April 29th May (x1), August (x1), September (x1)

Case Definition – Brighton Process

Objectives

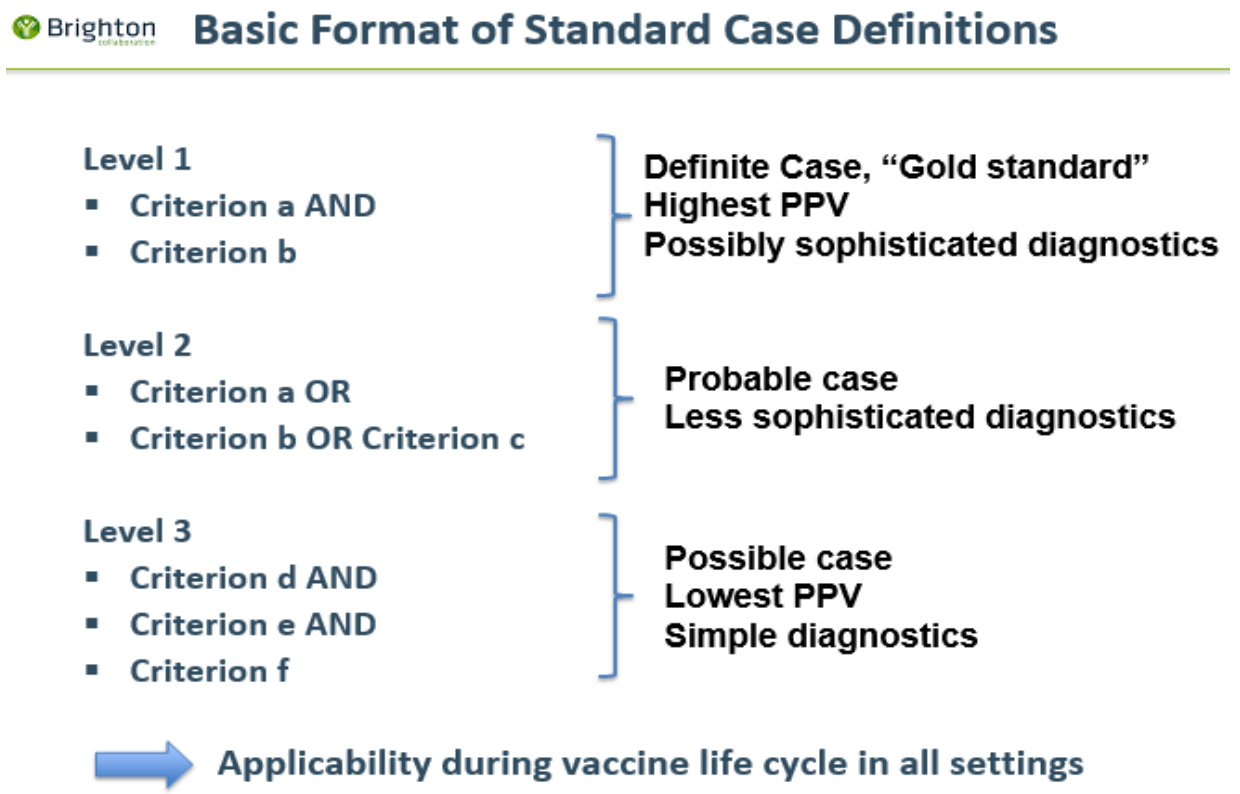
- Term and scope of the definition
  - Vaccine associated enhanced disease (VAED)
  - Vaccine associated enhanced respiratory disease (VAERD)

Literature review

Outline of manuscript

Assignment of topics

Development of Case Definition



VAED Decisions on Case Definition

Various pathways have been identified leading to disease enhancement

	Antibody-mediated		T cell–mediated
	ADE	VAERD	VAERD
Mechanism	Fc-mediated increase in viral entry	Immune complex formation and complement deposition	T_H2-biased immune response
Effectors	Macrophage activation and inflammatory cytokines	Complement activation and inflammatory cytokines	Allergic inflammation and T_H2 cytokines
Mitigation	Conformationally correct antigens and high-quality neutralizing antibody		T_H1-biasing immunization and $CD8^+$ T cells

Graham BS. Science 368 (6494), 945-46, May 2020.

Decisions on case definition

Vaccine associated enhanced disease (VAED)

- May occur in persons who receive a vaccine and who are subsequently infected with the pathogen that the vaccine is meant to protect against (assumes previously naïve vaccine recipients)
- May present as severe disease or modified/unusual clinical manifestations of a known disease
- May involve one or multiple organ systems (Lungs, heart, renal, hepatic, CNS, etc)

Vaccine associated enhanced respiratory disease (VAERD)

- Refers to the respiratory tract manifestations of vaccine associated enhanced disease

Approach for identification of cases in the context of clinical trials:

Clinical presentation complemented by Epidemiology and laboratory evaluation

Triggers to consider VAED/VAERD

Confirmed “severe” infection

Hospitalization

ICU admission

Death

Chart 1: The NEWS scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

SOFA SCORE

Variables	Score[a] 0	1	2	3	4
Respiratory					
$Pao_2:Fio_2$[b] or $Spo_2:Fio_2$[c]	≥400	300-399	200-299	100-199 With respiratory support	<100 With respiratory support
	≥292	264-291	221-264	148-220 With respiratory support	<148 With respiratory support
Coagulation					
Platelet count, $\times 10^3/\mu L$	≥150	100-149	50-99	20-49	<20
Hepatic					
Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular					
MAP by age group or vasoactive infusion, mm Hg or μg/kg/min[d]					
<1 mo	≥46	<46	Dopamine hydrochloride ≤5 or dobutamine hydrochloride (any)	Dopamine hydrochloride >5 or epinephrine ≤0.1 or norepinephrine bitartrate ≤0.1	Dopamine hydrochloride >15 or epinephrine >0.1 or norepinephrine bitartrate >0.1
1-11 mo	≥55	<55			
12-23 mo	≥60	<60			
24-59 mo	≥62	<62			
60-143 mo	≥65	<65			
144-216 mo	≥67	<67			
>216 mo[e]	≥70	<70			
Neurologic					
Glasgow Coma Score[f]	15	13-14	10-12	6-9	<6
Renal					
Creatinine by age group, mg/dL					
<1 mo	<0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥1.6
1-11 mo	<0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥1.2
12-23 mo	<0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥1.5
24-59 mo	<0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥2.3
60-143 mo	<0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥2.6
144-216 mo	<1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥4.2
>216 mo[e]	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5

CD: Vaccine Associated Enhanced Disease (VAED) or Vaccine Associated Respiratory Disease (VAERD): Disease occurring in a previously naive vaccinated individual infected with the pathogen targeted by the vaccine

Confirmed infection with disease manifestations involving one or more organ systems

AND

Increased severity of disease relative to known manifestations of natural disease in a specific population → **Clinical severity core**

AND

Increased frequency of event when compared to a non-vaccinated population → **Study control group Background rates**

AND

Evidence of **immunopathology** in target organs involved → **Supporting laboratory or pathology findings**

AND

No other identified alternative etiology

Diagnostic Tools for assessment of VAED

Evidence inadequate or unbalanced neutralizing antibody responses

- Low or inappropriate total binding (IgG, IgM, IgA) antibody titers
- Low neutralizing antibody titers
- Low ratio neutralizing:binding antibody
- Low absolute affinity of IgG antibody to receptor binding domain (RBD)
- Lack of acquisition or loss of affinity of IgG to RBD
- Increased viral load

Evidence of inadequate or inappropriately biased cellular immune responses

- Lymphopenia or lymphocytosis
- High CD4 lymphocyte subset and Low CD8 lymphocyte subset
- Th2 (IL-4, IL-5, IL-13) CD4 T cell predominant response over Th1 (INFg, TNF) responses (testing in vitro stimulation with viral peptides or proteins, ELISPOT, or intracellular cytokine staining assays).
- Low virus-specific cytotoxic T-cells (CTL)

Diagnostic Tools for assessment of VAED

Evidence of exuberant inflammatory responses

- Elevated IL-1, IL-6, IL-8
- Increased pro-inflammatory chemo/cytokines: INF-g, type 1-INF, TNF, CCL2, CCL7
- Reduced expression of type I interferons (eg. IFN-α, INF-b)
- Elevated C-reactive protein, Ferritin, Lactate dehydrogenase (LDH), D-dimers

Evidence of immunopathology in target organs involved, by histopathology

- Present or elevated tissue eosinophils in tissue
- Elevated pro-inflammatory Th2 cytokines in tissue (IL4, IL5, IL10, IL13)
- C4d tissue deposition (evidence for complement activation through immune complex deposition)
- C1q assessments of immune complexes in fluids
- Low C3 levels as evidence complement consumption

Other factors to consider

Differentiate Vaccine Failure vs. VAED

Age - expected severity by age group

Time of onset after new infection

Time of onset after vaccination

Control for confounders/comorbidities

- Co-infections, comorbidities, drug effects, toxicities

Circulation of the target pathogen

- endemic
- seasonal
- sporadic

Clinical course/Progression of symptoms

- Outcomes: hospitalization - death
- Worsening/deterioration over time
- Prolonged clinical course / long term sequelae
- Complications – new morbidities/diagnoses

Geographic and population specific variability in vaccine responses

  - Genetic factors
  - Nutritional status

Duration of follow up after vaccination - followed by population-based surveillance for disease.

ARDS
Level 1 Certainty: Confirmed ARDS

Proposed Case Definition for ARDS		
Category	*Adult*	*Pediatric*
Confirmed ARDS	**<u>Berlin Criteria</u>** 1) Timing: within 1 week of known clinical insult 2) Imaging: CXR with bilateral chest opacities not explained by other process 3) Origin of edema: not related to fluid overload or cardiogenic edema 4) Positive Pressure Requirement: - CPAP >/= 5 cmH20 5) Criteria for classification of hypoxemia - PaO2/FiO2 Ratio	**<u>PALICC Criteria</u>** 1) Timing: within 1 week of known clinical insult 2) Imaging: CXR with bilateral infiltrates consistent with parenchymal lung disease 3) Origin of edema: new infiltrate not related to fluid overload or cardiogenic edema 4) Positive Pressure Requirement - CPAP/= 5cm H20 5) Criteria for classification of hypoxemia - PaO2/FiO2, SpO2/Fio2 ratio for non-intubated patients - OI/OSI for intubated patients

CDC

Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

[i]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
[ii]Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

WHO

Preliminary case definition[a]

Children and adolescents 0–19 years of age with fever ≥ 3 days

AND two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

RCPCH

Case definition:

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (see listed in Appendix 1). This may include children fulfilling full or partial criteria for Kawasaki disease.

2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).

3. SARS-CoV-2 PCR testing may be positive or negative

MISC case definition “template”:
LOC 1 - HIGHEST LEVEL OF CERTAINTY

Children/adolescent <xx years (or all humans?) with fever ≥ xx days

AND

xx of the following clinical features:

*list of clinical features

AND

xx measures of disease activity:

*list of measurable disease markers

AND

xx evidence of inflammation as indicated by:

*options to confirm inflammatory state

AND

no other obvious infectious or other source for the presentation

AND

evidence of infection/exposure to SARS-CoV-2 indicated by options for infection/exposure

METHODS:

WG SURVEY + VOTE

and

CONSENSUS

Q&A I

Brighton Collaboration Standardized Templates for Benefit-Risk Assessment of VAccines by TechnOlogy (BRAVATO) Working Group* = Safety Templates

Robert T Chen, MD MA

Scientific Director
Brighton Collaboration

**** Previously Viral Vector Vaccines Safety Working Group (V3SWG)***

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)

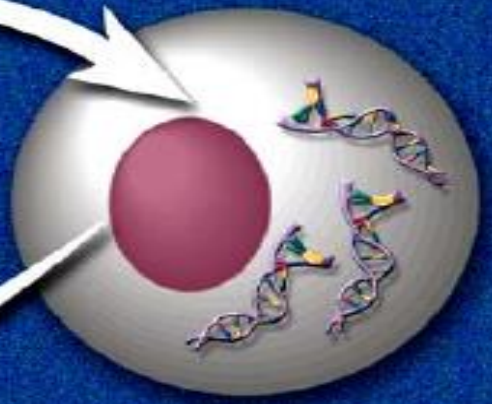
*Hance BJ, Chess C, Sandman P; Industry risk communication manual,Chelsea, MI; Lewis Publishers1990

CDC™

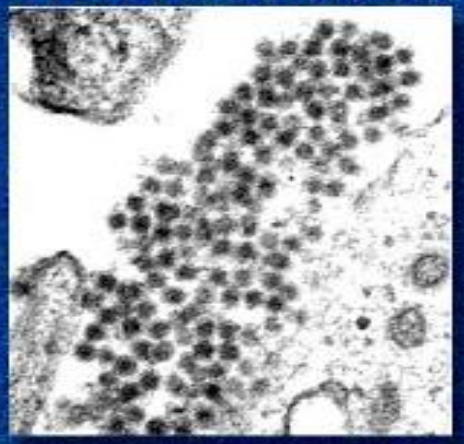
Construction of Chimeric Virus

Full length cDNA → SP6 transcribe to RNA

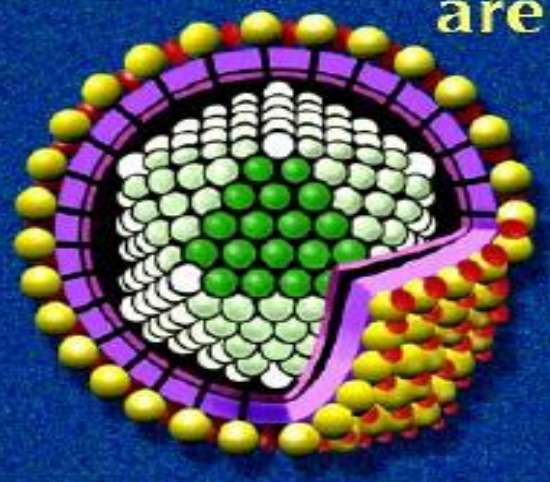
Transfect RNA
(Electroporation)



Grow virus
in Vero cell culture



Envelope
proteins
are JE



High tech
Many acronyms!!

Replicative ‘engine’ is YF 17D

Brighton Collaboration
Viral Vector Vaccines Safety Working Group (V3SWG)

- Formed in 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
- V3SWG 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 V3SWG + BC for peer review & publish + update

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

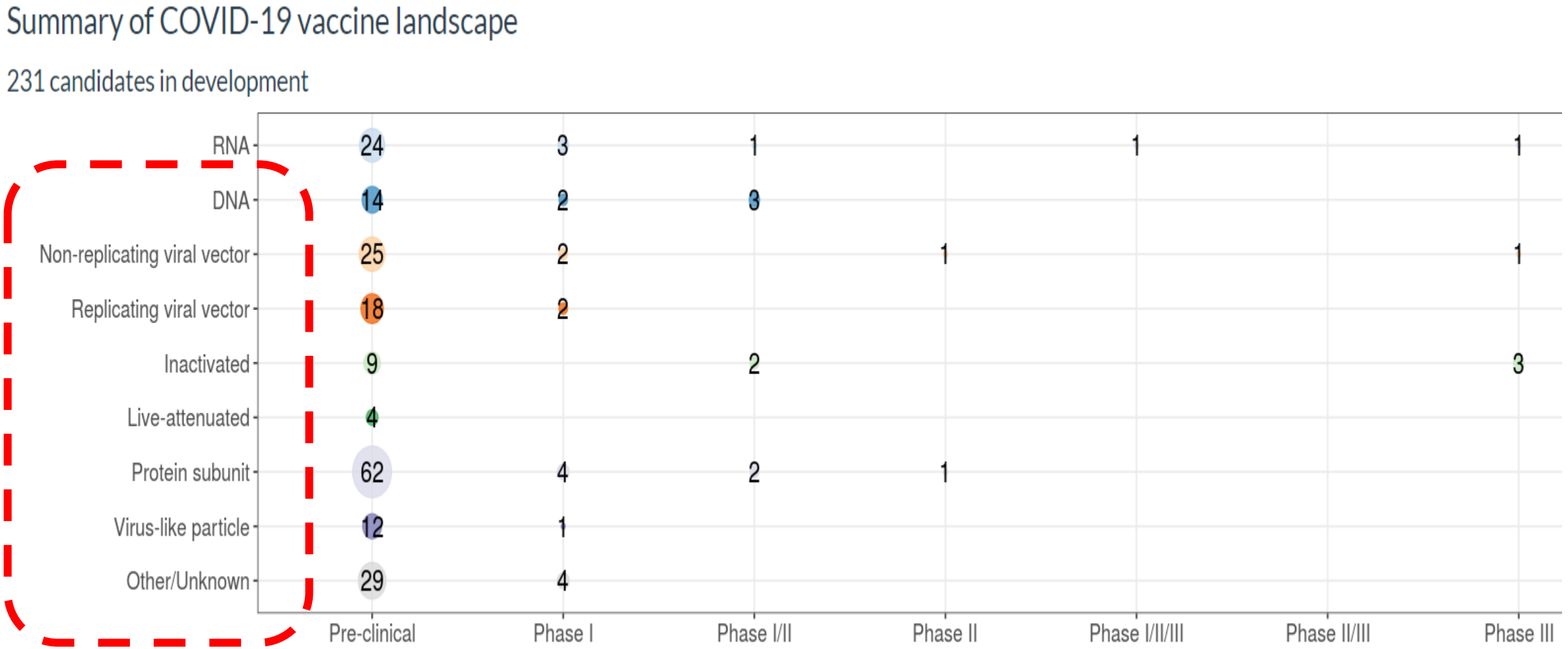
V3SWG Template Sect.1-3: Characteristics of Wild Type Agent

1. AUTHORSHIP
   - 1.1 Author
   - 1.2 Date completed/updated
2. BASIC VECTOR INFORMATION
   - 2.1 Vector name
   - 2.2 Vector origin (Family/Genus/Species)
   - 2.3 Vector replication in humans (replicating or non-replicating)
3. CHARACTERISTICS OF WILD TYPE VIRUS FROM WHICH VECTOR IS DERIVED
   - 3.1 Name (family/genus/species)?
   - 3.2 Natural host?
   - 3.3 How transmitted?
   - 3.4 Latent/persistent infection?
   - 3.5 Replicate in nucleus?
   - 3.6 Risk of integration in human genome?
   - 3.7. List any disease manifestations caused (strength of evidence, severity, and duration):
     - healthy natural host
     - healthy human host
     - in human Immunocompromised
     - in breast milk, human neonates, infants, children
     - during pregnancy and unborn in humans
     - any other special populations
   - 3.8. What cell types are infected and what receptors are used in the natural host and in humans?
   - 3.9 Mechanisms of immunity?
   - 3.10 Disease enhancement in vitro, animal models, human hosts
   - 3.11 Disease enhancement possible contributor to wildtype disease pathogenesis
   - 3.12 Background prevalence natural immunity?
   - 3.11 Vaccine available vs. wild-type virus? If yes, target pop & prevalence Immunity?
   - 3.12 Treatment available for wild disease?

Monath T. *et al.* Vaccine X 2019; PMID:31384731

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]

COVID-19 VACCINE LANDSCAPE August 16th, 2020



From London School of Hygiene Vaccine tracker

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

Nucleic Acid (DNA and RNA)

4. CHARACTERISTICS OF VACCINE TRANSGENE AND EXPRESSION

4.1 Nature of nucleic acid platform (DNA - synthetic, bacterial, plasmid, linear, >1 type/molecule, other; RNA- messenger, self-replicating, other)

4.2 Gene(s) incorporated into the vaccine

4.3 Factors enhancing/controlling gene expression

4.4 Non-expressed features impacting efficacy

4.5 Other sequence features that may impact safety

4.6 Transgene likely to induce immunity to all strains/genotypes of target pathogen

4.7 Immune response to vaccine

Protein Vaccine Template

4. CHARACTERISTICS OF ANTIGEN

4.1 Vaccine likely to induce immunity to all strains/genotypes of target pathogen

4.2 Immune response to vaccine

4.3 Homology in sequence of vaccine antigen and human proteins

5. ADJUVANT

5.1 Type, if tested in humans, commercialized, vaccines formulated with adjuvant

5.2 Novel adjuvant mechanism of action

5.3 Formulation with antigen

5.4 Impact on safety profile of vaccine

5.5. Safety findings

Inactivated Viral Vaccine

4. CHARACTERISTICS OF ANTIGEN

4.1 Virus strains, sequence (including homology among strains), source, propagation, disruption, whole virus or subunit/subvirion (if applicable)?

4.2 Vaccine likely to induce immunity to all strains/genotypes of target pathogen

4.3 Immune response to vaccine

5. INACTIVATION METHOD

5.1 Method's (e.g., thermal, beta propiolactone, UV, formaldehyde) and potential impact on safety

5.2 At what stage of the downstream process is inactivation/s performed and why?

5.3 QC/confirmation method/log reduction in viability

5.4 Could the inactivation method's compromise the antigenic structure of the vaccine (e.g., conformation of the protein antigens)

Live Attenuated Viral Vaccine

4. CHARACTERISTICS OF THE VECTOR FROM WHICH VACCINE(S) MAY BE DERIVED

4.1 Source of the vector (e.g. isolation, synthesis)

4.2. Basis of attenuation/inactivation of the wild type virus to create the vector?

4.3. Replication, transmission and pathogenicity of the vector in humans in:

In healthy people? In immunocompromised people? In breast milk, neonates, infants, children? During pregnancy and in the fetus? In gene therapy experiments? In any other special populations?

4.4. Is the vector replication-competent in non-human species?

4.5. Risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?

4.6 Vector genetically stable in vitro and/or in vivo?

4.7. Potential for shedding and transmission, including arthropod borne transmission, to humans or other species?

4.8. Does the vector establish a latent or persistent infection?

4.9. Does the vector replicate in the nucleus?

4.10. What is the risk of integration into the human genome?

Conclusion

- Standardized templates for vaccine technology platforms prepared to describe key considerations for benefit-benefit assessment
- May facilitate key stakeholders to anticipate potential safety issues and interpret or assess safety data
- May help improve communication and public acceptance of licensed vaccines
- CEPI using templates for its COVID-19 + other vaccines
- WHO/GACVS recommend use as it "offers a structured approach to evaluating safety."

Current BRAVATO Working Group Members

- **Robert Chen**, Brighton Collaboration
- **Richard Condit**, U. of Florida
- **Stephen Drew**, USA
- **Jean-Louis Excler**, IVI
- **Pat Fast**, IAVI/Stanford U.
- **Marc Gurwith**, Brighton Collaboration
- **Denny Kim**, Janssen
- **Najwa Khuri**, U. of Jordan
- **Bettina Klug**, Paul-Ehrlich-Institut
- Task Lead **Sonali Kochhar**, U. of Washington
- **Tamala Mallet Moore**, Sanofi
- Coordinator: **Emily Smith**, Brighton Collaboration
- **Jonathan Smith**, VLP Therapeutics
- **Tom Monath**, Crozet Biopharma
- **Jim Robertson**, UK
- **George Pavlakis**, NIH
- **Emmanuel Vidor**, Sanofi
- **Mike Whelan**, CEPI
- **David Wood**, WHO

DSMB Pool and Meta-DSMB

Cornelia Dekker, MD

DSMB Pool and 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.

Meta-DSMB: What data are requested from sponsors?

- Study protocols and CRFs should be shared with the liaison Meta-DSMB members so they can understand the study and data collection (Note: Meta-DSMB members will not approve protocols)

- Names of study DSMB members so that Meta-DSMB liaison can establish communication.

- The Meta-DSMB liaison member would have access to the same safety data as the sponsor DSMB Members including aggregate **blinded** data and DSMB minutes. Safety would normally be stratified by “group A” versus “group B” by outcome.

Additional **unblinded** data or patient level data would NOT be requested unless there was a specific safety concern. This would not be routine and would be by specific request of the sponsor and their DSMB.

Meta-DSMB: Two Possible Scenarios

•**Scenario 1**: In case a **signal across the platforms/vaccines** is discovered by the Meta-DSMB, it will inform SPEAC, CEPI, relevant study DSMBs and sponsors as soon as possible but within two working days at most.

- Contact with sponsor(s)' DSMB would be through the Meta-DSMB liaison.
- Contact with the sponsor and CEPI will be through SPEAC.
- Meta-DSMB would describe the concern and if appropriate make recommendations for any required actions.

•**Scenario 2:** In case of a **signal in one trial**: CEPI can request an opinion/review from Meta-DSMB who can query other related clinical trial sponsor DSMBs regarding any information they may have related to this issue.

- This request could also come from a sponsor or sponsor's DSMB.
- The Meta-DSMB would offer an opinion but any decision to stop or continue a study would be at the discretion of the sponsor DSMB.

Current Status: The Meta-DSMB

SPEAC Meta-DSMB

- SPEAC is providing liaison observer members for each CEPI funded vaccine trial.
- Liaisons 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: 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.
- One member is assigned per sponsor.
- Group has now met on 3 occasions to review progress on ongoing protocols.

Q&A II

Questions?

Email: *rtchen1135@gmail.com*