COVID-19 vaccine-related adverse events of special interest (AESIs): Case Definition

Omar Okasha

Date: 17-March-2021

Agenda

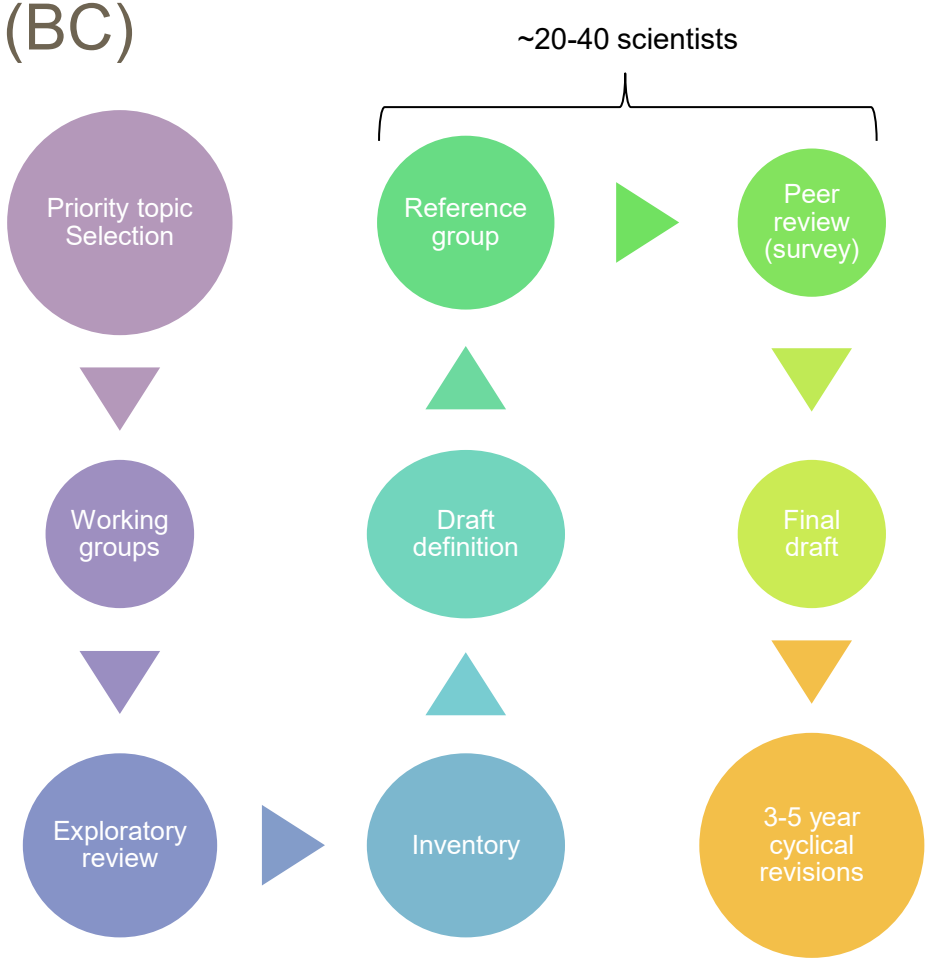
- Why standardize case definitions of AESIs?
- The Brighton Collaboration (BC)
  - Structure
  - Practical applications
  - COVID-19 AESIs: Landscape of case definitions
  - Case study

Rationale

- Unlike AEFI, case definitions are **critical** component in AESI surveillance
- Variations in case definitions across studies/surveillance systems lead to inconsistent findings (e.g., 120 vaccine safety studies using 9 different fever cut-off temperatures)
- A standardized case definition is:
  - *A globally harmonized set of criteria for **the identification** and **assessment** of a given AESI, **including guidelines for data collection, analysis, and presentation***
- Standardization enables comparability of vaccine safety data from different study designs**, including clinical trials and observational studies.**

The Brighton Collaboration (BC)

- Aims to provide standardized, validated and objective methods for monitoring safety profiles and benefit/risk ratios of vaccines.
- Independent body (since 2000) with >500 experts from >50 countries
- currently funded by CEPI, with many partners incl. WHO, EMA and FDA
- Workflow to develop BC case definitions includes **8 steps**

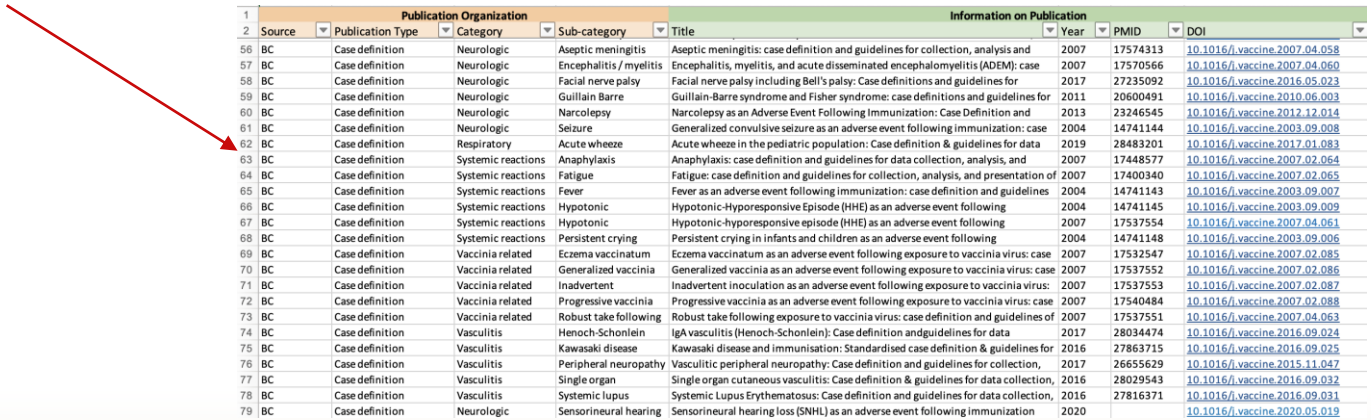


BC's case definitions

- **Structured, 3-component document:**
  - **Preamble (**Explains decisions made on case definition)
  - **Body of the case definition itself**
  - **Guidelines (data collection, analysis and presentation)**
- Mostly not based on the classic "definite, probable, and possible" public health case definitions:
  - **Not** intended to be used as a filter, as even those with lowest certainty should be analyzed

Practical application of case definitions

- Developing data collection forms to assure that prospectively collected information on a given AESI will reach a sufficient level of certainty
- In surveillance systems and epidemiologic studies, the documents can be used to guide follow-up on reported cases, thus ensuring collection of complete information
- A complete list of published BC's case definitions can be found on their website, at https://brightoncollaboration.us/category/pubs-tools/case-definitions/



	Publication Organization				Information on Publication			
2	Source	Publication Type	Category	Sub-category	Title	Year	PMID	DOI
56	BC	Case definition	Neurologic	Aseptic meningitis	Aseptic meningitis: case definition and guidelines for collection, analysis and	2007	17574313	10.1016/j.vaccine.2007.04.058
57	BC	Case definition	Neurologic	Encephalitis / myelitis	Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case	2007	17570566	10.1016/j.vaccine.2007.04.060
58	BC	Case definition	Neurologic	Facial nerve palsy	Facial nerve palsy including Bell's palsy: Case definitions and guidelines for	2017	27235092	10.1016/j.vaccine.2016.05.023
59	BC	Case definition	Neurologic	Guillain Barre	Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for	2011	20600491	10.1016/j.vaccine.2010.06.003
60	BC	Case definition	Neurologic	Narcolepsy	Narcolepsy as an Adverse Event Following Immunization: Case Definition and	2013	23246545	10.1016/j.vaccine.2012.12.014
61	BC	Case definition	Neurologic	Seizure	Generalized convulsive seizure as an adverse event following immunization: case	2004	14741144	10.1016/j.vaccine.2003.09.008
62	BC	Case definition	Respiratory	Acute wheeze	Acute wheeze in the pediatric population: Case definition & guidelines for data	2019	28483201	10.1016/j.vaccine.2017.01.083
63	BC	Case definition	Systemic reactions	Anaphylaxis	Anaphylaxis: case definition and guidelines for data collection, analysis, and	2007	17448577	10.1016/j.vaccine.2007.02.064
64	BC	Case definition	Systemic reactions	Fatigue	Fatigue: case definition and guidelines for collection, analysis, and presentation of	2007	17400340	10.1016/j.vaccine.2007.02.065
65	BC	Case definition	Systemic reactions	Fever	Fever as an adverse event following immunization: case definition and guidelines	2004	14741143	10.1016/j.vaccine.2003.09.007
66	BC	Case definition	Systemic reactions	Hypotonic	Hypotonic-Hyporesponsive Episode (HHE) as an adverse event following	2004	14741145	10.1016/j.vaccine.2003.09.009
67	BC	Case definition	Systemic reactions	Hypotonic	Hypotonic-hyporesponsive episode (HHE) as an adverse event following	2007	17537554	10.1016/j.vaccine.2007.04.061
68	BC	Case definition	Systemic reactions	Persistent crying	Persistent crying in infants and children as an adverse event following	2004	14741148	10.1016/j.vaccine.2003.09.006
69	BC	Case definition	Vaccinia related	Eczema vaccinatum	Eczema vaccinatum as an adverse event following exposure to vaccinia virus: case	2007	17532547	10.1016/j.vaccine.2007.02.085
70	BC	Case definition	Vaccinia related	Generalized vaccinia	Generalized vaccinia as an adverse event following exposure to vaccinia virus: case	2007	17537552	10.1016/j.vaccine.2007.02.086
71	BC	Case definition	Vaccinia related	Inadvertent	Inadvertent inoculation as an adverse event following exposure to vaccinia virus:	2007	17537553	10.1016/j.vaccine.2007.02.087
72	BC	Case definition	Vaccinia related	Progressive vaccinia	Progressive vaccinia as an adverse event following exposure to vaccinia virus: case	2007	17540484	10.1016/j.vaccine.2007.02.088
73	BC	Case definition	Vaccinia related	Robust take following	Robust take following exposure to vaccinia virus: case definition and guidelines of	2007	17537551	10.1016/j.vaccine.2007.04.063
74	BC	Case definition	Vasculitis	Henoch-Schonlein	IgA vasculitis (Henoch-Schonlein): Case definition andguidelines for data	2017	28034474	10.1016/j.vaccine.2016.09.024
75	BC	Case definition	Vasculitis	Kawasaki disease	Kawasaki disease and immunisation: Standardised case definition & guidelines for	2016	27863715	10.1016/j.vaccine.2016.09.025
76	BC	Case definition	Vasculitis	Peripheral neuropathy	Vasculitic peripheral neuropathy: Case definition and guidelines for collection,	2017	26655629	10.1016/j.vaccine.2015.11.047
77	BC	Case definition	Vasculitis	Single organ	Single organ cutaneous vasculitis: Case definition & guidelines for data collection,	2016	28029543	10.1016/j.vaccine.2016.09.032
78	BC	Case definition	Vasculitis	Systemic lupus	Systemic Lupus Erythematosus: Case definition and guidelines for data collection,	2016	27816371	10.1016/j.vaccine.2016.09.031
79	BC	Case definition	Neurologic	Sensorineural hearing	Sensorineural hearing loss (SNHL) as an adverse event following immunization	2020		10.1016/j.vaccine.2020.05.019

Practical application of case definitions

- Some AESIs are published with “companion document”, which includes:
  - Risk factors, background rates, diagnostic/MedDRA codes, and key caveats
  - Tools to facilitate capturing the specific clinical data needed to meet AESI case definitions:
    - Data abstraction and interpretation forms
    - Tabular checklists
    - Tabular logic and pictorial decision tree algorithms

BC's COVID-19 AESIs case definition landscape* (1/3)

AESI included because they have a proven or theoretical association with immunization in general	
Anaphylaxis [1,2]	Published
Thrombocytopenia[1,2,3,4]	Published
Generalized convulsion[1,2]	Published
Acute disseminated encephalomyelitis[4]	Published
Guillain Barré Syndrome[3,4]	Published

[1] *Proven association with immunization encompassing several different vaccines*
[2] *Proven association with vaccine that could theoretically be true for novel COVID-19 vaccines*
[3] *Theoretical concern based on wild type disease immunopathogenesis*
[4] *Theoretical concern related to viral replication during wild type disease*
[5] *Theoretical concern because it has been demonstrated in an animal model with ≥ 1 vaccine platform*

*SO2-D2.1.2 Priority List of COVID-19 Adverse events of special interest: Quarterly update December 2020

BC's COVID-19 AESIs case definition landscape (2/3)

AESI included because they have a proven or theoretical association with specific vaccine platform(s)	
Acute aseptic arthritis [r-VSV]	Published
Aseptic meningitis [Live vaccines]	Published
Encephalitis / Encephalomyelitis [Live vaccines]	Published
Idiopathic Peripheral Facial Nerve Palsy [Intranasal EColi Heat Labile Toxin Adjuvanted Vaccine]	Published
Vaccine associated enhanced disease [1(Formalin inactivated measles/RSV; HIV), 2(Chimeric YF Dengue), 5 (SARS / MERS-CoVs)]	In press (Vaccine)

[1] Proven association with immunization encompassing several different vaccines
[2] Proven association with vaccine that could theoretically be true for novel COVID-19 vaccines
[3] Theoretical concern based on wild type disease immunopathogenesis
[4] Theoretical concern related to viral replication during wild type disease
[5] Theoretical concern because it has been demonstrated in an animal model with ≥ 1 vaccine platform

BC's COVID-19 AESIs case definition landscape (3/3)

Example of prioritization

AESI included because they are seen with COVID-19 Disease [3,4]	
Acute respiratory distress syndrome	Submitted (Vaccine)
Multisystem inflammatory syndrome (children & adults)	Submitted (Vaccine)
Acute cardiovascular injury *(includes: myocarditis/pericarditis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia)*	Myocarditis/pericarditis near completion
Coagulation disorder *(includes: thrombotic disorders, bleeding disorders)*	
Anosmia, ageusia	
Chilblain – like lesions	
Erythema multiforme	
Single Organ Cutaneous Vasculitis	Published
Acute kidney injury	Published lab-based criteria (see *)
Acute liver injury	Published lab-based criteria (see #)
Acute pancreatitis NEW (Dec 2020)	Not yet started
Rhabdomyolysis NEW (Dec 2020)	Not yet started
Subacute thyroiditis NEW (Dec 2020)	Not yet started

TABLE 3. CARDIOVASCULAR INJURY PUBLICATIONS SINCE THE START OF THE COVID-19 PANDEMIC

Publication type / Focus / Topic (total)	Review	Meta-analysis	Patho-genesis	Guideline / Registry	Study	Case Report Or Series	Comment
Myocarditis (99)	4	1	2	1	6	77	8
Cardiac Injury (81)	10	6	22	2	18	9	14
Arrhythmias (57)	7	1	5	--	15	24	5
Acute coronary syndromes (49)	--	--	--	2	12	31	4

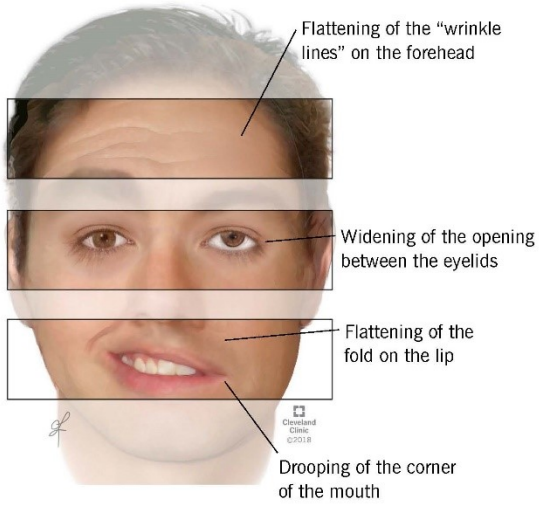
[1] *Proven association with immunization encompassing several different vaccines*
[2] *Proven association with vaccine that could theoretically be true for novel COVID-19 vaccines*
[3] *Theoretical concern based on wild type disease immunopathogenesis*
[4] *Theoretical concern related to viral replication during wild type disease*
[5] *Theoretical concern because it has been demonstrated in an animal model with ≥ 1 vaccine platform*

Take Home messages

- Standardized case definitions are crucial in assessment of AESIs
- Rigorous case definitions are published/updated by entities such as Brighton Collaboration (BC)
- Case definitions of most priority AESIs of COVID-19 vaccines have been published by BC
- Design of data collection should be guided by established standardized definitions, to ensure collection of essential data
- BC's definitions encompass multiple levels of certainty, and thus can be adapted to resource-limited settings

Case Study: Bell's palsy

- Inflammation of 7th cranial nerve
- Causes: autoimmune disease, diabetes, and viral infections
- Association with influenza and meningococcal vaccines
- Safety data from phase 3 studies of 2 mRNA COVID-19 vaccines showed vaccinated had more cases of Bell's palsy (est. RR of 7.0; p=0.07*):
  - Hypothesis: vaccine-induced innate immune activation via combined effect of mRNA + lipids, potentially including interferon production



Source: Clevelandclinic.org

*Ozonoff A. et al. Bell's palsy and SARS-CoV-2 vaccines. Lancet Inf Dis 2021

BC's case definition of facial nerve palsy: **Preamble**

- acute onset with rapid progression
- Includes partial/complete and bilateral cases
- Excludes **documented known** causes
- Level 3 is lab investigations-free (more suitable if low resources)

Vaccine 35 (2017) 1972–1983

Contents lists available at ScienceDirect

Vaccine

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

Facial nerve palsy including Bell's palsy: Case definitions and guidelines for collection, analysis, and presentation of immunisation safety data☆

Barbara Rath[a], Jane F. Gidudu[b], Helen Anyoti[c], Brigid Bollweg[b], Patrick Caubel[d], Yeoung-Hwang Chen[e], David Cornblath[f], Rohini Fernandopulle[g], Louis Fries[h], Jochem Galama[i], Neville Gibbs[j], Gualtiero Grilli[k], Patrick Grogan[l], Katharina Hartmann[m], Ulrich Heininger[n], Michael J. Hudson[o], Hector s. Izurieta[l], Indira Jevaji[p], Wiltshire M. Johnson[q], James Jones[b], Brigitte Keller-Stanislawski[r], Jerome Klein[s], Katrin Kohl[b], Panagiotis Kokotis[t], Yulin Li[n], Thomas Linder[u], James Oleske[v], Georgina Richard[w], Tarek Shafshak[x], Michael Vajdy[y], Virginia Wong[z], James Sejvar[b,*], for the Brighton Collaboration Bell's Palsy Working Group

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[e] Tri-Service General Hospital, Nei-Hu, Taipei, Taiwan
[f] Johns Hopkins University, Baltimore, MD, USA
[g] General Sir John Kotelawala Defence University, Sri Lanka
[h] Novavax, Inc., Rockville, MD, USA
[i] Radboud University Medical Center Nijmegen, Netherlands
[j] Food and Drug Administration (FDA), Rockville, MD, USA
[k] Public Health Service, Marche Region, Italy
[l] Wildford Hall Medical Center, San Antoni, TX, USA
[m] Crucell, Berne, Switzerland
[n] University Children's Hospital, Basel, Switzerland
[o] Public Health England, UK
[p] National Institutes of Health (NIH), Bethesda, MD, USA
[q] The Pharmacy Board of Sierra Leone, Freetown, Sierra Leone
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[s] Boston University School of Medicine, Boston, MA, USA
[t] Aeginitio Hospital, University of Athens, Athens, Greece
[u] Luzerner Kantonsspital, Lucerne, Switzerland
[v] Rutgers New Jersey Medical School, NJ, USA
[w] Tulane University, New Orleans, LA, USA
[x] Alexandria University, Egypt

BC's case definition of facial nerve palsy: **Definitions**

- **Peripheral facial nerve palsy:** Weakness of the facial muscles innervated **by cranial nerve VII**, which is **either** complete **(paralysis) OR incomplete (paresis)** and may manifest **unilaterally OR bilaterally**
  - **Level 1: acute-onset of lower ability to:**

    winkle forehead* OR *raise eyebrow(s)

  - **! No 2nd or 3rd levels**

BC's case definition of facial nerve palsy: **Definitions**

- ***Idiopathic*** **peripheral facial nerve palsy**:

  (All levels) ***Acute-onset*** **AND** ***initial rapid progression*** **AND** ***resolution***

  - **Level 1: known causes excluded by**

  - **Level 2: known causes excluded by**

  - **Level 3: known causes excluded by**

BC's case definition of facial nerve palsy: **Select Guidelines**

- **Data collection:**
  - Reporter/source
  - Vaccinee (demographics, clinical/immunization history)
  - Vaccine (time, name/dose/manufacturer/expiry date, route, anatomical site and location of immunization, storage)
  - The AESI (clinical characteristics, date and time of onset/end/outcome, neurological examination, lab/neuroimaging findings, severity, outcome)
- **Data analysis:**
  - Classification
  - Control group
  - Time interval/severity analysis using prespecified increments

Bell's palsy and vaccines

	Vaccine type	Study design and population	Study period	Summary of the results
Inactivated intranasal influenza vaccine[1]	Virosomal subunit vaccine	A matched case-control study and case-series among patients with Bell's palsy (≥18 years of age)	2000–01	During the 91-day exposure period, compared with controls, recipients of the vaccine had an adjusted odds ratio for Bell's palsy of 84·0 (95% CI, 20·1–351·9)
Parenteral inactivated seasonal influenza vaccine[2]	Protein-based split vaccine	Review of adverse events reported to VAERS	1991–2001	Proportional reporting ratio of Bell's palsy after influenza vaccine: 3·78 (95% CI not provided)
Monovalent pandemic H1N1 influenza vaccine[3]	Split virion adjuvanted with AS03	Retrospective cohort study among 1 024 019 individuals vaccinated with pandemic influenza vaccine	2009–10	Increased incidence of Bell's palsy compared with unvaccinated people, with a hazard ratio of 1·25 (95% CI, 1·06–1·48)
Monovalent pandemic H1N1 influenza vaccine[4]	Two protein-based vaccines: adjuvanted with MF59, or without adjuvant	Review of adverse events reported to NADRRS, Taiwan	2009–10	Increased risk for Bell's palsy 0–42 days post-vaccination; estimated-to-expected ratio of 1·48 (95% CI, 1·11–1·98)
Quadrivalent meningococcal conjugate vaccine[5]	Protein vaccine conjugated to a carrier protein	Self-controlled case-series analysis among 48 899 individuals immunized with meningococcal vaccine (11–21 years of age)	2011–13	Increased relative incidence for Bell's palsy in participants receiving concomitant vaccines (5·0, 95% CI, 1·4–17·8)

VAERS=US Food and Drug Administration's Vaccines and Related Biologic Products Advisory Committee. NADRRS=National Adverse Drug Reaction Reporting System.

Table: **Summary of studies reporting an association between vaccination and Bell's palsy**

Ozonof et al., Lancet 2021: https://www.thelancet.com/action/showPdf?pii=S1473-3099%2821%2900076-1

Bell's palsy and COVID-19 vaccines

- Pfizer/BioNTech: 4 cases, all in vaccine arm, one post-dose 1, 3 post-dose 2 (**unknown medical history/risk profile**)
- Moderna: 4 cases, 3 in vaccine arm (all post-dose 2), and 1 in placebo (**all had UMCs/history)**

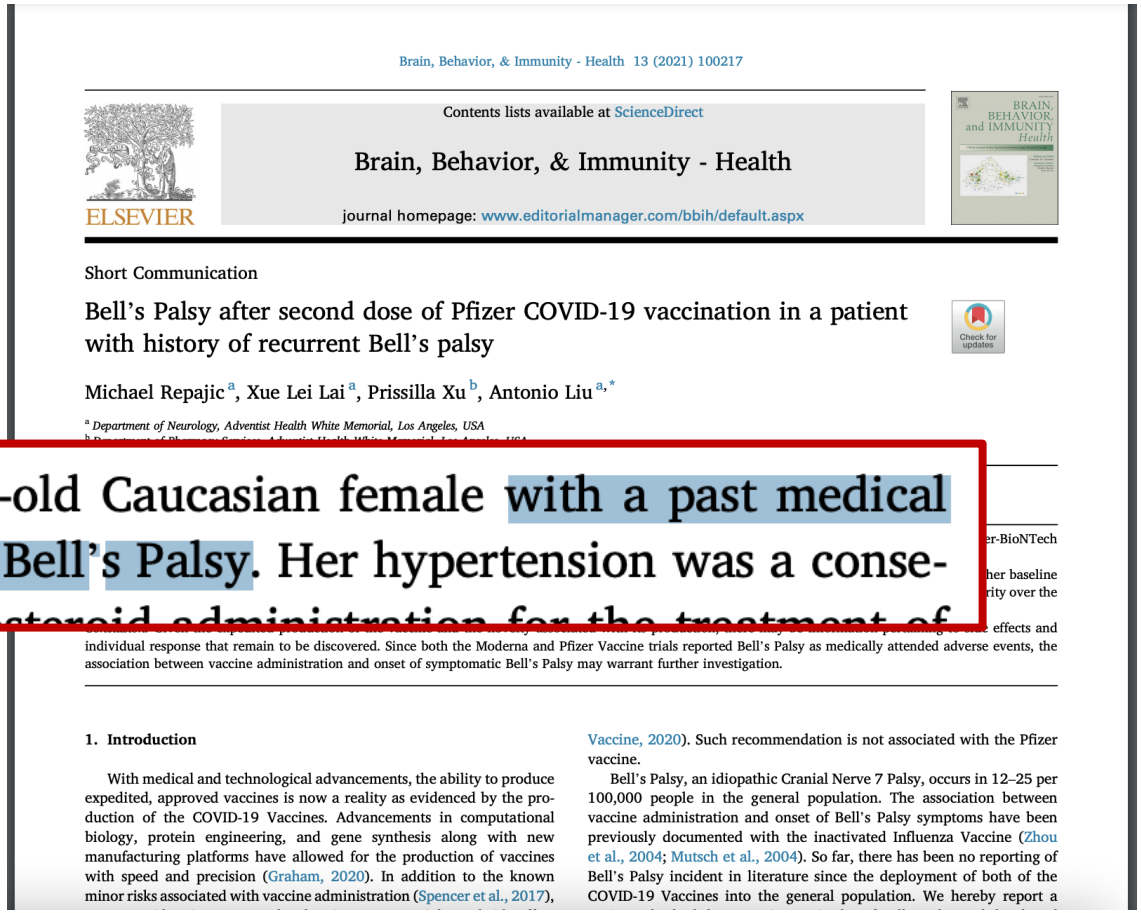
→ ***7 observed*** *cases in ~40,000 over 2 months vs.* ***1-2 expected****, based on background rate of 15-30/100,000 PYs**

- JnJ: 4 cases, 2 cases in vaccine arm and 2 in placebo (**5th case excluded as the patient did not have facial asymmetry**)

*Ozonof et al., Lancet 2021: https://www.thelancet.com/action/showPdf?pii=S1473-3099%2821%2900076-1

Bell's palsy and COVID-19 vaccines

Case#1, post-EMA in the US



Brain, Behavior, & Immunity - Health 13 (2021) 100217

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Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Short Communication

Bell's Palsy after second dose of Pfizer COVID-19 vaccination in a patient with history of recurrent Bell's palsy

Michael Repajic [a], Xue Lei Lai [a], Prissilla Xu [b], Antonio Liu [a,*]

[a] Department of Neurology, Adventist Health White Memorial, Los Angeles, USA

The patient is a 57-year-old Caucasian female with a past medical history of hypertension and Bell's Palsy. Her hypertension was a conse-

individual response that remain to be discovered. Since both the Moderna and Pfizer Vaccine trials reported Bell's Palsy as medically attended adverse events, the association between vaccine administration and onset of symptomatic Bell's Palsy may warrant further investigation.

1. Introduction

With medical and technological advancements, the ability to produce expedited, approved vaccines is now a reality as evidenced by the production of the COVID-19 Vaccines. Advancements in computational biology, protein engineering, and gene synthesis along with new manufacturing platforms have allowed for the production of vaccines with speed and precision (Graham, 2020). In addition to the known minor risks associated with vaccine administration (Spencer et al., 2017), Vaccine, 2020). Such recommendation is not associated with the Pfizer vaccine.

Bell's Palsy, an idiopathic Cranial Nerve 7 Palsy, occurs in 12–25 per 100,000 people in the general population. The association between vaccine administration and onset of Bell's Palsy symptoms have been previously documented with the inactivated Influenza Vaccine (Zhou et al., 2004; Mutsch et al., 2004). So far, there has been no reporting of Bell's Palsy incident in literature since the deployment of both of the COVID-19 Vaccines into the general population. We hereby report a

Bell's palsy and COVID-19 vaccines

Case#2, post-EMA in the US: 37y *otherwise healthy*

given that Bell's palsy is fundamentally a clinical diagnosis and that there is no specific laboratory test to confirm the disorder. Laboratory or other diagnostic tests can surely be useful in excluding other conditions such as Lyme disease (not common in our geographical area) or neuropathies such as Guillain–Barre' syndrome, or also brain tumours. These are especially useful when clinical presentation is not typical, and hence were not undertaken in our patient.

Journal of Neurology
https://doi.org/10.1007/s00415-021-10462-4

LETTER TO THE EDITORS

Bell's palsy following COVID-19 vaccination

Giuseppe Colella[1] · Massimiliano Orlandi[2] · Nicola Cirillo[1,3]

Received: 16 January 2021 / Revised: 7 February 2021 / Accepted: 10 February 2021

onolateral muscle weakness and attended the Max-
Unit at our University Hospital. He presented with
d facial droop accompanied by reduced mobility
with flattening of forehead's skin and marionette
l-buccal sulcus) ipsilaterally as well as mild flat-
the nasolabial fold (Fig. 1). Lagophthalmos and
l hypomobility was also recorded. This clinical
on was accompanied by a moderate Bell's sign
close the eye on the affected side with exposure
era). No history of trauma, cold or other identifi-
ers was reported and no other signs or symptoms
ent. Specifically, no history of a preceding infec-
ding recent SARS-CoV-2 infection, was reported
was no evidence of a cutaneous rash suggestive
Zoster infection. The patient was referred to the
Neurology Department with a provisional diagnosis of hemi-
facial paresis and discharged the same day with a clinical
diagnosis of Bell's palsy—an acute unilateral facial nerve
paresis or paralysis with onset in less than 72 h and with-
out identifiable cause [7]. No data are available concerning
neurophysiological and cerebrospinal fluid investigations,

vaccines [1, 2], consumer/patient information sheets of nei-
ther of the vaccines distributed in North America warn about
Bell's palsy as a possible adverse effect [6].

Here, we report a case of an otherwise healthy 37-year-
old white Caucasian male who developed facial palsy within
days after COVID-19 vaccination. We were given writ-

Deutsche Gesellschaft
für Internationale
Zusammenarbeit (GIZ) GmbH

Quiz!

Pre-lecture Quiz

Based on published case definitions by BC, which of the following statements are **incorrect**? **Select one or more:**

❒ A. “Child developed **high fever**” (temperature measured was 41 degree Celsius).

❒ B. “The child suffered from **afebrile seizures**” (body temperature was normal).

❒ C. “A **severe local reaction** occurred at the injection site” (the occurred swelling extended beyond the nearest joint and lasted for 3 days).

❒ D. “Patient developed symptoms of **encephalopathy** due to vaccination with DTP given 4 weeks before occurrence of symptoms”.

Answer

Based on published case definitions by BC, which of the following statements are **incorrect**? **Select one or more:**

❒ A. “Child developed **high fever**” (temperature measured was 41 degree Celsius).

Highly subjective words such as “high” should be avoided and the exact measurement of temperature, as read on thermometer, should be recorded

❒ B. “The child suffered from **afebrile seizures**” (body temperature was normal).

❒ C. “A **severe local reaction** occurred at the injection site” (the occurred swelling extended beyond the nearest joint and lasted for 3 days).

Either measurements or clinical descriptions (e.g., crossing joints/whole limb) should be used instead of subjective words such as “severe”

❒ D. “Patient developed symptoms of **encephalopathy** due to vaccination with DTP given 4 weeks before occurrence of symptoms”.

All BC definitions define a clinical entity without inference of a causal relation to a given exposure