Safety Platform for Emergency vACcines

SO2- D2.5.2.1 - AESI Case Definition Companion Guide for 1st Tier AESI

Guillain Barré and Miller Fisher Syndromes

Work Package: WP2 Standards and tools

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THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

DEFINITIONS & ACRONYMS

AESI	Adverse Events of Special Interest
AIDP	Acute inflammatory demyelinating polyneuropathy
AMAN	Acute motor axonal neuropathy
AMSAN	Acute motor and sensory axonal neuropathy
ADEM	Acute Disseminated Encephalomyelitis
BC	Brighton Collaboration
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CIDP	Chronic inflammatory demyelinating polyneuropathy
CM	Clinical Modification (relates to numbered versions of ICD codes)
CMV	Cytomegalovirus
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CUI	Concept Unique Identifier
EBV	Epstein Barr Virus
EEG	Electroencephalogram
EMG	Electromyelogram
GBS	Guillain Barré Syndrome
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
LOC	Level of certainty
LP	Lumbar Pucture
MedDRA	Medical Dictionary for Regulatory Activities
MF	Miller Fisher Syndrome
MRI	Magnetic Resonance Imaging
NCS	Nerve Conduction Sstudies
RBC	Red Blood Cell
SPEAC	Safety Platform for Emergency Vaccines
UMLS	Unified Medical Language System
VAAP	Vaccine Associated Paralytic Poliomyelitis
WBC	White Blood Cell

1. Background

CEPI has contracted with the Brighton Collaboration, through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

SPEAC Work Package 2 is creating resources and tools for the AESI including:

1. Tabular summaries of risk factors and background rates for each AESI.
2. Guidance on AESI real time investigation, data collection, analysis and presentation.
3. Spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.
4. Tools to facilitate capturing the specific clinical data needed to meet BC AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
    a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
    b. Tabular checklists that are a stand-alone tool useful for summarizing key clinical data needed to determine the level of diagnostic certainty for a given case definition.
    c. Tabular logic and pictorial decision tree algorithms, also stand-alone tools, to facilitate correct application of key clinical data to determine the level of diagnostic certainty for each AESI.
    d. Glossary of terms relevant to anaphylaxis and the neurologic AESI.

To guide timelines for the activities above, the AESIs have been prioritized into 4 tiers as shown in the Table below (process described in SO1-D2.0 Addendum to SO1-D2.2 & 2.3 Landscape Analyses Priority Tiers for All CEPI Vaccine Development AESI). This is available in the Developers Toolbox and on the Brighton Collaboration website.

TABLE 1. AESI PRIORITIZED BY TIER

Tier 1	Tier 2	Tier 3	Tier 4
Anaphylaxis	Vaccine associated enhanced disease	Sensorineural hearing loss	Acute/Chronic inflammatory rheumatism
Thrombocytopenia	Acute respiratory distress syndrome	Anosmia/ageusia	Total/partial loss of vision
Generalized convulsion	Acute cardiovascular injury	Chilblain like lesions	Optic neuritis
Aseptic meningitis	Coagulation disorder	Erythema multiforme	Alopecia
Encephalitis	Acute kidney injury	Acute aseptic arthritis	Neonatal sepsis
Myelitis	Acute liver injury	Single organ cutaneous vasculitis	Neonatal encephalopathy
Acute disseminated encephalomyelitis	Stillbirth	Maternal death	Neonatal neuro-developmental delay
Guillain Barré & Miller Fisher Syndromes	Spontaneous abortion and ectopic pregnancy	Neonatal death	
Peripheral facial nerve palsy	Pathways to Preterm birth & Preterm birth		

To simplify access to AESI specific tools and resources, companion guides to the Brighton AESI case definitions are being prepared for each AESI. This deliverable focuses on Guillain Barré Syndrome and Miller Fisher Syndrome hereinafter referred to simply as GBS and MF.

2. Objective of this deliverable

To collate SPEAC & BC tools, resources and guidance that have been developed for GBS.

3. Methods

The methods for developing each of the tools included in this guide were detailed in previously completed SPEAC deliverables as follows:

- GBS risk factors and background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates.
- GBS Case Definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- GBS Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- GBS Data Abstraction, Tabular Checklist and Level of Certainty Algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation.

The methods are briefly described in Appendix 8 of this Guide along with links to source documents which have more detailed methodology.

4. Results

The outputs are provided as separate appendices to simplify printing as needed. These are provided as shown below.

1. GBS Risk Factors
2. GBS Background Rates
3. GBS Case Definition key caveats for diagnosis, data analysis and presentation
4. GBS Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA
5. GBS Data Abstraction and Interpretation Form for Medical Chart Review
6. GBS Tabular Checklist for key case definition criteria and level of certainty algorithm
7. GBS Pictorial Level of Certainty Algorithm
8. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

5. Recommendations & discussion

This guide brings together resources and tools related to the AESI of GBS including risk factors, background rates, guidance for real time investigation, ICD-9/10-CM and MedDRA codes for data entry or database searching and provides tools for collecting and interpreting clinical data to apply the Brighton GBS case definition and determine the level of diagnostic certainty.

The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used in order to assign level of certainty for all identified AEFI with

features of GBS. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

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APPENDIX 1.
GBS Risk Factors

1.1. GBS Risk Factors

TABLE 1. GBS RISK FACTORS [1-12]

Age	• Incidence increases with age (see appendix 2).
Gender	• In general males have a higher incidence than females although this varies by age (see appendix 2).
Geography	• Prevalence of GBS type varies geographically: ○ AIDP: up to 90% of cases in North America and Europe versus 22-46% of cases in China, Japan, Bangladesh, Mexico [1,5] ○ AMAN/AMSAN: 30-65% of cases in China, Japan, Bangladesh, Mexico; about 5% of cases in North America and Europe [5] ○ MF variant: more prevalent in eastern Asia; overall about 5% of all GBS cases but up to 20% of cases in Taiwan, 25% of cases in Japan [1,5]
Comorbidity	• Malignancy, especially Hodgkin's and other lymphomas[1]
Infection	• Antecedent diarrheal or respiratory illness reported in 2/3 of cases [1-5] ○ *Campylobacter jejuni* the strongest association, and most notably in Asia, usually presenting as AMAN or Miller Fisher ○ Influenza, HIV, EBV, CMV, Enterovirus D68, *Mycoplasma pneumoniae* ○ Hepatitis E association noted in Netherlands, Bangladesh ○ Zika and Chikungunya infection
Vaccine	• Rabies vaccine cultured in mammalian brain tissues (e.g. Semple vaccine, made using mature sheep or goat brain or SMB vaccine made in suckling mouse brain) may induce T cells reactive to myelin basic protein. GBS was observed in about 1 in 7500 SMB vaccinees and made up about 7% of all hospitalizations following Semple vaccine.[1,7] • 1976 pandemic H1N1 swine influenza vaccine was associated with an attributable risk of about 1 case / 100,000 vaccinated[1,7] • A 2008 study using the UK General Practice Research Database found a higher relative incidence of GBS following influenza-like illness than after influenza vaccine.[8] • Institute of Medicine 2011[9] reviewed evidence for link between MMR, VZV, influenza, Hepatitis A/B, HPV, D/T/aP, meningococcal vaccines and GBS, and concluded evidence was inadequate to accept or reject a causal relationship. • A global collaborative study found a relative incidence of GBS of 2.42 (95% CI 1.58–3.72) in the 42 days following exposure to pH1N1 vaccine with no increased risk following adjuvanted vaccines.[10] • Updated review of evidence published since 2011 IOM report for similar range of vaccines had similar conclusion to IOM regarding no evidence to accept/reject causality[11] • Risk window for GBS as a vaccine product related reaction[12] ○ Inactivated or subunit vaccines –Immune-mediated mechanism for GBS likely similar to ADEM, where recommended risk window for individuals is 2-42 days: for epidemiologic studies 5-28 days for primary analysis, and 2-42 days for secondary analysis.

	○ Live attenuated vaccines – this should be based on the incubation period for the vaccine strain, adding as above, 5-28 days for primary analysis and 2-42 days for secondary analysis following the end of the incubation period.
Other	• Prior surgical procedure – reported following surgery for obesity[1]

APPENDIX 2.
GBS Background Rates

2.1 GBS Background Rates [13-79]

TABLE 1. GBS BACKGROUND RATES BY GEOGRAPHIC REGION: STUDIES OF ALL AGES OR ADULTS ONLY

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AFRICA					
Libya [13]	1983-1985	0-9 10-19 20-29 30-39 40-49 50-59 ≥ 60 **All ages**	0.3 (2) 1.8 (6) 3.1 (6) 5.9 (9) 1.7 (2) 1.5 (1) 1.1 (1) **1.73 (27)**	-- (0) 2.3 (4) 4.0 (4) 3.9 (3) 1.6 (1) -- (0) 2.1 (1) **1.62 (13)**	0.7 (2) 1.2 (2) 2.1 (2) 8.1 (6) 1.8 (1) 3.1 (1) -- (0) **1.85 (14)**
Tanzania [14]	1984-1992	12-29 30-49 ≥ 50 **≥ 12**	0.7 (25) 1.3 (28) 0.5 (6) **0.83 (59)**		
AMERICAs					
USA (Minnesota) [15]	1935-1980	≤17 18-39 40-59 ≥60 **All ages**	0.81 (8) 1.34 (13) 2.84 (16) 3.25 (11) **1.68[1.24-2.23] (48)**		
USA (California) [16]	1980-1986	<15	0.60 [0.48-0.73] (93)	0.64 [0.48-0.85] (51)	0.55 [0.44-0.74] (42)
USA (National data) [17]	2000 2001 2002 2003 2004	≥18	1.75 (993) 1.68 (963) 1.71 (986) 1.79 (1042) 1.65 (972)		
USA (Colorado) [18] i.Larimer county **ii.**Weld county	1975-1983	All ages	 i. 2.2 ii. 1.8		
USA (Michigan) [19]	1992-1999	All ages	6.3 (471)	7.4 [6.6-8.4]	5.3 [4.6-6.1]
USA (Vermont) [20]	1980-1985	<25 25-44 45-64 ≥65 **All ages**	0.86 (11) 0.97 (9) 2.52 (14) 4.73 (17) **1.6 (51)**	**2.0**	**1.3**

USA (Kansas) [21]	1984-1988	10-88	2.2 (43)		
USA (Virginia) [22]	1967-1987	0-9 10-19 20-29 30-39 40-49 50-59 60-69 ≥70 **All ages**	1.3 (10) 1.8 (16) 2.2 (18) 1.7 (14) 0.9 (6) 2.2 (11) 2.4 (11) 1.4 (6) **1.7 (92)**	1.3 (5) 1.5 (7) 1.4 (6) 1.9 (8) 1.2 (4) 1.6 (4) 3.6 (8) 1.4 (3) **1.7 (45)**	1.3 (5) 2.0 (9) 2.9 (12) 1.4 (6) 0.6 (2) 2.8 (7) 1.3 (3) 1.4 (3) **1.7 (47)**
Puerto Rico [23]	2013	3-82	1.7 (61)		
Canada [24]	2000-2002	1-4 5-22 **0.2-22**	2.1 [1.2-3.6] 0.6 [0.3-0.9] **0.8 [0.56-1.14] (33)**		
Canada [25] **(Alberta)**	1994-2004	1-110	1.6 (496)		
Canada [26] i. Quebec **ii.** Ontario	1983-1989	All ages	i. 1.51 (1302) ii. 1.78 (1031)		
Argentina, Brazil, Chile&Columbia [27]	1990-1994	1-4 5-14 **1-14**	0.86 [0.78-0.89] 0.52 [0.49-0.53] **0.62 [0.61-0.64] (2296)**		
Aruba [28]	2003-2011	14-77	3.93 (39)		
Brazil [29]	1990-1996	<15	0.46 (1678)		
Brazil [30]	1994-2007	All ages	0.3 (149)		
Brazil [31]	1995-2002	1-83	0.4 (95)		
Chile [32]	2001-2012	0-4 5-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 ≥80 **All ages**	2.17 2.23 1.61 1.22 1.57 2.21 2.81 3.60 4.30 3.46 **2.10 (4158)**		
Curaçao [33]	1987-1999	All ages	2.53 [1.87-3.35] (49)		
Honduras [34]	1989-1999	≤14	1.37 (394)		

Martinique & Guadalupe [35]	2011 2012 2013 2014 2015	All ages	1.76 (14) 1.89 (15) 1.65 (13) 3.45 (27) 1.93 (15)		
Paraguay [36]	1990-1991	<4 10-14 <15	1.7 0.1 1.1 (37)		
Latin America /Caribbean [37] i. Entire Region ii. North* iii. South * iv. Mexico v. El Salvador vi. Honduras vii. Brazil viii. Chile ** North: includes Cuba, Mexico, ElSalvador, Guatemala, Honduras, Panama, Columbia and Ecuador; South: includes Peru, Argentina, Brazil, Chile*	2000-2008	<15	i. 0.82 [0.72-0.90] ii. 1.08 [0.96-1.28] iii. 0.57 [0.49-0.67] iv. 1.14 v. 3.86 vi. 1.72 vii. 0.40 viii. 1.63		
ASIA					
China [38] **(Nanjing, Yancheng, Xuzhou)**	2008-2010	0-4 5-9 10-14 15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 ≥80	0.38 (15) 0.36 (11) 0.22 (10) 0.50 (29) 0.41 (26) 0.45 (29) 0.53 (33) 0.47 (29) 0.79 (43) 0.60 (31) 0.64 (30) 1.01 (43) 0.82 (32) 0.94 (26) 1.23 (27) 1.13 (18) 0.47 (9)		

		All ages	**0.59 (441)**	**0.72 (276)**	**0.45 (165)**
China [39] (Harbin)	1997-1998	0-9 10-19 20-29 30-39 40-49 50-59 ≥ 60 **All ages**	1.15 (10) 0.74 (7) 0.61 (7) 0.40 (4) 0.75 (4) 0.44 (2) 0.50 (2) **0.74 [0.46-1.13] (36)**	1.34 (6) 0.82 (4) 0.50 (3) 0.79 (4) 0.38 (1) 0.89 (2) 0.49 (1) **0.74 [0.46-1.13] (21)**	0.94 (4) 0.65 (3) 0.72 (4) -- (0) 1.10 (3) -- (0) 0.52 (1) **0.57 [0.32-0.94] (15)**
China [40] (Hong Kong)	1993-1998	>15	0.44 (20)		
Japan [41]	1988 1989 1990 1991 1992 **All years**	All ages	1.13 (7) 0.97 (6) 1.30 (8) 1.14 (7) 1.14 (7) **1.14 (32)**		
Taiwan [42]	1997-2011	0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 ≥80 **All ages**	0.76 0.56 0.92 1.04 1.36 2.12 4.10 6.35 6.34 **1.65 (5998)**	0.88 0.62 1.10 1.35 1.71 2.54 4.85 7.71 8.51 **1.99**	0.63 0.49 0.73 0.73 1.01 1.71 3.39 4.92 4.22 **29**
Taiwan [43]	1986-1990	≤15	0.66 (72)		
AUSTRALIA/OCEANIA					
Australia [44] i.New South Wales ii.West Australia	1995-1998	<15	i. 0.71 (37) **ii.** 1.02 (16)		
Australia [45]	1980-1984	>15	0.9 (110)		
Australia [46]	1980-1985	0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-90 **All ages**	1.13 (15) 0.62 (9) 1.61 (23) 1.32 (17) 0.68 (6) 2.07 (15) 2.60 (14) 1.77 (6) 3.30 (4) **1.35 (109)**	**1.49 (61)**	**1.20 (48)**

MIDDLE EAST					
Iran [47]	2002 2003 2004	5-14	0.68 (121) 0.76 (135) 0.65 (114)		
Iran [48]	2001 2002 2003 2004 2005 2006 **All years**	0-15	1.49 ([0.8-2.4] 1.95 [1.2-2.9] 3.44 [2.4-4.7] 2.14 [1.3-3.2] 2.04 [1.2-3.1] 2.57 [1.7-3.7] **2.27 [1.9-2.6] (143)**		
Iran [49]	2003	< 15 ≥ 15 **All ages**	2.28 2.06 **2.11 (76)**	**2.5 (45)**	**1.73 (31)**
Kuwait [50]	1992-1997	0-4 0-12	1.15 (10) 0.95 (19)		
EUROPE					
Denmark [51]	1965-1982	All ages	1.14 (51)		
Denmark [52]	1977-1984	20-90	2.0 (34)		
England [53]	1974-1986	0-4 5-14 15-24 25-34 35-44 45-54 55-64 65-74 ≥ 75 **All ages**	1.3 () 0.1 (1) 0.7 (9) 1.2 (12) 1.0 (8) 1.5 (10) 2.0 (12) 1.8 (9) 1.9 (6) **1.1 [0.8-1.4] (72)**	**1.0[0.6-1.3] (32)**	**1.2[0.8-1.6] (40)**
England [54]	1993-1994	All ages	1.2 [0.9-1.4] (79)	1.1 [0.7-1.4] (35)	1.3 [0.9-1.5] (44)
England & Wales [55]	1978	0-4 5-14 15-44 45-64 65-74 ≥ 75 **All ages**	0.5 (1) 0.6 (3) 1.1 (16) 1.4 (11) 1.9 (6) 1.1 (2) **1.1 (39)**	**1.32 (22)**	**0.95 (17)**
Scotland [56]	1980-1988	19-60 61-89 **≥19**	0.80 [0.46-1.15] 1.62 [0.80-2.43] **1.1 [0.81-1.40] (56)**		

UK [57]	1992-2000	0-14 15-24 25-34 35-44 45-54 55-64 65-74 75-84 85-100 **All ages**	**1.33 [1.15-1.50] (228)**	0.47 [0.19-0.96] (7) 0.63 [0.23-1.38] (6) 0.87 [0.43-1.56] (11) 1.00 [0.52-1.75] (12) 1.98 [1.24-3.00] (22) 3.15 [2.05-4.61] (26) 3.86 [2.50-5.70 {25) 2.85 {1.37-5.25] (10) 2.26 [0.27-8.14] (2) **1.45 [1.19-1.72] (121)**	0.42 [0.15-0.92] (6) 1.08 [0.52-1.98] (10) 1.11 [0.61-1.86] (14) 1.29 [0.72-2.13] (15) 1.21 [0.64-2.06] (13) 2.30 [1.39-3.23] (19) 1.86 [1.02-3.13] (14) 2.54 [1.39-4.27] (14) 0.86 [0.10-3.11] (2) **1.22 [0.98-1.46] (107)**
UK [58]	1995-1996	All ages	3.0 [1.0-6.0]		
Finland [59]	1980-1986	<15	0.38 [0.25-0.56] (27)		
Finland [60]	1981-1986	≤18 19-49 ≥50 **All ages**	0.58 (43) 0.67 (92) 1.35 (112) **0.84 (247)**		
Germany [61]	2003 2004 2005	All ages	1.78 (1466) 1.60 (1324) 1.89 (1559)		
Greece [62]	1989-2001	1.2-83	0.99(0.81-1.19](105)	1.2[0.93-1.53](65)	0.76[0.55-1.04](40)
Greece [63]	1996-2005	All ages	1.22 (46)		
Italy [64]	1981-2001	0-19 20-39 40-59 60-79 ≥80 **All ages**	0.53 (3) 0.98 (10) 2.01 (21) 3.24 (28) 4.30 (7) **1.91 [1.49-2.43] (69)**	0.35 (1) 1.16 (6) 2.81 (14) 4.62 (17) 1.98(1) **2.28 [1.62-3.12] (39)**	0.72 (2) 0.80 (4) 1.28 (7) 2.21 (11) 5.34 (6) **2.57 [1.06-2.24] (30)**
Italy [65]	1992-1993	0-9 10-19 20-29 30-39 40-49 50-59 60-69 ≥70 **All ages**	0.73 (4) 0.24 (2) 0.86 (10) 0.84 (9) 0/66 (7) 1.12 (12) 2.34 (24) 1.85 (19) **1.11 [0.89-1.36] (87)**		
Italy [66]	1996	<35 35-54 55-74 ≥75 **All ages**	0.79 [0.75-1.10] 1.33 [0.92-1.85] 3.22 [2.76-7.58] 4.67 [2.77-7.38] **1.55 [1.30-1.83] (138)**	**1.67 [1.3-2.11] (74)**	**1.43 [1.09-1.84] (64)**

Italy [67]	1995-1996	All ages	1.36 [1.13-1.63] (120)	1.78 [1.4-2.24] (74)	1.11[0.81-1.48] (46)
Italy [68]	1994-1995	All ages	0.92 [0.75-1.09] (109)		
Italy [69]	1981-1987	0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 **All ages**	0.86 (1) -- (0) -- (0) 0.58 (1) 3.25 (6) 0.50 (1) 3.98 (6) 0.72 (1) **1.08 (16)**	**1.39 (10)**	**0.81 (6)**
Italy [70]	1961-1980	2-75	0.4 (120)	0.41 (62)	0.39 (58)
Netherlands [71]	1987-1996	All ages	1.18[1.08-1.29] (476)	1.42[1.26-1.59]	0.94 [0.82-1.09]
Spain [72]	1975-1988	0-9 10-19 20-29 30-39 40-49 50-59 60-69 ≥70 **All ages**	0.59 (6) 1.57 (18) 0.79 (9) 0.64 (6) 1.05 (8) 1.41 (12) 1.23 (8) 0.32 (2) **0.95 (69)**	**1.18 (43)**	**0.71 (26)**
Spain [73]	1985-1990	20-29 30-39 40-49 50-59 60-69 70-79 ≥80 **All ages**	0.50 (45) 0.61 (48) 0.67 (46) 1.05 (62) 1.66 (86) 1.25 (40) 0.65 (10) **0.85 (337)**	**1.14 (218)**	**0.58 (119)**
Spain [74]	1998-1999	20-29 30-39 40-49 50-59 60-69 70-79 ≥80 **All ages**	0.45 (8) 0.64 (10) 1.03 (14) 1.72 (20) 2.42 (25) 2.32 (15) 1.91 (6) **1.25 (98)**	0.55 (5) 1.03 (8) 1.19 (8) 2.26 (13) 3.89 (19) 4.15 (1) 2.86 (3) **1.77 (67)**	0.34 (3) 0.26 (2) 0.87 (6) 1.19 (7) 1.10 (6) 1.05 (4) 1.44 (3) **0.76 (31)**
Sweden [75]	1978-1993	All ages	1.77 (2257)	2.01	1.54
Sweden [76]	1996	0-9 1-19	1.02 (6) 1.21 (6)	0.99 (3) 1.18 (3)	2.04 (3) 1.24 (3)

		20-29 30-39 40-49 50-59 60-69 70-79 ≥80 **All ages**	1.25 (8) 1.24 (8) 1.27 (8) 0.94 (5) 3.10 (12) 4.48 (16) 1.98 (4) **1.63 [1.28-2.05] (73)**	1.54 (5) 1.81 (6) 1.57 (5) 1.49 (4) 5.99 (11) 3.89 (6) 1.47 (1) **2.00 [1.28-2.05] (44)**	0.94 (3) 0.63 (2) 0.96 (3) 0.38 (1) 0.49 (1) 4.94 (10) 2.24 (3) **1.27 [0.85-1.83] (29)**
Sweden [77]	1973-1991	All ages	1.84 (556)	2.15 (281)	1.57 (275)
Sweden [78]	1973-1991	0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 ≥ 80 **All ages**	0.25 (2) 1.07 (9) 1.35 (12) 1.59 (15) 0.78 (6) 3.38 (19) 2.49 (11) 2.93 (8) 1.87 (2) **1.56 [1.24-1.93] (84)**	0.49 (2) 0.70 (3) 1.58 (7) 1.26 (6) 1.03 (4) 3.17 (9) 4.28 (9) 2.65 (3) -- (0) **1.64 [1.19-2.2] (43)**	-- (0) 1.45 (6) 1.13 (5) 1.93 (9) 0.53 (2) 3.59 (10) 0.86 (2) 3.14 (5) 2.73 (2) **1.46 [1.05-1.99] (41)**
European ADVANCE (Accelerated Development of Vaccine benefit-risk Collaboration in Europe) Project [79]					
All country data combined	2003-2014	0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	2.86 [2.43-3.37] 2.71 [2.35-3.13] 1.79 [1.63-1.97] 3.10 [2.90-3.32] 6.99 [6.79-7.21] 6.31 [6.11-6.52] 5.34 [5.11-5.58] 5.25 [5.15-5.34]		
Denmark (Aarhus University Hospital and Staten Serum Institute)	2003-2014 for all	0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	0.4 [0.17-0.82] 1.0 p0.68-1.48] 0.7 [0.51-0.85] 1.2 [0.99-1.41] 2.0 [1.83-2.23] 3.4 [3.12-3.66] 4.6 [4.19-5.00] 2.4 [2.27-2.49] (1711)		
Italy (Agenzia regionale di sanità)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	1.0 [0.47-2.09] 1.7 [1.03-2.67] 0.9 [0.64-1.29] 1.5 [1.14-1.96] 1.7 [1.47-1.94] 3.1 [2.79-3.43] 4.5 [4.14-5.00] 2.6 [2.49-2.80] (1085)		

Italy (Val Padana)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	0.0 0.0 1.1 [0.42-2.97] 1.2 [0.45-3.17] 1.8 [1.14-2.81] 2.8 [1.99-4.01] 5.7 [4.32-7.47] 2.8 [2.30-3.35] (109)		
Italy (Pedianet)		0-1 2-4 5-14 **All 0-14**	-- (0 cases) 1.9 [0.48-7.73] -- (0 cases) 0.5 [0.13-2.04] (24)		
Spain (Base de Datos para la Ivestigación Farmacoepidemiol ógica en Atención Primaria)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	0.4 [0.14-1.34] 0.5 [0.17-1.20] 0.5 [0.28-0.82] 0.5 [0.33-073] 1.0 [0.77-1.17] 1.6 [1.36-1.97] 1.8 [1.43-2.24] 1.1 [0.97-1.21] (321)		
UK (Royal College of General Practitioners Research and Surveillance Centre)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	0.8 [0.25-2.45] 1.2 [0.55-2.73] 0.5 [0.24-0.97] 1.0 [0.59-1.56] 1.4 [1.08-1.83] 2.2 [1.74-2.67] 3.4 [2.75-4.21] 1.8 [1.57-2.00] (257)		
UK (The Health Improvement Network)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	0.4 [0.19-0.93] 1.0 [0/67-1.60] 0.6 [0.48-0.87] 1.0 [0.76-1.25] 1.3 [1.15-1.50] 2.3 [2.12-2.60] 3.2 [2.86-3.57] 1.8 [1.67-1.89] (1021)		

APPENDIX 3

GBS Case Definition Key Caveats for Diagnosis, Data Analysis and Presentation

3.1. GBS Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

- Key elements of Case Definition (CD)
  - Both GBS and MF have 3 levels of diagnostic certainty and the lowest, level 3, is limited to clinical findings.
  - Critical for GBS to meet CD level 3 is demonstration of absent or decreased deep tendon reflexes in the same limbs that are weak. Without this it cannot meet any level of certainty.
  - Miller Fisher is an infrequent GBS subtype that includes bilateral ophthalmoparesis and ataxia, usually without limb weakness. GBS/MF overlap syndromes may occur, where there is weakness and features of MF. (See Appendix 7, Pictorial Algorithm). In such cases the level of certainty should be based on the GBS criteria, but it can also be described as GBS/MF overlap syndrome.
  - For both GBS and MF there must be sufficient follow-up to demonstrate a monophasic illness pattern (see Appendix 7, Pictorial algorithm) and no alternative diagnosis for weakness. That said, lack of testing for alternative diagnoses does not impact on the ability to meet the case definition.
  - CIDP must be distinguished from GBS; the clinical picture may be identical but CIDP tends to onset over 8 or more weeks and weakness tends to remit and relapse [1]

- Recommendations for real time assessment (see Appendix 7, Pictorial Algorithm)
  - Ensure that the degree and distribution of limb weakness is assessed and that deep tendon reflexes are assessed in all weak limbs.
  - If possible, seek assessment by a neurologist and ask that the following assessments be recorded: manual muscle testing using the Medical Research Council scale; deep tendon reflexes; sensory and cranial nerve examination; presence or absence of ataxia. Measures of functionality or disability would also be helpful. These are provided in the published case definition appendices and reproduced here in Appendix 5, Table 5.
  - Full assessments should ideally be done at:
    - Initial presentation to medical care
    - At clinical nadir (see below)
    - At all subsequent points where there is significant change in neurologic status until a final outcome endpoint is reached (recovery, death, end of follow-up). If not possible, assessments should be done weekly for 4 weeks, monthly for 5 months and then once every 3 months.
  - A date/time for the clinical nadir (defined as the worst state of clinical symptoms) should be determined. Normally for GBS there is a steady progression in weakness to a nadir point followed by a plateau, fatal outcome or gradual improvement. Therapies such as immunoglobulins or steroids may cause fluctuations in levels of weakness – all of which should be carefully documented. These are usually within the first 9 weeks.
  - Level 1 of certainty requires CSF WBC and protein results showing cyto-albuminologic disassociation (WBC <50, elevated protein) and characteristic electrophysiological test results (EMG, nerve conduction studies) as outlined in Appendix 7, Pictorial Algorithm. Of note electrophysiological tests can be normal if obtained in the first 7 days after symptom onset. If normal, testing should be repeated, if possible.
  - Level 2 of certainty can be reached with either CSF or electrophysiologic testing rather than both.
  - Nerve conduction studies may be normal if done within 7 days of onset of weakness. If normal at that time, they should be repeated after 1 to 2 weeks.

- Level 3 relies solely on clinical findings, of which the most important are the requirement, for GBS (not Miller Fisher variant) that the deep tendon reflexes be absent or decreased in the same limbs that are weak.
- Confirmed alternate etiologies that exclude a diagnosis of GBS, or Miller Fisher Syndrome are listed in Table 6 in Appendix 5. Investigation for these is not required to meet the case definition but if found do rule out GBS or Miller Fisher syndrome.
- If real time assessment is not possible, the SPEAC data abstraction and interpretation tool (Appendix 5, Tables 1 & 2) can be used in conjunction with medical records to gather the information needed to assess the level of diagnostic certainty.
- Testing for autoantibodies is not required for the case definition. May be relevant to type of GBS with anti-ganglioside antibodies absent in AIDP, but present in AMAN/AMSAN (GM1, GD1a) and Miller Fisher (GQ1b, GT1a). [5]

Data Collection Guidelines

- Gather detailed clinical descriptions of symptoms/signs and time course including severity of weakness at the clinical nadir, additional neurologic signs of GBS (e.g., fasciculations, atrophy, myoclonus).
- Document other concurrent signs, symptoms and diseases.
- Document the dates and results of all:
    - electrophysiologic studies (electromyography [EMG] and nerve conduction velocity studies [NCS].
    - additional neurophysiologic studies including electroencephalography [EEG], neuroimaging studies (computed tomography [CT] or magnetic resonance imaging [MRI].
    - CSF examinations including WBC (cells/uL), RBC (cells/uL), differential WBC count if available, protein (mg/dL), glucose (mg/dL) and if done a concomitant serum glucose. The upper limits of normal for the laboratory performing the CSF analysis should be documented.
    - Tests done to identify and/or rule out alternative etiologies for weakness.
- Document nature and dates of all therapy given for GBS/MF.
- Document the neurologic/functional outcome and disposition at last observation.

Data Analysis Guidelines

- In the setting of pre-licensure trials, it is unlikely that more than one or a few cases will be reported. The guidelines in the published case definition provide suggestions for data analysis and presentation of scenarios where several cases are assessed (e.g., self-controlled case series study). These are not reproduced here but can be easily found in the published guidelines section 3.2.[1]

APPENDIX 4
GBS Diagnostic Codes: ICD-9/10-CM and MedDRA

4.1 GBS Diagnostic Codes: ICD-9/10-CM and MedDRA

TABLE 1. CONCEPTS FOR GUILLAIN BARRÉ AND MILLER FISHER SYNDROMES

UMLS		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0018378	Guillain-Barre Syndrome	Guillain-Barre syndrome	10018767		G61.0
		Guillain Barre syndrome	10018766		
		Syndrome Guillain-Barre	10042812		
		Acute infective polyneuritis	10000813	357.0	
		Acute inflammatory demyelinating polyradiculoneuropathy	10067898		
		Paralysis ascending	10033803		
C0393799	Miller Fisher Syndrome	Miller Fisher Syndrome	10049567		G61.0
		Fisher's syndrome		357.0	

No broader concepts identified.

APPENDIX 5

GBS Data Abstraction Form and Interpretation form for Medical Chart Review

5.1. GBS Data Abstraction and Interpretation Form for Medical Chart Review

Instructions are provided with each table. The focus is on the specific data needed to meet and/or exclude GBS or MF based on the Brighton case definition.[1] This form will be most applicable to situations where a hospital/other institutional chart is available and used retrospectively to gather the information needed to validate that a case coded as GBS meets or does not meet the Brighton case definition. It may also serve as a guide for the type of data to be collected and investigations to be done at the time a possible case is identified or reported during a clinical trial or active surveillance for cases as part of pharmacovigilance. A neurologic glossary of terms is available as well.

Six tables are included in the form.

- Table 1 is a guide to likely sources of information for the key case definition clinical and laboratory criteria.
- Table 2 is the main data abstraction form. Use it to record data from the chart and based on the evidence to assign a value to each case definition criterion. Space is limited and additional paper can be used as appropriate to capture key clinical and laboratory data.
- Table 3 should be used to summarize the criterion values as determined once table 2 is completed.
- Table 4 is the key to determine the level of certainty based on the summary data in Table 3. It follows the logic of the Brighton case definition.
- Table 5 is the Medical Research Council manual muscle testing scale for assessing severity of weakness at clinical nadir and follow-up
- Table 6 is a checklist of alternative causes for weakness from brain to muscle which can be used to record investigations that were done for differential diagnoses.

TABLE 1. GBS/Miller Fisher key 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; 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	

TABLE 2. Data abstraction form

NOTE: glossary of neurologic terms available as a separate document.

1. Record specific information, to the extent possible, for all column 1 criteria in the results column 2 below.
2. Use recorded results to circle most appropriate BCCD criterion value based on the formulae in column 3.

<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 Table 5 below)</td><td>* wherever ‘yes’ is chosen, indicate the worst grade of muscle strength during course (See Appendix 1. Assessment of Muscle Strength)
<table><tr><td>R = right; L = left</td><td>1.
R Leg</td><td>2.
L Leg</td><td>3.
R Arm</td><td>4.
L Arm</td></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 & both arms have normal muscle strength or graded strength = 5
Else A = Not met if neither A-1 nor A-2

B = B-1 IF Deep tendon reflexes are absent or decreased in weak limbs
B = B-2 IF absent or reduced tendon reflexes in both legs and/or both arms despite absence of weakness
Else B = Not met if neither B-1 nor B-2</td></tr>
<tr><td>Criterion C
Monophasic temporal illness pattern</td><td>a) Weakness onset date: (dd/mon/yy): __ / ___ /__
b) Date when weakness at its worst (nadir): (dd/mon/yy): __ / ___ /__
c) Interval between (a) and (b)(if same day record the interval in hrs):
____Hrs OR ___Days OR ___unknown
d) Date of last observation: (dd/mon/yy): __/___/___ __unknown
e) Clinical status at the last observation:
___complete recovery to baseline status
___partial recovery but still has some residual weakness / disability
___no change in weakness from the nadir
___dead
f) Fluctuation in degree of weakness between:
1. onset and nadir: __Yes __No __ Not documented</td><td>C = YES IF: interval from onset to weakness nadir is between 12 hrs and 28 days

C = NO IF: interval from onset to weakness nadir is <12 hours OR >28 days

C = UNKNOWN IF: unable to calculate a value for interval from onset to weakness nadir</td></tr>
</table>

	2. nadir and last observation: __Yes __No __ Not documented If 'Yes' for f-1 and/or f-2, were the fluctuations associated with disease modifying therapies (e.g. IVIG, steroids)? __ Yes* __No __not described * if Yes, provide details:	
Criterion D **Ophthalmo-paresis**	a) **R extraocular muscle weakness:** __Yes __No __Not described b) **L extraocular muscle weakness:** __Yes __No __Not described	**D = Present** IF yes for both R & L **D = Absent** IF No for both R & L **D = UNKNOWN** IF not described for R+/ or L
Criterion E Ataxia	**Ataxia** __ Present __Absent __Not described	**E = Present or Absent** if either is checked **OR = UNKNOWN** IF Not described checked
Criterion F. **Altered level of consciousness**	**Reduction or alteration of level of consciousness:** ___ Present ___ Absent ___ Not described	**F = Present** or **Absent** if either is checked **F = Unknown** IF Not described checked
Criterion G **Corticospinal tract signs**	**Corticospinal tract signs were:** __Present __Absent ___Not described (e.g., extensor plantar responses, spasticity, Increased muscle tone)	**G = Present or Absent** if either is checked **G = Unknown** IF Not described is checked
Criterion H **Alternative cause for weakness found**	Complete Table 6 checklist as completely as possible and then choose the best choice for the statement: **An identified alternative diagnosis for weakness was:** __Present* __ Absent (check if no testing done) *Describe alternative cause and basis for diagnosis:	**H = circle whatever is checked** **Present** **Absent**

Laboratory Criteria	Results	
Criterion I **Electro-physiologic findings**	**Neurophysiologic testing:** __DONE* __Not Done __Unknown if Done or Results unavailable *if DONE check the result that is most consistent with the report a. ___Acute Inflammatory Demyelinating Polyneuropathy (AIDP) b. ___Acute Motor Axonal Neuropathy (AMAN) c. ___Acute Motor and Sensory Axonal Neuropathy (AMSAN) d. ___Sensory abnormalities only e. ___Inexcitable or unknown pattern f. ___normal result g. ___other (describe):	**I = I-1 "Typical for GBS"** IF a **(AIDP) OR b (AMAN) or c (AMSAN) checked** **I = I-2** if d (sensory only) or g (normal) checked **I = I-3** if testing Not done OR unknown if done OR results unavailable OR Done and e checked (inexcitable / unknown pattern). *NOTE: If g(other) checked, seek expert help for interpretation.*
Criterion J **Lumbar puncture (LP) and CSF exam**	**Lumbar Puncture:** __DONE* __Not done __Unknown if Done * If DONE: Date (dd / mon / yy) __ / ___ / __) **CSF protein** (mg/L if known ____): __Normal __Elevated __Unknown **CSF total WBC count:** __ <50 / uL __≥50/uL __Unknown (actual count in cells/uL if known ____):	**J = J-1 'cytoalbuminologic dissociation'** IF **CSF WBC < 50/uL and CSF protein elevated** **J = J-2** IF **CSF WBC <50/ul** and **CSF protein normal or result unknown** **J = J-3** IF **LP not done or CSF results unavailable or ≥ 50/uL**

TABLE 3. Record criterion values from table 2 above by circling the correct value in each row below – and record it in the right most column

A. Flaccid Weakness	A	A-1	A-2	Not Met	A =
B. Deep tendon reflexes	B	B-1	B-2	Not Met	B =
C. Monophasic illness pattern	C	Yes	No	Unknown	C =
D. Bilateral ophthalmoparesis	D	Present	Absent	Unknown	D =
E. Ataxia	E	Present	Absent	Unknown	E =
F. Altered level of consciousness	F	Present	Absent	Unknown	F =
G. Corticospinal tract signs	G	Present	Absent	Unknown	G =

H. Alternative cause for weakness	H	Present	Absent		H =
I. Electrophysiology results	I	I-1	I-2	I-3	I =
J. CSF test results	J	J-1	J-2	J-3	J =

TABLE 4. Use answers in Table 3 and formulae below to determine level of certainty for GBS (4A) or Miller Fisher syndrome (4B)

Level of Certainty	4A. GBS
Level 1	[A = A1] & [B = B1] & [C=YES] AND [H = Absent] AND [I = I-1] AND [J = J-1]
Level 2	[A = A1] & [B = B1] & [C=YES] AND [H = Absent] AND EITHER i. [I = I-1] AND [J = J-2 or J-3] OR ii. [I = I-3] AND [J = J-2]
Level 3	[A = A1] & [B = B1] & [C=YES] AND [H = Absent] 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 = Present]

Level of Certainty	4B. Miller Fisher Syndrome*
Level 1	[A=A2] & [B = B2] & [C =YES] & [D&E]=Present & ([F & G & H]=Absent) & [I = I-2] & [J = J1]
Level 2	[A=A2] & [B = B2] & [C =YES] & [D&E]=Present & ([F & G & H]= Absent) AND EITHER i. [I = I-2] AND [J = J-2 or J-3] OR ii. [I = I-3] AND [J = J-2]
Level 3	[A=A2] & [B = B2] & [C =YES] & [D&E]=Present & ([F & G & H]= Absent) AND [I = I-3] AND [J = J-3]
Level 4	Reported as Miller Fisher Syndrome but insufficient information available to meet any level of case definition.
Level 5	Not a Case : [NO to any of [B-2 OR C] or Absent for [D or E] OR [Present for any of [F, G or H]

** if limb weakness (A = 1) is present the illness may be GBS/Miller Fisher overlap syndrome. If so, apply the criteria for GBS to determine level of diagnostic certainty.*

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TABLE 5. Criteria for Assessment of Severity of Weakness at Clinical Nadir and Follow-up for final outcome

Medical Research Council Manual Muscle Testing Scale

Grade	Muscular capability
0	No contractile activity
1	Muscle activity can be palpated when performing action, with gravity eliminated
2	Patient can move limb with gravity eliminated through partial range of motion
3	Patient can't hold against resistance, but is able to move limb against gravity through range of motion
4	Patient can hold the position against moderate resistance, has full range of motion
5	Patient can hold the position against maximal resistance and through complete range of motion

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TABLE 6. Investigation(s) for alternative diagnoses[1-3,5] for weakness: for any 'yes' answers: provide detail below table or on back of page

Nervous System Level	Investigated?	Alternative explanation for weakness	Present
Intracranial		Encephalitis, ADEM	Yes No Unknown
		Carcinomatous meningitis	Yes No Unknown
		Brain stem stroke or encephalitis (Bickerstaff's)	Yes No Unknown
		Wernicke's encephalopathy (thiamine deficiency)	Yes No Unknown
Spinal Cord		Infarct	Yes No Unknown
		Myelitis	Yes No Unknown
		Compression	Yes No Unknown
Anterior horn cells of spinal cord		Viral infection: Polio / VAPP, West Nile Virus, Zika Virus	Yes No Unknown
		Amyotrophic lateral sclerosis	Yes No Unknown
		Progressive spinal muscular atrophy	Yes No Unknown
Spinal nerve roots		Chronic inflammatory demyelinating polyneuropathy (CIDP)	Yes No Unknown
		Cauda equina compression	Yes No Unknown
Peripheral nerves		Metabolic derangements (magnesium, phosphates etc.)	Yes No Unknown
		Tick paralysis	Yes No Unknown
		Heavy metal toxicity (arsenic, gold or thallium)	Yes No Unknown
		Drug-induced neuropathy (vincristine, platinum, nitrofurantoin, paclitaxel)	Yes No Unknown
		Porphyria	Yes No Unknown
		Critical illness neuropathy	Yes No Unknown
		Vasculitis	Yes No Unknown
		Diphtheria, Lyme disease	Yes No Unknown
		Thiamine deficiency	Yes No Unknown
Neuromuscular junction		Myasthenia gravis	Yes No Unknown
		Organophosphate poisoning	Yes No Unknown
		Botulism	Yes No Unknown
Muscle		Critical illness myopathy	Yes No Unknown
		Polymyositis	Yes No Unknown
		Dermatomyositis	Yes No Unknown
		Hypo / hyperkalemia	Yes No Unknown
		Rhabdomyolysis	Yes No Unknown
		Mitochondrial disease	Yes No Unknown

APPENDIX 6
GBS Tabular Checklist for Key Case Definition Criteria and Level of Certainty Algorithm

6.1 GBS Tabular Checklist for Key Case Definition Criteria and Level of Certainty Algorithm

TABLE 1. STEP 1. Using available information circle status for each listed criteria (A-J). 'Yes' means criterion as described is documented to be present; 'No' means it is documented to be absent; 'unknown' means there was no documentation of clinical findings OR a test was not done OR it is unknown if the test was done OR test results are unavailable.

Clinical Criteria	
A. Flaccid weakness	__A1 Both (legs +/or arms) weak __A2 No limb weakness __Not Met neither A1 nor A2 true
B. Decreased or absent deep tendon reflexes (DTRs)	__B1 Yes in same limbs that are weak (essential for GBS)[1] __B2 Yes but in absence of limb weakness __NOT MET IF DTRs normal/increased/unknown EITHER in weak limbs OR in absence of weakness; OR if DTRs absent/decreased on one side only)
C. Monophasic illness pattern[2] with symptomatic nadir 12 hours to 28 days after onset, followed by clinical plateau, death or improvement	__YES __ NO __ UNKNOWN
D. Bilateral ophthalmoparesis	__Present __ Absent __ UNKNOWN
E. Ataxia	__Present __ Absent __ UNKNOWN
F. Altered level of consciousness	__Present __ Absent __ UNKNOWN
G. Corticospinal tract signs	__Present __ Absent __ UNKNOWN
H. Alternative cause for weakness[3]	__Present __ Absent __ UNKNOWN
I. Electrophysiologytest results[4] (electromyelogram, nerve conduction studies)	__I-1. Typical for GBS (AIDP, AMAN, AMSAN) __I-2. Normal or sensory abnormalities only __I-3. Not done, results unavailable or inexcitable or unknown pattern
J. Cerebrospinal fluid (CSF) test 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

[1] For GBS absent/decreased DTRs must be demonstrated in the same limbs that are weak to meet the case definition; having absent/decreased DTRs in unaffected limbs does not impact the case definition.
[2] Monophasic illness patterns (from Case Definition [1] footnote): "fluctuations in level of weakness, before reaching nadir, or during the plateau or improvement phases, occur in some cases, usually associated with use of disease-modifying therapies (steroids, IVIG, plasma exchange). Such fluctuations usually occur within the first 9 weeks after onset and are followed by eventual improvement"
[3] Testing for alternate causes of weakness is not required to meet the case definition; but IF FOUND, then not a case
[4] Tests may be normal if done sooner than 7 days after weakness onset; in such cases should be repeated

TABLE 2. STEP 2. Apply Criterion values from checklist above to formulae below to determine level of certainty (LOC)

Level of Certainty	4A. GBS
Level 1	[A = A1] + [B = B1] + [C=YES] + [H = Absent] + [I = I-1] + [J = J-1]
Level 2	[A = A1] + [B = B1] + [C=YES] + [H = Absent] AND : EITHER i. [I = I-1] + [J = J-2 or J-3] OR ii. I = I-3] + [J = J-1 or J-2]
Level 3	[A = A1] + [B = B1] + [C=YES] + [H = Absent] + [I = I-3] + [J = J-3]
Level 4	Reported as GBS but Insufficient information to meet any level of case definition.
Level 5	A=(A2orA3) OR B=NOT MET OR C=NO +/OR H=Present

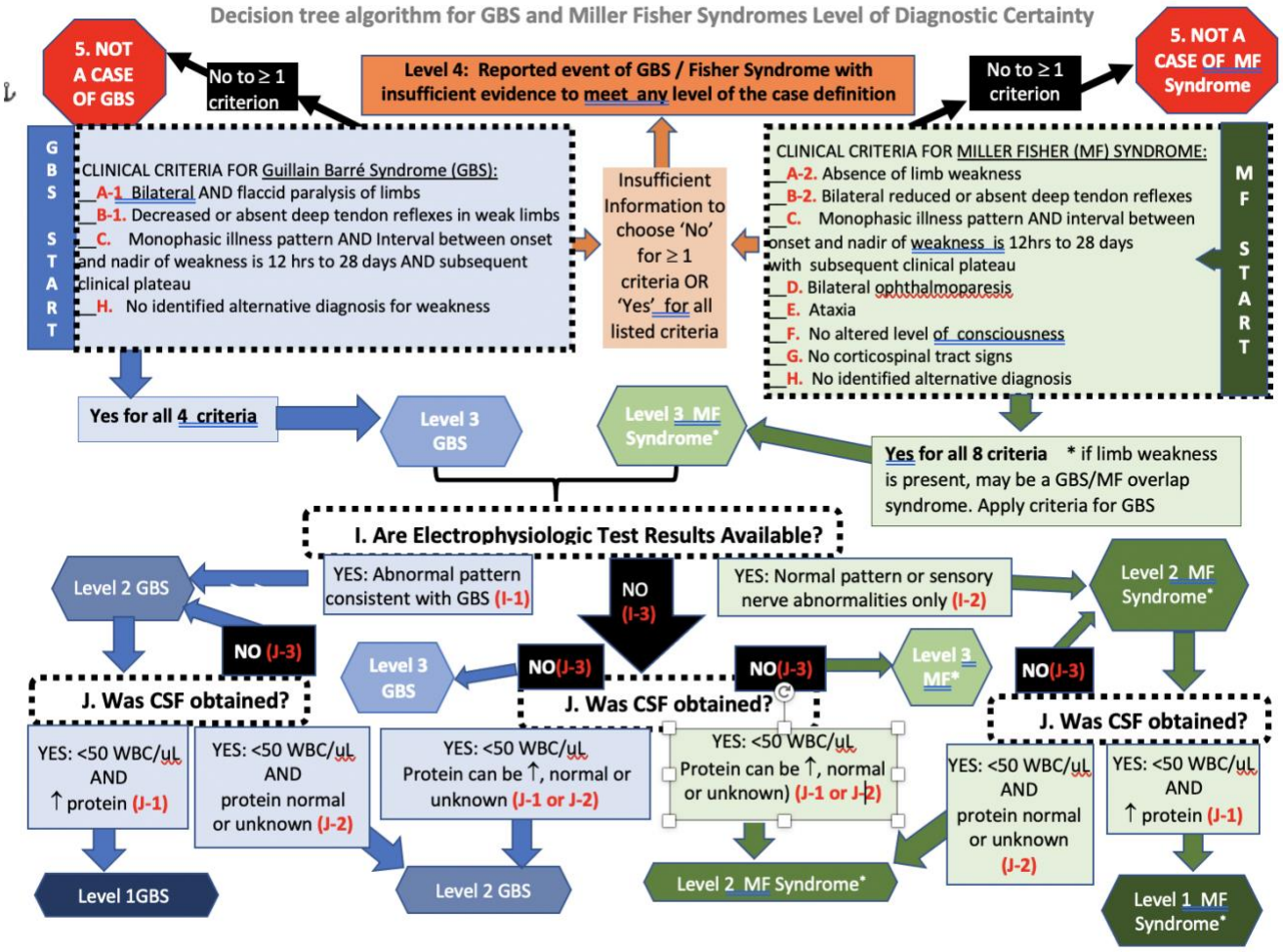
Level of Certainty	4B. Miller Fisher Syndrome*
Level 1	[A=A2] & [B = B2] & [C =YES] & [D&E]=Present & ([F & G & H]=Absent) & [I = I-2] & [J = J1]
Level 2	[A=A2] & [B = B2] & [C =YES] & [D&E]=Present & ([F & G & H]= Absent) AND EITHER i. [I = I-2] AND [J = J-2 or J-3] OR ii. [I = I-3] AND [J = J-2]
Level 3	[A=A2] & [B = B2] & [C =YES] & [D&E]=Present & ([F & G & H]= Absent) AND [I = I-3] AND [J = J-3]
Level 4	Reported as Miller Fisher Syndrome but insufficient information available to meet any level of case definition.
Level 5	Not a Case : [NO to any of [B-2 OR C] or Absent for [D or E] OR [Present for any of [F, G or H]

** if limb weakness (A = 1) is present the illness may be GBS/Miller Fisher overlap syndrome. If so, apply the criteria for GBS to determine level of diagnostic certainty.*

APPENDIX 7

GBS Pictorial Level of Certainty Algorithm

7.1 GBS Pictorial level of certainty algorithm: Use available clinical history, examination and laboratory investigation results to determine level of diagnostic certainty for GBS or Miller Fisher Syndrome. Note: red alpha-numeric criteria match those in data-abstraction form (5.1) and tabular checklist (6. 1)



APPENDIX 8.

Methodology: Brief Summary

8.1. GBS Risk Factors [1-12]

A risk factor is "an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor". According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:

1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.
2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attribute includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published Brighton Case Definition[1] for GBS was reviewed for evidence related to associated risk factors. In addition, review articles published after the Brighton case definition were retrieved and reviewed in depth regarding known risk factors for GBS.[2-4] Additional articles were identified in the citations of the first four. [5-12]

8.2. GBS Background Incidence [13-79]

A systematic literature search to estimate the incidence of acute GBS in the population was conducted using the following search strategy:

("Guillain-Barre Syndrome"[Mesh:noexp] OR "Guillain Barre"[ti] OR "Guillain-Barre"[ti] OR "Guillain-Barré"[ti] OR "GBS"[ti] OR "Miller Fisher Syndrome"[Mesh:noexp] OR "Miller Fisher"[ti] OR "Miller-Fisher"[ti] OR "Fisher Syndrome"[ti]) AND ("Incidence"[Mesh:noexp] OR "incidence"[tiab]) AND English[lang] AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT]) AND ("Meta-Analysis"[Publication Type] NOT ("animals"[Mesh:noexp] NOT "humans"[Mesh:noexp]) NOT ("Coronavirus"[Mesh:noexp] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti]) NOT ("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR trial[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti]).

Articles had to meet the following criteria:

1. Original research/meta-analysis
2. Population-based study (selecting the entire population or using probability-based sampling methods)
3. Reported an incidence estimate (or raw numbers that allowed the calculation of an estimate).

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all nonoverlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for GBS were extracted. GBS

incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a single medical reviewer (BL). Screened in articles were then reviewed independently by two reviewers and relevant data abstracted for inclusion in the background rate table (MRV).

The spreadsheet with all extracted background incidence data is available in the on the Brighton Collaboration website.

8.3. GBS Case Definition[1] key caveats for diagnosis, data analysis and presentation

The published Brighton case definition for Guillain Barré and Miller Fisher syndromes was reviewed, and key aspects identified with particular relevance to real time assessment of GBS in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published GBS case definition was reviewed, and key recommendations identified for data collection, analysis and presentation.

For a more detailed description of methodology see SO1-D2.7 Guidance for CEPI Developers which is available in the CEPI Developers' Toolbox.

8.4. GBS ICD-9/10-CM and MedDRA Codes [80-84]

An initial set of codes were retrieved through the CodeMapper tool. Subsequently they were reviewed and classified into narrow or broad codes

CodeMapper[80] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[81] CodeMapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[82,83] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[84] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMED-CT, MeSH, ICPC-2 and Read-CTv3.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with the mouse. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.

3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

CodeMapping was conducted by MS. The output of the CodeMapper concepts was reviewed by a medical expert (BL) familiar with the GBS Brighton case definitions for all Tier 1 AESI. The concepts identified for GBS were considered relevant for background incidence rate determination as well as to study hypotheses related to GBS as a vaccine-product related reaction.

For a more detailed description of methodology see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available in the CEPI Developers' Toolbox and at the Brighton Collaboration website.

8.5. Data Abstraction & Interpretation Form, Tabular Checklist and Algorithms for Level of Certainty Determination

The Brighton Collaboration case definition for GBS[1] was thoroughly and repeatedly reviewed by one individual (BL) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define each and every case definition level of certainty.

The GBS criteria were displayed in a tabular format to enable recording of all relevant clinical data (based on history, physical examination, laboratory investigation and temporal criteria as relevant to each case definition) needed to meet each criterion. A guide was developed for each criterion in the data abstraction table to ensure a standard approach to assigning a value to the criterion. For most criteria the following terms were used with the meaning as noted below:

- Yes: criterion was documented to be present (for some the term 'True' or 'Met' was used instead of 'Yes').
- No: criterion was documented to be absent (for some the term 'Not True' or 'Not met' was used instead of 'No').
- Unknown: criterion was not assessed, or not mentioned, or no results were available, so it was not possible to document it as either present or absent.

In some cases, lettered or numbered values were assigned to a given criterion. Rules to assign these values to the criterion were embedded within the data abstraction table or the tabular checklist depending on the specific tool, further described in results below.

Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition. Two types of algorithm were developed for each case definition. For one, formulae based on the logic in the case definition were put into tables with each row representing a level of certainty. For the second a more visual decision tree algorithm was developed. Both however, were based on the logic inherent in the published case definition.

For a more detailed description of methodology see Tabular checklist and Level of Certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation which is available in the CEPI Developers' Toolbox.