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

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1. Preamble

1.1. Need for developing a standardized case definition and guidelines for Guillain–Barré syndrome (GBS) and Fisher syndrome (FS) as an adverse event following immunization

Among the various events reported as adverse outcomes following immunizations, neurologic adverse events following immunization (AEFI) are among the most severe and the most difficult to assess. The multifaceted presentation of neurologic illness, the relative lack of familiarity of many clinicians with the approach to and diagnosis of neurologic disease, and the relative scarcity of trained neurologists in many parts of the world make neurologic AEFI some of the most challenging issues in clinical vaccinology. Further, the severity of central and peripheral nervous system events in individual patients often heightens the concern when such illnesses are associated with antecedent immunizations. The lack of a common definition of GBS and FS hinders comparability and uniform reporting of these adverse events.

Sections 2 and 3 of this paper provide the case definitions and guidelines for data collection, analysis, and presentation that the *Brighton Collaboration GBS Working Group* (hereafter referred to as the Working Group) has developed for the standardized collection and assessment of information about GBS and FS. Widespread use of these definitions with their guidelines will improve data comparability and allow for a better understanding of these neurological events that are *applicable* in study settings with different availability of resources, in health care settings that differ by availability of and access to health care, and in different geographic regions.

1.2. Methods for the development of the case definition and guidelines for GBS as an adverse event following immunization

Following the process described in the overview paper [1] a Brighton Collaboration *GBS* Working Group was formed in November 2005 with 34 members with public health, regulatory, clinical and academic, and industry backgrounds. The Working Group identified the key clinical and epidemiologic features required for case definitions for GBS and FS. Aspects of the necessary criteria for classification of GBS were based upon group discussion and a consensus process; these decisions were, to the fullest extent possible, based upon evidence available from peer-reviewed literature and unpublished data. The member composition and results of the web-based surveys completed by the reference group with subsequent discussions in the Working Group can be viewed at: http://www.brightoncollaboration.org/internet/en/index/working_groups.html.

To guide the decision-making for the case definition and guidelines, a literature search was performed by a Cochrane Collaboration professional search person for Guillain–Barré syndrome and other peripheral neuropathies in the context of immunization (MEDLINE 1976–2006; search terms included among others "Guillain–Barré syndrome", "acute inflammatory demyelinating polyradiculoneuropathy", "peripheral neuropathy", "peripheral demyelination", "vaccine", and "immunization"). The search also included reviews of textbooks and study protocols and included searching the literature for pertinent papers on GBS/FS until 2008. Based on a review of the title and abstract of the >3000 references identified, we reviewed 429 potentially relevant articles. Case definitions for GBS that have previously appeared in the literature were reviewed in detail, and the salient aspects of each that were considered by the Working Group as central or core to any case definition for GBS were incorporated.

1.2.1. Guillain–Barré syndrome

Guillain–Barré syndrome (GBS) constitutes an important proportion of acute flaccid paralysis cases world-wide. It is a condition characterized by various degrees of weakness, sensory abnormalities, and autonomic dysfunction due to damage to peripheral nerves and nerve roots [2]. Although the underlying etiology and pathophysiology of GBS are not completely understood, it is believed that immune stimulation plays a central role in its pathogenesis [3]. It is considered to be an immune-mediated disorder resulting from generation of autoimmune antibodies and/or inflammatory cells which cross-react with epitopes on peripheral nerves and roots, leading to demyelination or axonal damage or both [4]. First described by French neurologists Guillain, Barré, and Stohl in 1916, understanding of the disorder has increased tremendously in the past 2 decades [5].

The annual incidence of GBS has been estimated at between 0.4 and 4.0 cases per 100,000 population per year, depending upon study methodology and case ascertainment; most well-designed prospective studies in developed countries have suggested an incidence of 1–2 per 100,000 population per year [6–8]. In North America and Europe, GBS is more common in adults, and steadily increases with age [8,9]. Many studies have suggested that men are more likely to be affected than women. Most cases are sporadic and there does not appear to be a seasonal pattern, with some exceptions [9].

Clinically, GBS is characterized by the acute or subacute onset of varying degrees of weakness in limbs or cranial nerve-innervated muscles, associated with hypo- or areflexia, and a characteristic profile in the cerebrospinal fluid (CSF) [2,10]. Patients typically experience progressive limb weakness, most often beginning in the legs and progressing to the arms and bulbar muscles. The weakness is associated with decreased or absent deep tendon reflexes, and tends to be relatively symmetric. Paresthesias and subjective numbness or tingling may be an early feature and tends to affect the distal extremities. The weakness progresses in an acute to subacute fashion, reaching its clinical nadir of weakness within 2–4 weeks, although in some cases rapidly progressive weakness reaching nadir within several hours may be seen. In approximately a quarter of cases, involvement of innervation to the diaphragm and intercostal muscles may lead to neuromuscular respiratory failure requiring mechanical ventilatory support, a manifestation associated with poorer outcome [2,11,12]. Cranial nerve palsies, including involvement of the facial nerve resulting in facial weakness or extraocular motor nerve involvement or bulbar palsy may be seen. Autonomic dysfunction may occur and can result in signs including postural hypotension, ileus, and labile heart rate. The CSF is characterized by cytoalbuminologic dissociation, with protein elevation but no increase of white blood cell count. In a small percentage of cases, however, particularly if CSF is obtained early in the course of illness, CSF protein may be normal [2,13]. Overall, GBS is generally associated with eventual favorable outcome, with most patients experiencing clinical improvement over weeks to months, although anecdotal evidence suggests that outcomes may be less favorable in resource-poor settings with limited access to treatment and intensive care. In infants and children, recovery is more rapid and tends to be complete, with fatalities rare [14,15]. Elderly patients have a worse prognosis. Requirement of mechanical ventilation, severe weakness at nadir, and rapid onset of weakness have been identified as poor prognostic features [16]. Overall, approximately 5–15% of patients die, and continued disability after 1 year has been estimated to be seen among 20% of patients. Complete recovery is common in the remainder, although persistent mild weakness, numbness, pain, and fatigue may be reported [17].

Currently, GBS is considered to encompass a spectrum of clinicopathological subtypes. In North America and Europe, the most common type is acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which is characterized pathologically and electrodiagnostically by focal demyelination of motor and sensory peripheral nerves and roots [13,18]. In other areas of the world,

a subtype predominated by axonal damage, primarily of motor nerves, is seen and has been termed acute motor axonal neuropathy (AMAN) [19,20]; the reasons for this phenotypic difference are not clear. A subtype of GBS, characteristically consisting of the triad of ataxia, areflexia, and ophthalmoplegia may be seen and is referred to as FS [21,22]. Other less common variants include acute motor and sensory axonal neuropathy (AMSAN). Overlap syndromes between GBS and FS may be seen [2,23,24].

As an immune-mediated disorder, auto-antibodies may form in response to a variety of antigenic stimuli, such as bacterial or viral infection; approximately two-thirds of persons with GBS report an antecedent infectious illness, most commonly a diarrhoeal or respiratory illness, in the days or weeks preceding neurologic signs. One of the strongest associations between an antecedent infectious pathogen and subsequent GBS has been that of infection with the gastrointestinal bacterium *Campylobacter jejuni* [25,26]. Infection with *C. jejuni* may lead to generation of antibodies that react with glycoconjugates within the bacterial cell wall as well as specific peripheral nerve gangliosides. Although infection with *C. jejuni* may be followed by any subtype of GBS, it is most strongly associated with acute axonal damage resulting in AMAN, as well as FS [21,25–27]. While immunologic evidence is strongest for antecedent *C. jejuni* infection, other infectious agents have been temporally associated with subsequent GBS and have included influenza viruses, *Mycoplasma pneumoniae*, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and possibly others [28–32]. In rare cases, other stimuli have been associated with GBS, and include surgical procedures and some malignancies, particularly Hodgkin's disease and other lymphomas [33,34].

Antigenic challenge by an antecedent infection or immunization leads to antigen-specific humoral and/or cellular immunity, and as such, this immune stimulation could theoretically result in GBS through a number of possible mechanisms. The concept of "molecular mimicry" involves a situation in which epitopes of a pathogen or vaccine protein could initiate development of antibodies and/or T-cells that could cross-react with epitopes on peripheral nerve myelin or axonal glycoproteins or ganglioside moieties [35,36]. Activated macrophages could potentially be targeted to antigens on the myelin sheath and subsequently invade the basement membrane resulting in demyelination or, alternatively, invade at the nodes of Ranvier to result in axonal damage [37]. Alternatively, antibody binding could lead to subsequent complement fixation and subsequent damage to the Schwann cell or axon [38,39]. Perturbation of immunoregulatory mechanisms, interfering with self-tolerance of host myelin or axonal proteins, may lead to immune-mediated damage. Pathogen or vaccine-associated proteins may theoretically mediate direct destruction of axonal or myelin membranes, or the insertion of antigen-specific polypeptides into host cell membranes may result in humoral or cell-mediated immune response to the infected cell [38]. Although host genetic or other phenotypic factors are likely to influence susceptibility to development of GBS in certain individuals, an association with specific HLA subtypes or other immunogenetic susceptibility factors has not been consistently identified by existing studies.

GBS has been associated temporally with numerous vaccines; however, such temporal association must be differentiated from causality. In general, specific biological markers indicative of a cause-and-effect association with a particular pathogen or vaccine are absent in GBS. In rare cases, an association with a particular vaccine based upon biological or epidemiological evidence appears to have been demonstrated. Historically, "neuroparalytic accidents" consistent with GBS have been seen following administration of the Semple rabies vaccine, which was produced by inoculation of mature goat or sheep brain with rabies virus subsequently inactivated with phenol, and with rabies vaccine derived from suckling mouse brain [40–42]. In both cases, T-cells reactive to myelin basic protein were demonstrated in vaccine recipients, presumably on the basis of the presence of neural proteins in the vaccine. Subsequent rabies vaccine formulations generated in chick embryo cells have been infrequently associated with GBS. In 1976, concern over a particularly virulent strain of influenza prompted a mass influenza vaccination campaign in the United States. Passive adverse event surveillance suggested an unusually large number of reports of GBS; a subsequent case-control study demonstrated a statistically significant increase in risk of developing GBS in the 6 weeks following vaccination with this swine influenza vaccine, with a risk ratio of 7.3 (95% Confidence Interval [CI] 6.7–8.6) among vaccinees [43,44]. This led to an immediate cessation of the vaccination campaign. Despite strong epidemiologic data of an association with that vaccine, biologic mechanisms remain to be demonstrated, although a recent study found that remnant samples of 1976 swine influenza vaccine induced anti-GM1 antibodies in mice, as did vaccine formulations from 1991 to 1992 and 2004 to 2005, which were not associated with an increase in reports of GBS [45]. Thus, biological significance of this finding remains unclear. Subsequent studies assessing risk of GBS following other formulations of influenza vaccine have failed to consistently demonstrate a more than marginal increased risk of GBS [46–53].

With these notable exceptions, most association of vaccines with subsequent GBS is of a temporal nature only. Thus, it is recognized by the GBS Working Group and should be emphasized to parents, patients, health care providers, and others concerned with immunization safety, that GBS – or any other adverse event – which follows administration of an inactivated component or live vaccine may be temporally *associated with*, but is not necessarily *the result of*, administration of a vaccine. In particular, the presence of an antecedent, presumed initiating event has been an important aspect of prior classification schema for GBS. However, because the definition itself defines a clinical entity without inference of a causal relation to a given exposure, the time interval from immunization until onset of the event cannot be part of the definition itself, but should be assessed as described in the guidelines.

The diagnosis of GBS is suggested by the clinical findings consistent with acute peripheral neuropathy and characteristic CSF profile. Neurophysiologic testing, including nerve conduction studies and needle electromyography, are important in the substantiation of the diagnosis, and electrophysiologic criteria for the diagnosis of AIDP and other forms of GBS have been published [54,55], although specific consensus definitions have not been agreed upon. In North America, Europe, and Australia, most studies will document a demyelinating polyradiculoneuropathy. In other parts of the world, axonal patterns occur more frequently. Electrophysiologic studies performed early in the course of illness, particularly sooner than 7 days following weakness onset, may be normal, and, although it is recommended to perform studies "as soon as possible", depending upon the timing of performance, it may be important to perform follow-up or repeat electrophysiologic studies. In addition, "normal" studies may occur in otherwise typical cases of GBS. However, cases with persistently "normal" studies will not meet Level 1 criteria. Whenever possible, clinical suspicion of GBS should be substantiated by careful and thorough electrophysiologic testing by a technically competent and experienced clinician. Alternative etiologies of acute neuropathy, such as vasculitis, vitamin deficiency, toxic neuropathy, tick paralysis, or porphyria, should be entertained and excluded based upon history or testing (see also Appendix A.3). Treatment of adult patients with either plasmapheresis or intravenous immune globulin (IVIG) has been demonstrated to improve clinical outcomes [56–60], and these are considered the gold standards for treatment. Treatment appears to be most efficacious when administered early. Clinical trials have suggested that there is no efficacy in GBS from treatment

with corticosteroids, and in fact several studies have suggested that corticosteroid treatment is associated with a worse outcome [61,62]. Treatment efficacy data are more limited for children; however, open studies suggest that treatment effects could be similar as in adults.

1.2.2. Fisher syndrome

A clinical syndrome characterized by a triad of ataxia, ophthalmoplegia, and areflexia was first described by C Miller Fisher in 1956 and was hypothesized to be a form of GBS [21]. While the classic triad is often clinically recognized and occurs in the absence of limb weakness, in some cases there is clinical overlap with GBS, with limb weakness present; such cases are considered to be GBS-FS overlap syndromes [21,63,64]. FS is thought to represent a considerably higher proportion of cases of GBS in eastern Asia than in other parts of the world, with estimates of up to 20% of cases in Taiwan and 25% in Japan [21,22]. Certain features of FS, including the general interval between onset and clinical nadir and presence of cytoalbuminologic dissociation, are similar to that for GBS. In general, electrodiagnostic findings are normal, or abnormalities limited to sensory nerves [21,65]. FS is generally considered to be a benign, self-limited illness, and prognosis is generally quite favorable, with most patients experiencing complete resolution of symptoms and signs by 6 months. Treatment of FS with plasmapheresis or IVIG has not been adequately evaluated in controlled trials to allow for substantive conclusions.

Similar to GBS, FS is frequently associated with a preceding antigenic stimulus such as infectious illness. The most common association has been with recent infection with *C. jejuni* (see Section 1.2.1), with one series demonstrating serologic evidence of recent *C. jejuni* infection in 18% of 65 patients [63,64]. FS is frequently associated with the presence of specific anti-ganglioside antibodies, in particular anti-GQ1b and anti-GT1a antibodies, and the presence of these antibodies has allowed for a more thorough understanding of the spectrum of clinical illness in FS, GBS-FS overlap, and related disorders including Bickerstaff's brainstem encephalitis [27,64].

1.3. Rationale for decisions about the case definitions for GBS and FS

While some of the clinical signs and symptoms listed in the definition and guidelines may be subjective and culturally influenced, it should be recognized that such subjectivity is an unavoidable part of standard medical practice.

It is recognized by the Working Group that the case definitions developed for GBS and FS may not capture some of the clinical variants that nonetheless may be related and are regarded by others as forms of "GBS". However, these variants are considered to be rare and comprise less than 1% of overall GBS cases. Thus, the number of cases missed by these definitions is expected to be low.

The Working Group has stated in the guidelines to the case definition that limb weakness in GBS should be "bilateral and relatively symmetric", and it should be noted that weakness is usually, but not exclusively, symmetric in nature, and generally has a pattern of progression from legs to arms and bulbar muscles. However, other patterns of progression, such as from the bulbar muscles down to the arms and then legs, may be seen, and such patterns should be assessed within the context of the overall clinical picture, and should not serve as exclusionary factors.

Weakness has also been stated to be "monophasic in nature, with nadir from onset of weakness reached between 12 h and 28 days, followed by clinical plateau and subsequent improvement, or death". While these time periods are arbitrary, rapid development of weakness with nadir reached within hours in the setting of GBS is unusual and should cast doubt on the diagnosis. On the other end of the spectrum, the onset phase in some patients may last up to 4 weeks, with the majority of patients reaching clinical nadir within 2 weeks. Additionally, fluctuations in the level of weakness prior to reaching nadir, or during the plateau or improvement phase may occur in some cases, particularly in the setting of disease-modifying therapies. These criteria have been included in an attempt to discern GBS from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), which is thought to be clinically and pathologically distinct from GBS. CIDP more typically has an onset phase of >8 weeks, and the weakness may remit and relapse [66,67]. The Working Group recognizes, however, that a small percentage of persons with GBS will have one or more episodes of worsening after initial improvement and that such cases may appear to overlap with CIDP. However, initial episodes of worsening in the setting of treatment of GBS may be fluctuations rather than separate episodes of recurrence of symptoms. In some cases, differentiation of CIDP from GBS may only be possible retrospectively, in the setting of longitudinal follow up.

The Working Group feels that electrophysiologic data are important in substantiating the diagnosis of GBS and in classifying the subtype and are required to meet Level 1 criteria. Neurophysiologic criteria for various subtypes of GBS are provided in Appendix A.1. However, it should be recognized that the quality of electrophysiologic data is operator-dependent, in part depending upon the experience and competence of the performer; thus whenever possible, raw data, rather than summaries or reports, should be documented. Nerve conduction studies (NCS) should be performed as soon as possible after presentation; however, studies performed early in the course of illness, particularly sooner than 7 days following weakness onset, may be normal, and repeat studies within 1–2 weeks may demonstrate abnormalities. In addition, "normal" studies may rarely occur in otherwise clinically typical cases of GBS; however, cases with persistently "normal" studies will not meet Level 1 criteria. In some cases of GBS, assignment of a subtype is not possible; this is particularly true when motor nerves are inexcitable. Needle electromyography (EMG) may be useful in assessing potential axonal loss and for prognostic purposes. The Working Group recognizes that the capacity to perform electrophysiologic testing, due to the absence of diagnostic equipment and/or personnel with expertise, will not be available in some settings. Such cases, however, will not achieve Level 1 criteria. This will also be true for pediatric cases, in which EMG is not frequently performed due to limited experience, the invasive nature of the exam, and the generally favorable outcome in this population.

CSF findings are also important in the diagnosis of GBS. Cytoalbuminologic dissociation has been defined as an elevation of CSF protein levels (above normal reference values for the laboratory doing the testing) in the relative absence of pleocytosis (elevation of CSF WBC). Based upon the best available evidence, the Working Group has used a CSF WBC cutoff value of <50 WBC/μl for what would be consistent with GBS. It is recognized that in some cases of otherwise clinically typical GBS, CSF may be "normal", particularly if obtained within the first week of illness. However, cases with persistently "normal" CSF, or with CSF characterized by >50 WBC/μl, will not meet Level 1 criteria. Traumatic lumbar puncture (LP) occurs when the spinal needle used for the CSF draw penetrates the vascular epidural space and contaminates the CSF sample with blood. The visual threshold for blood contamination is approximately 400 red blood cells (RBC)/μl, which is often used as a working definition for traumatic LP. Traumatic LP makes interpretation of WBC count of a CSF sample difficult since peripheral WBCs from blood are likely to be introduced into CSF, making differentiation of the presence of WBCs due to intrathecal synthesis or infiltration difficult. Several methods for interpretation of CSF parameters following traumatic LP have been suggested. Predicted CSF WBC count can be estimated on the basis of peripheral

blood count and CSF RBCs. True leukocytosis of CSF is present if the observed CSF WBC count exceeds the predicted count. Alternatively, a simple leukocyte:erythrocyte ratio of 1:100 or greater in CSF is highly sensitive and specific in diagnosing meningitis cases with more than 500 erythrocytes/μl in CSF [68].

1.3.1. Fisher syndrome

Specific diagnostic criteria have been drafted for FS because it represents one of the more common subtypes of the GBS spectrum. A separate, specific case definition for FS was needed because it has clinical and electrophysiologic features that would not be captured with the standard GBS case definition. Monitoring and surveillance for GBS should, however, include FS. FS has classically been described as consisting of the triad of ataxia, ophthalmoplegia, and loss of deep tendon reflexes, with preservation of limb strength. If this triad is present along with limb weakness, the standard GBS case definition should be used. Certain aspects of the FS case definition, including intervals to clinical nadir and CSF parameters, are the same as for GBS. Electrophysiologic studies have not been required as part of fulfillment of Level 1 criteria for FS, since these studies are frequently normal. However, if electrophysiologic studies are performed, they should be normal, or abnormalities should be relegated to sensory nerves, and the results of these electrophysiologic studies should be documented.

1.3.2. Use of the case definition in children <2 years of age

The clinical and electrophysiologic criteria specified in these case definitions have been drafted for use in all age groups. However, it is necessary to keep in mind that various neurologic and laboratory criteria used to define the presence of peripheral neuropathy in general and GBS in particular differ in infants and young children, in whom the nervous system has not achieved the same level of development as in older children and adults [69,70]. The neurologic examination, CSF profile, and electrophysiologic features continually evolve after birth, most rapidly over the first weeks and months of life. By approximately 2 years of age, most of the aspects of the neurologic examination have reached a point of maturation, and as such these neurologic examination features should not change significantly from 2 years onward. However, whenever possible, infants and children under 2 years of age should be evaluated by a clinician familiar with the neurologic evaluation of young children, and such evaluations should be performed in an age-appropriate fashion. In particular, strength assessment should be performed taking into account the age and expected strength of the individual. Electrophysiologic studies may not be well tolerated in infants and children, and as a result, the Working Group recognizes that these studies may not be able to be performed adequately in children. It should be noted, however, that GBS in children, particularly those under 6 months of age, is very uncommon [71].

1.3.3. Use of the case definitions, and the guidelines for data collection, analysis and presentation

Recognizing the many variables and uncertainties affecting both the definition and the diagnosis of GBS, the Brighton Collaboration GBS Working Group has attempted to establish useful and practical guidelines for standardizing the collection, analysis and presentation of data on GBS in the setting of pre- and post-licensure clinical trials, surveillance and retrospective epidemiological studies of vaccine safety. The guidelines are *not* intended to establish criteria for management of infants, children or adults with GBS. Rather, they *represent suggestions and recommendations for collection, analysis, and presentation of additional data as deemed necessary by the investigators*. This is particularly relevant for surveillance of GBS as an adverse event following new vaccines against chronic diseases (e.g. diabetes mellitus, rheumatoid arthritis); therapeutic vaccines (e.g. tumor vaccines); and genetically engineered vaccines, mucosal vaccines, or vaccines with slow-release delivery systems, all of which may require different standards.

The Working Group recognizes that other criteria, case definitions, and recommendations for categorization of GBS and FS exist, both in peer-reviewed literature and in other formats [72–75]. Case definitions will differ based upon currently available data, intended use, and the clinical setting to which the case definition is to be applied. The Brighton GBS Working Group's consensus decisions were based upon an attempt to provide both sufficient sensitivity and specificity in the identification of cases of GBS and FS in a variety of settings involving vaccine safety monitoring activities, and particularly guided by the aim of developing case definitions with sufficient specificity for case confirmation.

1.3.4. Case definition structure

The case definitions are structured in three GBS and three FS levels of diagnostic certainty each as described in the overview paper [1]. It should be stressed that, although potentially applicable in a clinical setting, the level of diagnostic certainty is primarily intended for epidemiologic purposes and not as a criterion for treatment. Similar to other Brighton Collaboration definitions, the definition itself defines a clinical entity without inference of a causal relation to a given exposure. The guidelines are structured according to the steps of conducting a study, i.e. data collection, analysis, and presentation. The guideline section includes the information necessary to assess GBS as an AEFI.

The Working Group has emphasized the need for developing case definitions with sufficient specificity for confirmation of cases of GBS/FS. As such, persons reported to have GBS or FS, for which no alternative diagnosis is apparent, but lack sufficient documentation to fulfill minimal case criteria (e.g., Level 3) will be considered as "reported cases of GBS/FS" (Level 4). The Working Group recognizes that the definitions proposed herein may differ in these parameters from other proposed case definitions. For analysis of reported events, these additional categories for analysis include these categories 4 and 5 for persons not meeting the Level 1–3 case definition criteria. In study reports or publications, it may be appropriate to indicate the number of persons meeting the Category 4 (i.e., a reported event of GBS or FS, with insufficient evidence to meet the case definition). In particular, Category 4 should be used if there has been insufficient duration of follow-up to determine clinical nadir, or if clinical information on specific items (e.g., documentation of deep-tendon reflexes) is unknown. This should especially be considered when the size of the Category 4 group is not negligible compared to the analyzed cases group. Sometimes, it may be appropriate to also perform sensitivity analyses with and without the Category 4 group (or a particular subset of the Category 4 group). For example, when early interim analysis is desirable, such as ongoing assessment of prospectively collected surveillance data, sufficient duration of follow-up may not yet be available on suspected GBS cases. A sensitivity analysis that includes at least the Category 4 patients who meet the other criteria for GBS might be useful, while awaiting additional follow-up to assess the timing of the illness nadir.

Monitoring and surveillance for GBS should generally include FS, as feasible.

1.3.5. Periodic review

It is the recommendation of the GBS Working Group, that pre- and post-licensure studies be specifically designed to investigate GBS as described in this document.

Review and, when indicated, revision of the definition and guidelines is planned on a regular (every 3 to 5 years) or "as needed" basis by the Brighton Collaboration GBS Working Group.

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.

- *No* alterations in consciousness or corticospinal tract signs[21]
  AND
- Absence of identified alternative diagnosis.[22]

Level 2 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
- Cerebrospinal fluid (CSF) with a total white cell count <50 cells/μl])[19] (with or without CSF protein elevation above laboratory normal value)
  OR
- Nerve conduction studies are normal, OR indicate involvement of sensory nerves only[20]
  AND
- *No* alterations in consciousness or corticospinal tract signs[21]
  AND
- Absence of identified alternative diagnosis[22].

Level 3 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
- *No* alterations in consciousness or corticospinal tract signs[21]
  AND
- Absence of identified alternative diagnosis[22].

3. Guidelines for data collection, analysis, and presentation of GBS and FS as adverse events following immunization

It was the consensus of the Brighton GBS Working Group to recommend the following guidelines to enable meaningful and standardized collection, analysis, and presentation of information about GBS and FS[23]. However, the implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographic region, and whether the source of information is a prospectively designed clinical trial, a post-marketing surveillance or epidemiologic study, or an individual case report of GBS or FS. Also, as explained in more detail in the overview paper [1], these guidelines are not considered a mandatory requirement for data collection, analysis or presentation.

3.1. Data collection

These guidelines are recommended for the collection of data on GBS or FS cases to allow for comparability of data, and as an addition to data collected for the specific study question and setting. These guidelines are not intended to replace local legal reporting requirements but as a guide towards harmonization of vaccine safety reporting of GBS to a surveillance system or study monitor. Investigators developing a data collection tool based on these data collection guidelines also need to refer to the criteria in the case definition in Section 2 which are not repeated in these guidelines.

The guidelines below have been developed to also address data elements for the collection of adverse event information as specified in general drug safety guidelines by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use [76], and the form for reporting of drug adverse events by the Council for International Organizations of Medical Sciences (CIOMS) [77]. These data elements include an identifiable reporter and patient, one or more prior immunizations, and a detailed description of GBS and FS as an adverse event.

These guidelines are suggested for the collection of data on GBS within the context of vaccine clinical studies or safety surveillance to allow for comparability of data. Additional information may be collected depending on the study question and setting.

3.1.1. Source of information/reporter

For all cases ascertained by surveillance and/or clinical studies, the following information should be recorded as appropriate:

(1) Date of report.
(2) Name and contact information of person reporting and/or assessing or diagnosing GBS (e.g., medical provider including professional status, parent/patient, other third party reporter), in accordance with country specific data protection law.
(3) Geographic location of subject within study area including country if a multi-country study as appropriate.

3.1.2. Vaccinee

For all cases and/or all study participants, as appropriate, the following information should be recorded:

3.1.2.1. Demographics.

(4) Case/study participant identifiers (first name initial followed by last name initial), or code (if clinical trials), or as otherwise specified in country-specific data protection laws.
(5) Date of birth, (specify calendar used if not the commonly used Julian calendar)[24] age, sex, ethnicity (if appropriate).
(6) For infants (<12 months), record gestational age and weight at birth, APGAR score[25].

3.1.2.2. Clinical and immunization history.

(7) Medical history of any pre-immunization condition (including surgery) that may affect the evaluation of GBS/FS as an adverse event following immunization (AEFI). In particular, the pre-vaccination neurological status should be recorded (e.g., no sensory or motor deficits, altered deep tendon reflexes, weakness).
(8) Any drug/toxin or medication history prior to, during, or after immunization by any route, biologics and prescription

[21] Presence of these findings, including extensor plantar responses, would be suggestive of Bickerstaff's Brainstem Encephalitis. Brain magnetic resonance imaging (MRI), if performed, should be normal, or, if abnormal, should not demonstrate brainstem lesions consistent with encephalitis. MRI findings that would be suggestive of Bickerstaff's Brainstem Encephalitis would include: presence of patchy or confluent lesions that are hypointense on T1-weighted images and hyperintense on T2- and fluid-attenuated inversion recovery (FLAIR) sequences in the brainstem (with or without involvement of other cerebral structures).

[22] Including, but not limited to, Wernicke's encephalopathy, botulism, diphtheria.

[23] Unless otherwise specified in the text, the term "GBS" will be used to refer to all the clinical subtypes of GBS, including FS.

[24] The Julian Calendar is the common calendar widely used. The average length of a year in the Julian calendar is 365.25 days (one additional 'leap' day being added every 4 years). http://www.hermetic.ch/cal_stud/cal_art.html#Julian_Calendar.

[25] The APGAR (Activity, Pulse, Grimace, Appearance, and Respiration) score was devised in 1952 by Dr. Virginia Apgar as a simple and repeatable method to quickly assess the health of newborn children immediately after childbirth.

and non-prescription medication (e.g., herbal or homeopathic medication) with long half-life or long-term effect (e.g., immunoglobulins and blood transfusion, immununosuppressants) that could affect the evaluation of GBS/FS, but excluding treatment given for GBS or FS.

(9) Immunization history, including exact dates of administration and vaccines given including their number in series; indicate the history for previous immunizations as well as any adverse events following these immunizations. In particular, the occurrence of a prior episode of GBS/FS prior to immunization or after a previous immunization should be specifically noted.

At a minimum, any immunizations given within 6 weeks[26] prior to onset of neurologic illness should be carefully documented, according to Guidelines under Section 3.1.3.

(10) Any clinical or laboratory evidence of antecedent infectious illness (e.g., upper respiratory symptoms, gastrointestinal symptoms, febrile illnesses, microbiological/serological test results) occurring or identified within the 6 weeks[26] prior to onset of neurologic signs, should also be carefully documented, including temporal relationship to immunization.

As the hypothesized immune-mediated physiologic responses resulting in GBS/FS are suspected, based upon biological and epidemiological evidence, to require time to develop and clinically manifest [3,44,78], short intervals between antecedent events and GBS/FS, particularly those occurring <3 days prior to onset, may be considered less plausible.

3.1.3. Details of the immunization

For all cases and/or all study participants, as appropriate, the following information should be recorded:

(11) Date(s) and time(s) of immunization(s), specify if a 12 or a 24 h clock was used. The 24 h clock is preferred, as it avoids potential confusion about a.m. and p.m. times.

(12) If multiple immunizations, or separate immunizations, are given on the same day or on different days, dates and times of each individual immunization should be recorded.

(13) Description of vaccine(s): trade name and generic name of vaccine, lot number, expiration date, manufacturer, dose, multi- or mono-dose vial, pre-filled syringe, volume (e.g., 0.5 ml) and number of dose (if part of a series of immunizations against the same disease), diluent lot number (if used), adjuvants, preservatives, buffer preparation (for some oral vaccines), expiration date, preparation of vaccine, e.g., for multidose vials of lyophilized vaccines, whether reconstituted vaccine was used within the specified time. Where surrogate information such as the brand name of a vaccine would specify several of the characteristics above, data collection forms should be simplified accordingly.

(14) Detailed description on combination vaccines: if used, provide the trade name and generic names if present. Specify the antigen components and if the vaccine was a combined one (single shot).

(15) Anatomical sites[27] (including left or right side) of all immunizations (e.g., vaccine A in proximal left lateral thigh, vaccine B in left deltoid, vaccine C oral) and needle length and gauge.

(16) Route and method of administration (e.g., oral, intranasal, intramuscular, intradermal, subcutaneous, needle-free such as transcutaneous patch [including type and size] or other injection devices).

Storage conditions of the vaccine: vaccines should be stored at temperatures according to the manufacturer's recommendations. If possible, temperature logs, type of refrigerator, power outages, and vaccine storage conditions should be reviewed and noted, especially in prospective studies.

3.1.4. The adverse event

For all cases and/or all study participants, as appropriate, the following information including a detailed clinical description of GBS/FS is recommended. It is recognized that availability of clinical data will vary significantly in differing settings. These guidelines are provided as reference tools and recommendations as to the ideal body of clinical information that will help determine the likelihood that an illness meets definition criteria for GBS/FS. They also serve as guidance mechanisms for pertinent, important, and relevant clinical and epidemiologic information that, in an ideal setting, would assist in the evaluation of possible cases of GB/FS. They are not intended to dictate clinical practice.

(17) For all cases at any level of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet a case definition and other signs or symptoms indicative of GBS should be recorded

(18) For all cases, detailed clinical descriptions of clinical manifestations and course is recommended, in particular making careful note of the following including the respective dates of:

- The specific clinical findings, laboratory features, and/or electrophysiologic features suggestive of GBS contributing to the classification of the case of GBS.
- Severity of weakness at clinical nadir (e.g., by use of the Medical Research Council Manual Muscle Testing Scale (see Appendix A.2), the GBS Disability scale (see Appendix A.5), or clinical descriptors).
- Additional neurologic signs of GBS (e.g., fasciculations, atrophy, myoclonus).
- Concurrent signs, symptoms, and diseases.
- Results of all electrophysiologic studies (e.g., electromyography/nerve conduction velocity studies [EMG/NCS]), including dates of performance (footnote) and the clinical subtype (as outlined in Appendix A.1) or the inability of its ascertainment.
- Results of any additional neuropysiologic studies, including electroencephalography [EEG], neuroimaging studies (e.g., computed tomography [CT] or MRI), including dates of performance.
- Results of cerebrospinal fluid (CSF) examination, including WBC (in cells/μl), red cell count (RBC, in cells/μl), differential leukocyte count (when available), protein level (in mg/dL), glucose level (in mg/dL), concomitant serum glucose level (in mg/dL) including the dates of performance and upper limits of normal for these parameters for the particular laboratory performing the CSF analysis.

[26] While duration of surveillance for potential development of GBS following an antecedent event is arbitrary, based upon available epidemiologic data, the Working Group suggests that a duration of 6 weeks following any identified antecedent event would represent a reasonable period of surveillance, beyond which biological plausibility of an association with an identifiable antigenic stimulus (e.g., infectious illness, vaccination) declines. The evidence for the most appropriate time interval is limited, largely based on certain studies of the 1976–1977 influenza vaccine. Other surveillance intervals may be considered, and if used, reported in addition to a 6-week interval.

[27] Please refer to the case definition of the overall local reaction document that has specific medical illustrations as a guide to record local reactions if they exist [84].

- Results of any additional laboratory testing that is performed which may be useful in identifying an etiology of weakness other than GBS (see Appendix A.3).

(19) Document date and time of onset, and first observation and of diagnosis.[28,29]

(20) Neurologic consultation should be obtained when possible. Detailed notes from the neurologic examination should be provided if possible. It is recommended that the neurologist be asked to record:
1. Manual Muscle Testing assessment using the Medical Research Council Scale (see Appendix A.2).
2. Deep Tendon Reflex assessment.
3. Sensory examination assessment.
4. Cranial nerve examination.
5. Presence or absence of ataxia (for FS).

In addition to recording of the standard neurologic examination details above the following measurements and functional scales may be of utility, and their use in the documentation of clinical features and outcomes is encouraged:
1. Modified Rankin Functional Score (see Appendix A.4);
2. GBS disability score (Appendix A.5).

(21) For patients prospectively enrolled in clinical trials, measurements at the following intervals could be considered:
- Initial presentation to medical care.
- At clinical nadir.[30]
- At all subsequent points of significant change in neurologic status until the end of the clinical course (recovery, death, or end of follow up), if possible, otherwise weekly for 4 weeks, then monthly for 5 months, then every 3 months.
- Additional measurements will be determined by clinical course.

For retrospective studies involving data collection from existing medical records, partial record of a hospitalization such as discharge summary only, often may not include sufficient detail. Many parts of the entire record for the acute care hospital stay will be useful, often including progress notes (e.g., to assess evolved weakness and symmetry based on muscle strength scores, and to assess whether nadir occurred within 28 days after onset).

(22) The duration of surveillance for GBS and FS, when collected as a pre-specified adverse event in clinical trials, may vary, depending on:
- biologic characteristics of the vaccine (e.g., live attenuated versus inactivated);
- composition of the vaccine (including adjuvant, if present);
- biologic characteristics of the vaccine-targeted disease;
- biologic characteristics of GBS or FS, including patterns identified in previous trials (e.g., early phase trials); and
- biologic characteristics of the vaccinee (e.g., underlying disease like immunosupressing illness and any pre-existing neurological condition.

(23) Ideally, patients should be followed until death attributable to the acute illness occurs, or until full recovery is achieved. In persons with persisting deficits, long-term monitoring may not be practicable or possible, and should be performed as long as possible, with documentation of the duration of surveillance if lost to follow-up.

Most cases will reach clinical nadir prior to 28 days. However, if it is unclear whether a patient has reached clinical nadir and the duration of monitoring is less than 28 days, this should be specifically noted. For some patients, nadir and subsequent clinical improvement will be evident by the time of discharge from acute hospitalization. Although not always feasible, it may be desirable to obtain records from multiple providers or facilities, as GBS patients may be initially treated in an acute care hospital, sometimes transferred to another acute care setting, discharged to a rehabilitation facility and/or followed in an outpatient setting over the course of their illness.

(24) The outcome should be recorded including the date of final outcome or last observation. The following are suggested details and terms for reporting outcome:
- A. Neurologic/Functional Outcome
  - (i) Recovered, no sequelae, back at pre-morbid baseline status;
  - (ii) recovered, neurologic sequelae present at time of final follow up;
  - (iii) died;
  - (iv) outcome unknown; or
  - (v) other outcome (describe).
- B. Disposition at last follow-up
  - (i) Disposition to home, independent living;
  - (ii) disposition to home, dependent living;
  - (iii) disposition to pre-illness residence other than home (nursing home, skilled facility, etc.), independent living or pre-illness baseline status;
  - (iv) disposition to assisted living or rehabilitation;
  - (v) died;
  - (vi) disposition unknown; or
  - (vii) other disposition (describe).
- C. Immunotherapy
  - (i) Immunotherapy rendered (intravenous immune globulin, plasmapheresis, corticosteroids, etc.); or
  - (ii) no immunotherapy rendered.

3.1.5. Miscellaneous/general recommendations

(25) Methods of data collection should be consistent within and between study groups, if applicable. Reports of GBS/FS should be collected/included in the database regardless of the time elapsed between immunizations and the adverse event. If not feasible, the study period during which safety data are being collected and/or included in the database should be clearly defined.

(26) Follow-up of reported events should attempt to verify and complete the collection of information as outlined in the data collection guidelines 1 through 28.

3.2. Data analysis

The following guidelines are suggested for analysis of data on GBS to allow for comparability of data, in addition to data analyzed for the specific study question and setting.

(27) Reported events should be classified in one of the following five categories. Events that meet the case definition should be classified according to the levels of diagnostic certainty as specified in the case definition. Events that do not meet the

[28] The date and/or time of onset is defined as the time when signs or symptoms suggestive of neurologic illness as self-reported by the patient or surrogate, or by documentation or observation by a health care provider, were first experienced and/or described. The onset date should then be assessed in relation to the vaccine administration to evaluate the hours or days after (or before) vaccination when the event started.

[29] The date of diagnosis of an episode is the day the event met the lowest level for meeting the case definition as determined by study personnel or a health care professional.

[30] Clinical nadir is operationally defined at the point at which clinical symptoms (e.g., limb or respiratory weakness) are felt to be at the clinical worst; this nadir will need to be defined and identified by the health practitioner on a case-by-case basis. Ideally, interval between illness onset and symptomatic nadir should be documented, or at least whether the nadir occurred within 28 days after onset.

case definition should be classified in the additional categories for analysis. It should be attempted to reach the highest level possible, e.g., if Level 2 is fulfilled proceed to see if Level 1 is also fulfilled.

3.2.1. Event classification in 5 categories[31]

3.2.1.1. Event meets case definition. Main categories with subcategories

1. Level 1: criteria as specified in the case definition for GBS or FS.
2. Level 2: criteria as specified in the case definition for GBS or FS.
3. Level 3: criteria as specified in the case definition for GBS or FS.

3.2.1.2. Event does not meet case definition. Additional categories for analysis

4. Reported event of GBS or FS, with insufficient evidence to meet the case definition.[32]
5. Not a case of GBS or FS.[33]

(28) If there is evidence, clinically or diagnostically, of both FS and GBS, and the case meets both GBS and FS case definitions, it should be classified as GBS.

(29) The interval between immunization(s) and onset of GBS should be determined from the date of immunization(s) and date/time of onset, or first observation or diagnosis, whichever is available. Whatever dates are used, they should be used consistently within and across study groups. For limited numbers of cases, the exact time course should be assessed for each case. For large case series or data sets, total number of persons developing GBS should be reported over the total number of subjects. All intervals should be analyzed and categorized by day (e.g., numerator/denominator [%] on day or interval X post-immunization). For example:

Interval	Number	Percent
Day 0–3		
Day 4–7		

(30) The interval (days) between onset of neurologic signs and symptoms and
- clinical nadir (as determined by the investigator)[30];
- performance of electrodiagnostic studies (recording all such intervals if multiple electrodiagnostic studies performed);
- collection of CSF (recording all such intervals if multiple CSF specimens collected).

should be analyzed and compared between study arms.

(31) Items to analyze in assessments of GBS include the following:
- The interval between the date of onset[24], if known, or date of first observation[24] or date of diagnosis[26] to the date of outcome at last follow up (mean, median, range).
- Neurologic index scores (Appendices A.1–A.5) at the designated intervals.
- The mean, median, and range for the following parameters of CSF profile should be given:
  (i) WBC (/μl);
  (ii) RBC (/μl);
  (iii) Protein (mg/dL);
  (iv) Glucose (mg/dL).

(32) The following data should be collected and compared, as best as possible, between patients. Documentation of these additional neurologic signs may be performed as follows:
- Number of patients meeting the case definitions for GBS with the following neurologic signs at any point in illness
  (i) Bilateral and relatively symmetric limb weakness.
  (ii) Decreased or absent deep tendon reflexes.
  (iii) Cranial nerve abnormalities (specify).
  (iv) Respiratory weakness/failure.
  (v) Dysarthria/dysphagia (specific comment of presence or absence; FS).
  (vi) Ataxia (specific comment of presence or absence; FS).
  (vii) Ophthalmoparesis (specific comment of presence or absence; FS).
- Number of patients with:
  (i) Abnormal electrodiagnostic studies. If abnormal electrodiagnostic studies found, the number of patients with clinical subtypes as outlined in Appendix A.1 should be noted.
  (ii) Abnormal CSF profiles. Among those with abnormal CSF profiles, the number demonstrating WBC >5 but <50 cells/μl should be noted.
  (iii) Abnormal CT/MRI findings (if performed).
- Number of patients:
  (i) Receiving intravenous immunoglobulin.
  (ii) Receiving plasmapheresis.
  (iii) Receiving corticosteroids.
  (iv) Receiving antibiotics/antiviral medication.
- Clinical and functional outcome:
  (i) Number of patients who died, who were discharged to home, who were discharged to long-term care facilities [Dispositions outlined in (28B)].
  (ii) Number of patients who survived (with and without neurologic sequelae), who died, and who had other outcomes [Functional outcomes outlined in (28A)].

(33) Data on GBS/FS in subjects receiving a vaccine should be compared with those obtained from appropriately selected and documented comparison group(s), and should be analyzed by study arm and dose, where possible, e.g., in prospective clinical trials.

3.3. Data presentation

These guidelines are suggestions for the presentation and publication of data on GBS to allow for comparability of data. Additional information collected and analyzed may be presented depending on the study question and setting. The guidelines are NOT guidelines for primary reporting of GBS/FS to a surveillance system or study monitor. It is recommended to also refer to existing guidelines including CONSORT (Consolidated standards of reporting trials), QUORUM (Improving the quality of reports of meta-analyses of randomized controlled trials), TREND (Transparent reporting of evaluations with non-randomized designs), STROBE (Strengthening the reporting of observational studies in epidemiology) and MOOSE (Meta-analysis of observational studies in epidemiology) for presentation and publication of randomized controlled trials, meta-analyses, non-randomized designs, observational studies, and systematic reviews of vaccine safety studies,

[31] To determine the appropriate category, the user should first establish whether a reported event meets the criteria for the lowest applicable level of diagnostic certainty (i.e., Level 3). If there is evidence that the criteria of the next higher level (Level 2) of diagnostic certainty are met, the event should be classified in the next category. This approach should be continued until the highest level of diagnostic certainty for a given event can be determined. If the lowest level of the case definition(s) is not met, it should be determined that any of the higher levels of diagnostic certainty are similarly not met, and the event should be classified in category 4 or 5.

[32] If the evidence available for an event is insufficient to permit classification at any level of diagnostic certainty (e.g., because of missing information), such an event should be categorized as "reported GBS with insufficient evidence to meet the case definition". Notations should be made as to what evidence is missing.

[33] An event does not meet the case definition if investigation reveals a negative finding of a necessary criterion or if an exclusion criterion is met. Such an event should be rejected and classified as "Not a case of GBS".

respectively [79–83].

(34) All reported events of GBS/FS should be presented in accordance with data analysis guidelines (e.g., by category of diagnostic certainty, age group). In the event that sufficient numbers of events/cases are available to present in tabular or collated format, this presentation should be used.
(35) All reported cases of GBS/FS should include the calculation of the variables, preferably in table form, outlined in "Data Analysis" above.
(36) Data on GBS should be presented in accordance with data collection guidelines 1–25 and data analysis guidelines 28–33.
(37) Data should be presented with numerator and denominator (n/N) and not only in percentages.

Although in immunization safety surveillance systems denominators are usually not readily available, attempts should be made to identify approximate denominators. The source of the denominator data should be reported and calculations of estimates described (e.g., obtained from manufacturer, Ministry of Health and coverage/population-based data doses distributed, as appropriate). Describe the numerator and denominator used in detail including any limitations.

(38) The incidence[34] and prevalence[35] of cases in the study population should be presented and clearly identified as such in the text.
(39) If the distribution of data is skewed, the median and range are more appropriate statistical descriptors than a mean.
(40) Any publication of data on GBS should include a detailed description of the methods used for data collection and analysis. It is essential to specify

- the study design of clinical trials or epidemiologic studies;
- for surveillance systems:
  - the type of surveillance system (e.g., passive surveillance, active surveillance);
  - the characteristics of the surveillance system (e.g., population served, mode of report solicitation);
  - the search strategy in surveillance databases;
  - expected number of cases in a comparable background population.
- comparator group(s), if used for analysis;
- whether the day of immunization was considered "day one" or "day zero" in the analysis; and
- whether the date of onset[26] and/or the date of first observation[26] and/or the date of diagnosis[27], end of episode[36] or final outcome[37] was used for analysis. Whatever dates are used, they should be used consistently within and across subjects and described; and
- Reference the case definition (s) used (Brighton Collaboration or other) in the abstract or methods section of a publication[38].

[34] Total of 10 cases of GBS/FS in 2000 study participants or 1 case per million during 5 days; use as appropriate. For data comparability the format n/million/year is recommended.
[35] E.g., cases of GBS/FS on day 1: 2 cases, day 2: 10 cases, day 3: 3 cases, etc. For data comparability the format n/million is recommended.
[36] The end of an episode is defined as the time the event no longer meets the case definition, or the clinical illness reaches a plateau.
[37] GBS/FS not resolved at the time of reporting or evaluation may be followed up as clinically necessary and additional reporting should be encouraged in order to describe progress until the final outcome at the last time of follow-up. "Sequelae" are long-term clinical consequences resulting from the event.
[38] Use of this document should be referenced by referring to the link on the Brighton Collaboration website (http://www.brightoncollaboration.org/internet/en/index/definition_guidelines/document_download.html).

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Appendix A.

The validated tools in the appendix have been suggested by this working group to assist the user of the proposed case definitions for GBS and FS in identifying possible tools for clinical assessment based on their widespread use or experience with these tools in previous studies, and because use of identical tools in study settings would further allow for data comparability

A.1. Neurophysiologic criteria for various subtypes of GBS

Neurophysiologic Criteria for Subtypes of Guillain–Barré Syndrome: Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP), Acute Motor and Sensory Axonal Neuropathy (AMSAN), Acute Motor Axonal Neuropathy (AMAN) [Adapted from Reference 2].

A.1.1. AIDP

At least one of the following in each of at least 2 nerves, or at least two of the following in one nerve if all others inexcitable and

dCMAP > 10% LLN:

1. Motor conduction velocity <90% LLN (85% if dCMAP < 50% LLN).
2. Distal motor latency >110% ULN (>120% if dCMAP <100% LLN).
3. pCMAP/dCMAP ratio <0.5 and dCMAP >20% LLN.
4. F-response latency >120% ULN.

A.1.2. AMSAN[39]

None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP <10% LLN.

Sensory action potential amplitudes <10% LLN.

A.1.3. AMAN[39]

None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP <10%LLN.

Sensory action potential amplitudes normal.

A.1.4. Inexcitable

dCMAP absent in all nerves or present only in one nerve with dCMAP <10% LLN.

dCMAP = compound muscle action potential after distal stimulation; pCMAP = compound muscle action potential after proximal stimulation; LLN = lower limit of normal; ULN = upper limit of normal.

A.2. Medical research council scale of manual muscle testing: grading

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

A.3. Exclusionary criteria for a diagnosis of Guillain–Barré syndrome

There are multiple other pathologic processes that may occur at various localizations in the central and peripheral nervous system that may present with a clinical picture similar to or identical to that of Guillain–Barré syndrome. If such a diagnosis explaining flaccid weakness/paralysis is present, this effectively excludes a diagnosis of Guillain–*Barré syndrome, and the subject is considered* "*Not a case*".

Examples of other diagnoses, grouped according to typically affected region, are provided below; this is not intended to be an exhaustive list, but rather to highlight the localizations within the nervous system that lesions or illness might occur, with examples provided:

- *Intracranial*
  - Carcinomatous meningitis.
  - Brain stem encephalitis.
- *Spinal cord*
  - Infarct, myelitis, compression.
- *Anterior horn cells of spinal cord*
  - Polio and other viruses producing poliomyelitis, including West Nile virus.
- *Spinal nerve roots*
  - Chronic inflammatory demyelinating polyneuropathy.
  - Cauda equina compression.
- *Peripheral nerves*
  - Metabolic derangements such as hypermagnesemia or hypophosphatemia.
  - Tic paralysis.
  - Heavy metal toxicity such as arsenic, gold and thallium.
  - Drug-induced neuropathy, (e.g., vincristine, platinum compounds, nitrofurantoin, paclitaxel).
  - Porphyria.
  - Critical illness neuropathy.
  - Vasculitis.
  - Diphtheria.
- *Neuromuscular junction*
  - Myasthenia gravis.
  - Organophosphate poisoning.
  - Botulism.
- *Muscle*
  - Critical illness myopathy.
  - Polymyositis.
  - Dermatomyositis.
  - Hypo/hyperkalemia.

A.4. Modified rankin scale (MRS)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

SCORE (0–6): _____

Patient name: _____

Rater: _____ Date: ___/___/____ ___:___

A.5. Guillain–Barré syndrome disability scale [85]

0	Healthy
1	Minor symptoms or signs of neuropathy but capable of manual work/capable of running
2	Able to walk without support of a stick (5 m across an open space) but incapable of manual work/running
3	Able to walk with a stick, appliance, or support (5 m across an open space)
4	Confined to bed or chair bound
5	Requiring assisted ventilation (for any part of the day or night)
6	Death

[39] In the original definitions the difference between AMSAN and AMAN is implied but not stipulated.

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