Vaccine 28 (2010) 3488–3495

Contents lists available at ScienceDirect

Vaccine

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

Evaluating the *Brighton Collaboration* case definitions, aseptic meningitis, encephalitis, myelitis, and acute disseminated encephalomyelitis, by systematic analysis of 255 clinical cases

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ARTICLE INFO

Article history:
Received 21 November 2007
Received in revised form 9 February 2010
Accepted 15 February 2010
Available online 1 March 2010

Keywords:
AEFI
Meningitis
Encephalitis
Myelitis
Case definitions

ABSTRACT

Aims: Brighton Collaboration (BC) case definitions are independent from presumed causes or triggers, hence should be applicable in routine clinical settings.
Scope: 255 cases with discharge diagnoses of aseptic meningitis (ASM; $n = 164$), encephalitis (ENC; $n = 48$), myelitis (MYE; $n = 8$), ADEM ($n = 10$), or bacterial meningitis (BM; $n = 59$; control group) were tested against the BC case definitions ASM, ENC, MYE, and ADEM. Overall rates of agreement between BC criteria and discharge diagnoses were 70%, 78%, 97%, and 97% for ASM, ENC, MYE and ADEM, respectively.
Conclusion: BC case definitions are easily applicable in retrospective chart reviews allowing causality assessments with minimal selection bias.

1. Introduction

The *Brighton Collaboration* (BC) is an international voluntary collaboration to facilitate the development, evaluation, and dissemination of high quality information about the safety of human vaccines [1–3]. To date, the *Brighton Collaboration* has developed multiple case definitions of different clinical conditions which may follow immunisations, such as "fever" [4], "intussusception" [5], "swelling at or near injection site" [6], and many others (see http://www.brightoncollaboration.org). Two recently completed documents are the case definitions for "aseptic meningitis" [7] and "encephalitis/myelitis/acute disseminating encephalomyelitis (ADEM)" [8].

Brighton Collaboration case definitions are designed as standalone criteria for the verification of clinical events as "cases", independent from potential causes or triggers (such as allergens, infections, autoimmune diseases, vaccines, or unknown causes) [3]. BC definitions serve as evidence-based tools to assign levels of diagnostic certainty not only in pre-and post-marketing surveillance of vaccines, but also as outcome measures in randomized clinical trials or retrospective chart reviews [9]. Several investigators have tackled the issue of creating standard criteria and prediction rules for the differential diagnosis of meningitis [10–17]. Up until today, however, there is no international consensus or gold standard method for the clinical diagnosis of meningitis, encephalitis, myelitis or ADEM [16,18–24].

Depending on the availability of laboratory and neuroimaging facilities on site, these diagnoses may be based on different criteria in different clinical settings [25–27]. The *Brighton Collaboration* Levels of Diagnostic Certainty are aimed to account for such differences while allowing comparability of clinical diagnoses in resource-rich and resource-poor settings. This study aimed to validate the usefulness of the *Brighton Collaboration* case definitions for aseptic meningitis [7] and encephalitis/myelitis/acute disseminated encephalomyelitis (ADEM) [8] in the context of a retrospective chart review at the University Children's Hospital, Basel (UKBB). The objectives of the study were twofold: To define rates of agreement between the clinician's discharge diagnoses and the categorizations according to the BC case definitions; and to systematically analyze discordant cases. The results of this investigation will be used to issue suggestions for the improvement of the respective BC case definitions as well as recommendations for evidence-based clinical practice.

Abbreviations: AEFI, adverse events following immunization; ADEM, acute disseminated encephalomyelitis; ASM, aseptic meningitis; MYE, myelitis; ENC, encephalitis; BM, bacterial meningitis.

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doi:10.1016/j.vaccine.2010.02.053

2. Materials and methods

2.1. Study design and case selection

The study protocol was approved by the Institutional Review Board at the University of Basel (Ethikkommission Beider Basel, EKBB) in September of 2006. Clinical report forms and a corresponding SPSS database were created accounting for all relevant information required for the *Brighton Collaboration* case definitions for meningitis, encephalitis, myelitis and ADEM. Subsequently, a retrospective chart review was performed to include all patients hospitalized at UKBB, during the 6-year period 2000–2005 with the discharge diagnoses of meningitis, encephalitis, myelitis or ADEM. Patient records were identified from two different sources:

(a) Systematic screening of the following ICD-10 codes: (G00) bacterial meningitis, not elsewhere classified, (G01) meningitis in bacterial diseases classified elsewhere, (G02) meningitis in other infectious and parasitic diseases classified elsewhere, and (G03) meningitis due to other and unspecified causes, (G04) encephalitis, myelitis and encephalomyelitis, and (G05) encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere.
(b) Electronic query of all discharge summaries using the following pre-defined search terms: "meningitis", "encephalitis", "enzephalitis", "myelitis", "encephalomyelitis", and "enzephalomyelitis" (accounting for two possible ways of spelling the word "Encephalitis" in German).

Eligible clinical cases (identified by either search method) were pooled and verified, duplicate entries excluded. Only the first hospitalization of any given patient was counted. Only cases providing written documentation of a definite or suspected diagnosis were considered eligible for this study and were included in a final listing of 255 clinical cases.

2.2. Applying "clinical tags" according to the documented discharge diagnoses

Eligible cases were sorted by "CD+" for "Clinical diagnosis present", and "CD−" for "clinical diagnosis absent" in each diagnostic category: "meningitis", "encephalitis" (ENC), "myelitis" (MYE), "ADEM" (ADEM). Cases with a discharge diagnosis of "meningitis" were further classified as "aseptic meningitis" (ASM), "bacterial meningitis" (BM) or "unspecified meningitis" (UM). In 7 cases "meningitis" was coded as one of the discharge diagnoses, but the letter indicated that the diagnosis had, in fact, been excluded during hospitalization. These cases were tagged with "ND" for "no diagnosis".

2.3. Applying the Brighton Collaboration algorithm

An independent investigator (BR), who had not previously been involved in the care of the patients, reviewed the medical records in a blinded fashion using the structured clinical report form (CRF). The extracted data in the CRF were confined to the variables required for the Levels 1–3 of the respective BC case definitions. [7,8]. The following labels were applied to all cases in each category (MEN, MYE, ENC, ADEM): "BC+" for "*Brighton Collaboration* Definition fulfilled", "BC−" for "*Brighton Collaboration* Definition not fulfilled".

2.4. Data analysis

The clinical tags were then unblinded and compared to the respective diagnostic categories according to the BC algorithm. In the absence of a gold standard for the diagnoses of encephalitis, meningitis, myelitis and ADEM, sensitivities and specificities cannot be calculated. The new test (i.e. the BC algorithm) was therefore tested against an imperfect, previously available reference test (i.e. the clinician's diagnosis in the discharge summary). As a result, we determined overall rates of agreement (ORA), positive percent agreement (PPA) and negative percent agreement (NPA), respectively, including the 95% confidence intervals for a total sample size of 255 cases (See Appendices A1 and A2) [33,34]. Kappa scores were calculated (Stata Version 9.0se; College Station, TX) in order to find the probability of exceeding agreement expected by chance alone, when comparing the BC definition to the clinical assessment.

2.5. Individual analysis of cases with discordant results

Cases with discordant results between the physician's diagnosis and BC category were reviewed individually. The aim of this subanalysis was to probe, on a case-by-case basis, the ability of the BC algorithm to consistently differentiate between aseptic meningitis, myelitis, encephalitis and ADEM, or "none of the above" from a pool of cases with any of the diagnoses of interest.

3. Results

3.1. Case selection

The ICD 10 (G00-05) search according to the methods described above yielded a total of 73 cases (ICD-10 database). Electronic search of discharge summaries for the terms "meningitis", "encephalitis", "enzephalitis", "myelitis", "encephalomyelitis", and "enzephalomyelitis" yielded a total of 902 cases (clinical database). The clinical database and the ICD-10 database were merged and duplicate entries and multiple hospitalizations were again deleted. Fig. 1 provides an overview of the merging process.

3.2. Applying "clinical tags" according to the documented discharge diagnoses

The diagnostic labels according to the diagnoses listed in the discharge summary yielded the following distribution of unique and overlapping diagnoses (Fig. 2)

3.3. Applying the Brighton Collaboration algorithm

Applying the *Brighton Collaboration* algorithms yielded a distribution, which was considerably less complex (Fig. 3). A total number of 108 cases were ruled out entirely.

3.4. Data analysis

3.4.1. Overall rates of agreement, positive percent agreement (PPA) and negative percent agreement (NPA) for each level of diagnostic certainty

Diagnostic labels and BC levels of diagnostic certainty were compared. Overall rates of agreement (ORA), positive percent agreement (PPA) and negative percent agreement (NPA) were calculated for each level of diagnostic certainty. Table 1 demonstrates that ORA ranged from of 77 to 98% for ENC, MYE, and ADEM. Again, as expected for a confirmatory test, levels of positive percent agreement (PPA) were lower than values for negative percent agreement (NPA). The comparison of ASM showed 67% ORA in Level 1, but a significantly lower value at Level 2 (38%), reflecting the overlap with cases of bacterial meningitis (see Section 3.5.2). Point estimates and 95% confidence intervals were constructed, using the total sample

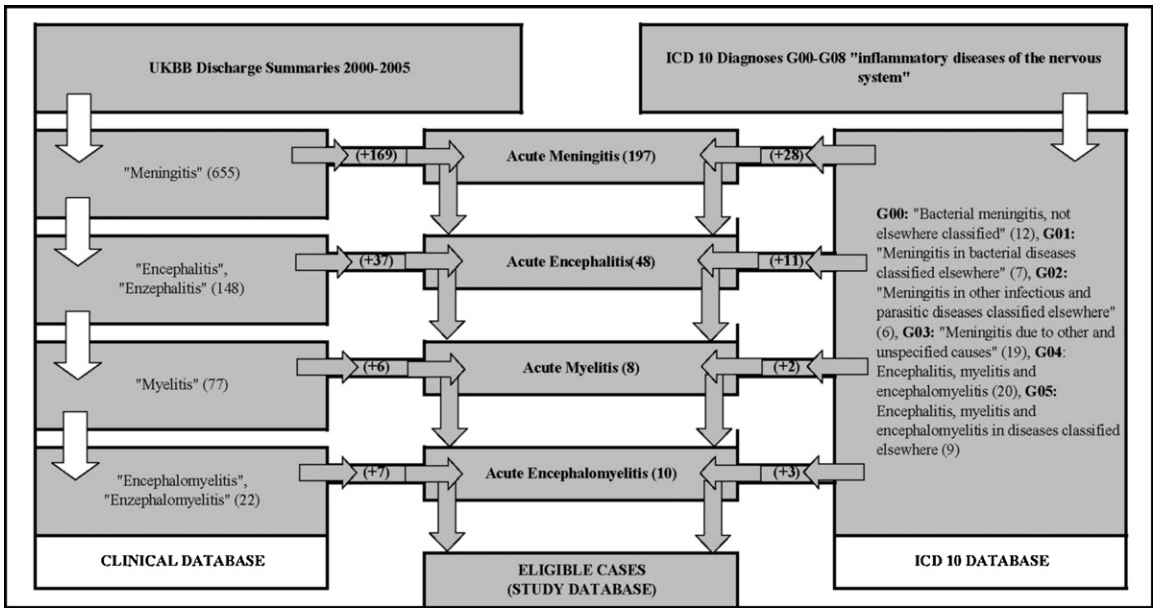

Fig. 1. Merging search results and identification of eligible cases.

size for which comparative assessments were available ($n = 255$) for all calculations.

3.4.2. Overall rates of agreement, positive percent agreement, negative percent agreement and Kappa scores for any level of diagnostic certainty

Table 2 shows the results for ASM, BM, ENC, MYE, and ADEM for any level of diagnostic certainty. In most instances, NPA was higher than PPA, which is consistent with a confirmatory test rather than a screening tool, as reported previously in the evaluation of BC definitions [35,36].

As mentioned previously, cases of BM were included as negative controls and tested against the BC definition for ASM. As expected, we found significantly lower levels of agreement between a clinical case of BM and the BC category of ASM.

3.5. Individual analysis of cases with discordant results

3.5.1. Cases with the clinical diagnosis of "aseptic meningitis" ($n = 140$)

Of the 140 cases with an exclusive clinical diagnosis of aseptic meningitis, 96 (68.6%) fulfilled the BC definition for ASM, 44 cases did not fulfill the definition for ASM. In 39 of these discordant cases, no documented gram stain report was available upon chart review. A negative gram stain is a major criterion and required for any level of diagnostic certainty in the *Brighton Collaboration* definition of

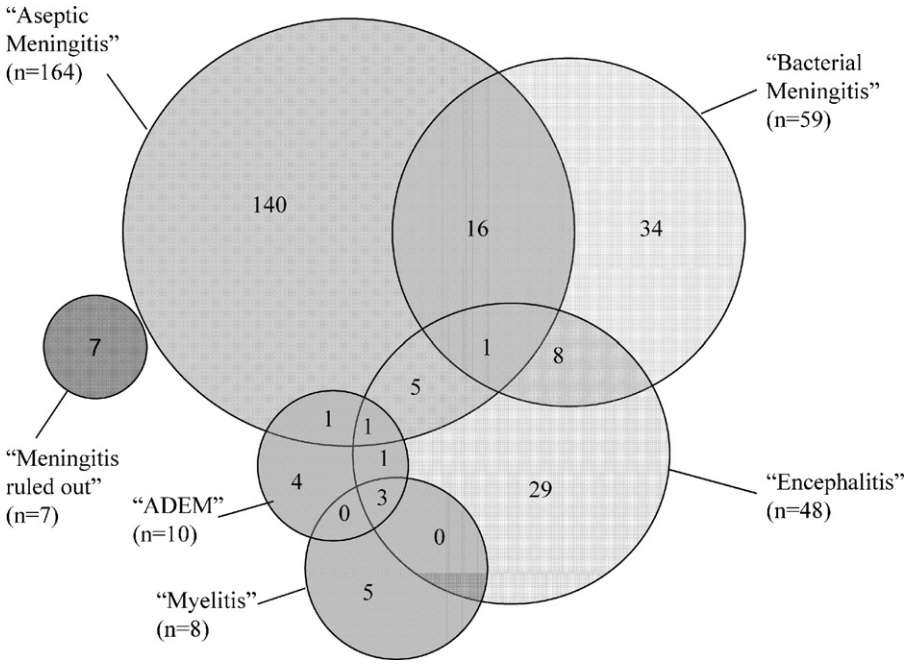

Fig. 2. Clinical diagnoses ($n = 255$).

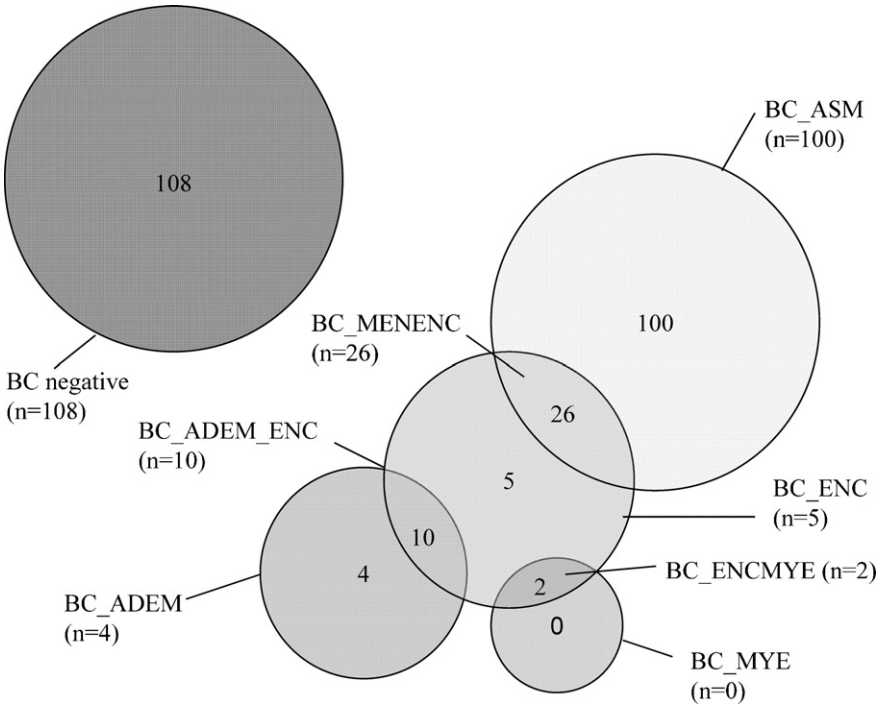

Fig. 3. Results according to BC definitions ($n = 255$).

ASM. Of the remaining 5 cases, 3 had positive bacterial CSF cultures only after discharge from the hospital but had been classified as "viral meningitis" in the discharge summary, 1 case had no CSF cell count available, 1 had normal CSF cell counts and culture (the diagnosis was worded as "strong clinical suspicion of meningitis lacking laboratory confirmation").

3.5.2. Cases with the clinical diagnosis of "bacterial or aseptic meningitis" (n = 16)

In 16 cases the discharge letter was undecided as to whether a case should be classified as aseptic or bacterial meningitis. The majority (11 cases, 65%) did not meet the Brighton ASM criteria. In 2 cases the CSF had been obtained after antibiotic treatment was initiated (*Brighton Collaboration* Level 2 criteria for ASM). In the remaining 3 cases, the clinician had included the diagnosis of bacterial meningitis despite negative CSF gram stain and culture results based on concurrent findings, such as positive bacterial blood cultures in a newborn with suspected sepsis/meningitis.

3.5.3. Cases with the clinical diagnosis of "bacterial meningitis" (n = 34)

As expected, the majority of cases (82%) with an exclusive discharge diagnosis of "bacterial meningitis" did *not* meet the *Brighton Collaboration* criteria for aseptic meningitis. In 6 of 34 cases, the BC ASM criteria were indeed fulfilled: In 3 of these 6 cases, negative bacterial CSF cultures had been obtained after initiation of antibiotic therapy (fulfilling BC ASM criteria, Level 2). The remaining 3 cases were considered "bacterial meningitis" by the clinician based on pronounced CSF pleocytosis, simultaneous bacterial sepsis, or positive bacterial CSF-PCR results. Based on negative gram stain and culture, these cases fulfilled the BC case definition for ASM.

3.5.4. Cases with the clinical diagnosis of "meningitis" but with a note in the discharge letter indicating that the diagnosis had been "ruled out" (n = 7)

As expected, none of the seven "rule-out meningitis"-cases fulfilled the BC ASM criteria.

3.5.5. Cases with the clinical diagnosis of "encephalitis" (n = 29)

Of the 29 cases with a discharge diagnosis of "encephalitis", 19 (65%) initially fulfilled the BC criteria for ENC; the remaining 10 cases had occurred in the context of a systemic illness, most commonly disseminated VZV infection ($n = 7$). When the exclusion criterion "no other illness" was applied, however, only 9 (31%) of the clinical cases of "encephalitis" still met the *Brighton Collaboration* criteria for ENC. In the remaining cases, additional differential diagnoses were listed in the discharge summaries, such as progressive CNS malignancy or HIV disease.

3.5.6. Cases with the clinical diagnosis "meningoencephalitis" (n = 15)

A total of 13 (87%) cases of "meningoencephalitis" initially fulfilled the BC criteria for ENC, the remaining 2 were cases of viral infection with insufficient data to fulfill the ENC component. After exclusion of concomitant illness or systemic disease, only 5 of 15 cases (38%) fulfilled the ENC definition. Four of these cases fulfilled both ENC and ASM.

3.5.7. Cases with the clinical diagnosis "myelitis" (n = 5)

Of the 5 cases with an exclusive diagnosis of myelitis, none fulfilled the BC definition due to Guillain Barré Syndrome or other alternative diagnoses. In the discharge summaries, "myelitis" had mostly been listed as one of several differential diagnoses.

3.5.8. Cases with the clinical diagnosis "encephalomyelitis" (n = 4)

Of the 4 cases with a clinical diagnosis of "encephalomyelitis", 3 met the ENC criteria. Two of these 3 cases met both, ENC and MYE criteria and 1 met the criteria for both ENC and ADEM. The remaining case carried alternative diagnoses, including TIA and focal seizure.

3.5.9. Cases with the clinical diagnosis of "ADEM" (n = 5)

Five cases carried an explicit clinical diagnosis of "ADEM". Four of these 5 cases fulfilled the BC criteria for ADEM, 1 carried the

Table 1
Overall rates of agreement (ORA), positive percent agreement (PPA), and negative percent agreement (NPA) for each level of diagnostic certainty (95% CI in parentheses).

Categories	Aseptic meningitis		Encephalitis			Myelitis			ADEM		
	Level 1	Level 2	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
BC definition (ASM) fulfilled	113	16	0	34	10	0	1	2	0	6	22
BC definition (ASM) NOT fulfilled	142	239	255	221	245	255	254	253	255	249	233
Clinical diagnosis present (CD+)	164		48			8			10		
Clinical diagnosis absent (CD−)	91		207			247			245		
Agreement BC+/CD+	97	11	0	12	5	0	0	2	0	5	0
Disagreement BC+/CD−	16	5	0	22	4	0	1	0	0	1	21
Disagreement BC−/CD+	67	153	48	36	43	8	8	6	10	5	10
Agreement BC−/CD−	75	86	207	185	203	247	246	247	245	244	224
Summary	Aseptic meningitis		Encephalitis			Myelitis			ADEM		
	Level 1	Level 2	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
Overall rate of agreement per level (95% CI)	67% (61–73)	38% (32–44)	81% (75–87)	77% (71–83)	82% (76–88)	97% (91–100)	96% (90–100)	98% (92–100)	96% (90–100)	98% (92–100)	88% (82–84)
Positive percent agreement per level (95% CI)	59% (53–65)	7% (1–13)	0% (0–6)	25% (19–31)	10% (4–16)	0% (0–6)	0% (0–6)	25% (19–31)	0% (0–6)	50% (44–56)	0% (0–6)
Negative percent agreement per level (95% CI)	82% (76–88)	94% (88–100)	100% (93–100)	89% (83–95)	98% (92–100)	100% (94–100)	99% (93–100)	100% (94–100)	100% (94–100)	99% (93–100)	91% (85–97)

differential diagnosis of "ADEM versus chronic encephalomyelitis disseminata (MS) with neuritis of the optic nerve".

3.5.10. Cases not fulfilling any of the four BC definitions (BC−; n = 108)

108 of 255 cases (42%) did not fulfill any of the BC case definitions for ASM, ENC, MYE, or ADEM. Among these 108 cases, 35 were negative control cases carrying either a discharge diagnosis of "bacterial meningitis" ($n = 28$), or the text indicated that meningitis had been "ruled out" ($n = 7$). In additional 10 cases, the clinician considered two possibilities, "bacterial or aseptic meningitis", but the cases failed to meet BC ASM criteria. 39 of 108 cases carried a diagnostic label of "aseptic meningitis" but failed to fulfill the BC criteria for ASM: 34 due to unavailable gram stain results, 1 due to unavailable CSF counts, 1 with normal CSF results. Three cases were discharged with a diagnosis of "aseptic meningitis", but positive bacterial culture results received after discharge from the hospital excluded from the BC criteria. Twenty-four cases carried a clinical diagnosis of "encephalitis" ($n = 12$) or "meningoencephalitis" ($n = 5$), "encephalomyelitis" ($n = 1$), "myelitis" ($n = 5$), or "ADEM" ($n = 1$) but simultaneous evidence of alternative diagnoses excluded from the respective BC definitions.

4. Discussion

The reported study illustrates the added value of using the *Brighton Collaboration* case definitions for aseptic meningitis, encephalitis, myelitis, and ADEM in retrospective chart reviews. In the absence of universally applicable gold standard methods for the diagnosis of aseptic meningitis, encephalitis, myelitis, or ADEM, we are restricted to comparing the BC algorithm as a new diagnostic test or "confirmatory tool" to an imperfect reference standard: the clinical diagnosis [28–32]. Clinical diagnoses as reported in hospital discharge summaries, are observer-dependent, diagnostic procedures may or may not be available, and overlap between competing CNS diagnoses is common. Clinical guidelines may diminish some of this variability, but analyses have shown that very few of the currently practiced decision rules to discriminate between bacterial and aseptic meningitis for example, have ever been validated [52]. While the clinician may be well advised to "err on the side of caution", for example to suspect bacterial meningitis rather than withholding antibiotic treatment, the case ascertainment process in the context of epidemiological investigations requires a different degree of conceptual clarity.

Prospective clinical trials and paired studies of diagnostic accuracy will be required to determine the sensitivity and specificity of BC algorithms as well as the sensitivity and specificity of routine clinical diagnoses [53,54]. To this end, a gold standard procedure would be required to discriminate true positives from false positives. In the instance of CNS disease, a gold standard method would likely entail invasive procedures, limiting its feasibility in large-scale prospective settings. New surrogate markers and clinical prediction models are being developed [55,56,57] with the goal to avoid invasive procedures and discomfort to the patient.

In the reported retrospective analysis, we chose a combination of electronic ICD-10 query with a search string approach to identify a maximum number of cases where any of the diagnoses of interest (meningitis, encephalitis, myelitis, or ADEM) had been considered. We then verified and categorized the selected cases, into bacterial and/or aseptic meningitis, encephalitis, myelitis, and/or ADEM, based on documented discharge diagnoses. In a blinded fashion, we applied the BC algorithms for aseptic meningitis, encephalitis, myelitis, and/or ADEM to the same cases using clinical parameters as they were available in the medical records. Using a standard procedure for the evaluation of a new test (BC algorithm) with

Table 2
Overall rates of agreement, positive percent agreement and negative percent agreement for any level of diagnostic certainty.

Categories	Aseptic meningitis (any level)	Bacterial meningitis (negative control)	Encephalitis (any level)	Myelitis (any level)	ADEM (any level)	Total *n*
BC definition fulfilled (BC+)	129	129	43	3	27	255
BC definition not fulfilled (BC−)	126	126	212	252	228	
Clinical diagnosis present (CD+)	164	59	48	8	10	255
Clinical diagnosis absent (CD−)	91	196	207	247	245	
Agreement BC+/CD+	108	15	17	2	5	255
Disagreement BC+/CD−	21	114	26	1	22	
Disagreement BC−/CD+	56	44	31	6	5	
Agreement BC−/CD−	70	82	181	246	223	

Summary	Aseptic meningitis (any level)	Bacterial meningitis (negative control)	Encephalitis (any level)	Myelitis (any level)	ADEM (any Level)	255
Overall rate of agreement	70%(64–76)	38%(32–44)	78%(72–74)	97%(91–100)	97%(91–100)	
Positive percent agreement (PPA)	66%(60–72)	25%(19–31)	35%(29–41)	25%(19–31)	50%(44–56)	
Negative percent agreement (NPA)	77%(71–83)	42%(36–48)	87%(81–93)	99%(93–100)	91%(85–97)	
Kappa scores $^{*}p<0.0$; $^{**}p<0.01$; $^{***}p<0.001$	0.283***	−0.231	0.238***	0.353***	0.226***	255

an imperfect reference standard (the clinical diagnosis) we tested levels of overall, positive or negative agreement [28–32]. Individual subanalyses were performed to investigate any discrepancies between clinical diagnoses and BC categories.

As evident from this study, the *Brighton Collaboration* case definitions can be applied independently and consistently to provide an objective, transparent and evidence-based method for case ascertainment. Based on simple clinical parameters combined with imaging and laboratory findings, each clinical case can be "dissected" into separate clinical variables, to be analyzed using pre-defined algorithms yielding standardized and examiner-independent observations.

Brighton Collaboration case definitions are primarily used in the assessment of known or postulated adverse events following immunization (AEFI) in regulatory settings, observational studies and clinical trials. The case verification process is hereby separated from the causality analysis. In the first two years of the study period reported herein, we found an increased incidence of mumps meningitis (data not shown). Those cases that have now been confirmed using BC criteria could then be analyzed further with respect to vaccination history, laboratory results, and other epidemiologic data to discriminate between vaccine failures versus mumps outbreak in an under-vaccinated population versus adverse events following immunization.

This study has several limitations. Retrospective chart reviews provide only limited insight into the clinician's decision making process. Exclusion criteria in the BC definitions (such as: "no other illness to explain clinical signs and symptoms" [8]) are difficult to apply in retrospective settings where the investigator relies on the documentation of pertinent negatives. Incomplete documentation of medical data in the patient records may lead to underreporting of cases when a standard algorithm is used.

Several key scenarios identified in the subanalyses may be used to extrapolate best practice recommendations to improve the representation and coding of diagnoses in discharge summaries: first and most importantly, a negative gram stain result (in addition to clinical signs of meningitis) is a *conditio sine qua non* for all levels of diagnostic certainty in the BC definition for aseptic meningitis. Gram stains ought to be part of any workup for bacterial or aseptic meningitis, which apparently has not been consistently applied in our institution in the past. False-negative CSF cultures are not uncommon [37] and a diagnosis of bacterial meningitis should not be ruled out in the absence of gram stain data [15,17,38,39]. Had gram stain data been available in all cases in this study, 39 additional cases could have met the BC criteria for ASM and the rates of agreement would have been: OPA = 85%, PPA= 89%, and NPA = 77%.

Second, as stated in the BC case definition document for aseptic meningitis, "an upper reference value for pleocytosis is not used as a criterion in the case definition to distinguish bacterial from aseptic meningitis because pleocytosis of several thousand leukocytes/μl of CSF has been described in patients with aseptic meningitis of confirmed viral etiology [7,40]." Based on purulent CSF samples, several cases in the reported study were labeled as "bacterial meningitis" in the discharge summary, even though gram stain and culture results remained negative. The differential diagnosis of aseptic meningitis should always be considered, even if CSF cell counts are highly elevated [37,41].

Third, encephalitis was underrecognized in the discharge diagnoses whenever a concomitant diagnosis of aseptic meningitis seemed to "fit". Encephalitis, however, is often associated with concomitant meningitis but the prognosis worsens considerably with the presence of parenchymal infection [42]. Therefore, the *Brighton Collaboration* Aseptic Meningitis and Encephalitis Working Groups recommended that "aseptic meningitis should be reported only for cases in which meningeal inflammation is present in the absence of clinical or diagnostic features of encephalitis [7,8]." Overlapping cases should be listed as "(meningo-)encephalitis". The limited case numbers in this study for encephalitis, myelitis, and ADEM, however, allow only limited conclusions. Additional evaluation studies are needed for these BC case definitions.

The design of the reported study also shows several strengths: the study used a closed system with a standardized tool for the diagnosis of complex medical entities. Several approaches (ICD-10 search and electronic search of discharge summaries by pre-defined terms) were used to identify cases consistently representing the clinical assessment as accurately as possible. The investigator was independent from the clinical care of the patients and blinded to the discharge diagnoses during the data entry and case evaluation process. We report the first study to evaluate several *Brighton Collaboration* definitions simultaneously evaluating each case definition for aseptic meningitis, encephalitis, myelitis and ADEM individually, but also the discriminatory power of standardized definitions in a dataset of 255 pooled routine clinical cases, including negative controls. The simple design of this study lends itself to being reproduced easily, allowing the comparability of clinical data across different countries and clinical settings.

The most important benefit in using the BC criteria for the confirmation of aseptic meningitis cases lies in the combination of clinical symptoms with key laboratory findings. The typical clinical signs and symptoms of meningitis are not always present [43] and are particularly nonspecific in neonates and infants [44,45]. Neck stiffness or nuchal rigidity (used synonymously with "Meningismus" in German) are estimated to be present in only 39–53% of

patients [46–48]. As indicated above, negative gram stains and culture results are required to rule out bacterial meningitis. Applying the BC criteria demands both clinical and laboratory evidence therefore preventing premature conclusions based on clinical signs and symptoms or laboratory values alone.

Reversely, the lessons learnt in this study are suggestive of several modifications to the BC definitions which may further improve the applicability of these useful research tools: First, newborns and pediatric patients with evidence of bacterial sepsis such as positive peripheral blood cultures and signs of systemic illness, are often also treated for presumed (bacterial) meningitis [44]. An additional rule or footnote specific to this age group should further improve the specificity of the ASM definition.

Furthermore, cases of abscess, ventriculitis, or shunt infection may present with negative CSF cultures and could be misclassified as aseptic meningitis according to the BC definitions. Cases with any evidence of abscess, ventriculitis, or foreign bodies in the CNS, either clinically or by neuroimaging, should be excluded from the *Brighton Collaboration* case definition for aseptic meningitis.

Cerebellitis, tumors, cerebral tuberculosis, neuroborelliosis, monoradiculitis, chronic disseminated encephalomyelitis [49], Bell's Palsy and Guillain Barré syndrome seem to fall into separate categories and their role in relation to the existing BC case definitions should be clarified. New case definitions for Guillain Barré synrome [50] and Bell's Palsy as an AEFI [51] are in development and will be complementary to and compatible with the existing definitions.

In conclusion, *Brighton Collaboration* definitions are easily applicable in clinical settings. Once cases have been defined and assessed uniformly, possible causes and triggers of such clinical events can be investigated while avoiding selection bias. The results of this study will be compatible to any other site using the same *Brighton Collaboration* definitions. A systematic approach to the diagnosis of meningitis, encephalitis, myelitis, and ADEM is urgently needed. The BC definitions are an important first step to improve evidence-based research and data comparability in the area of CNS infections.

Acknowledgements

This work has in part been presented at the 47th Interscience Conference on Antimicrobials and Anti-infective Chemotherapy (ICAAC), September 2007, in Chicago. IL. This work also forms the medical thesis of Barbara Rath, MD, at the Medical Faculty, University of Basel, Switzerland. The authors kindly thank Jane Gidudu, MD, MPH in the Brighton Secretariat at the US Centers for Disease Control, Atlanta, USA, as well as the *Brighton Collaboration* Steering Committee, in particular Brigitte Keller-Stanislawski, MD, Paul-Ehrlich Institute, Langen, Germany, for their comments. We also kindly acknowledge the support through the University-Children's Hospital (UKBB) and by Prof. Urs Beat Schaad. The study was funded by a UKBB Matching Funds Grant.

Appendix A.

A.1. Overall rates of agreement

Overall rates of agreement were calculated according to the formula: $100\% \times (a+d)/(a+b+c+d)$.

A.2. Positive percent agreement and negative percent agreement

To better differentiate between the agreement on the positives and agreement on the negatives, positive percent agreement (PPA) with respect to the imperfect reference standard positives and negative percent agreement (NPA) with respect to imperfect reference standard negatives were also computed for each cell, according to the formula:

Imperfect Reference Test.

	CD+	CD−	
BC+	a	b	$a+b$
BC−	c	d	$c+d$
	$a+c$	$b+d$	$a+b+c+d$

New Test.

a = BC+/CD+
b = BC+/CD−
c = BC−/CD+
d = BC−/CD−

$$\text{PPA} = 100\% \times a/(a+c)$$
$$\text{NPA} = 100\% \times d/(b+d)$$

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