

## Aseptic meningitis: Case definition and guidelines for collection, analysis and presentation of immunization safety data<sup>☆</sup>

Terhi Tapiainen<sup>a,b</sup>, Rebecca Prevots<sup>c</sup>, Hector S. Izurieta<sup>d</sup>, Jon Abramson<sup>e</sup>, Roman Bilynsky<sup>f</sup>, Jan Bonhoeffer<sup>a,\*</sup>, Marie-Claude Bonnet<sup>g</sup>, Kimberly Center<sup>h</sup>, Jochem Galama<sup>i</sup>, Paul Gillard<sup>j</sup>, Monika Griot<sup>k</sup>, Katharina Hartmann<sup>k</sup>, Ulrich Heininger<sup>a</sup>, Michael Hudson<sup>l</sup>, Annette Koller<sup>k</sup>, Nino Khetsuriani<sup>m</sup>, Najwa Khuri-Bulos<sup>n</sup>, S. Michael Marcy<sup>o</sup>, Raimonda Matulionyte<sup>p</sup>, Ines Schöndorf<sup>q</sup>, James Sejvar<sup>m</sup>, Russell Steele<sup>r</sup>,

The Brighton Collaboration Aseptic Meningitis Working Group<sup>1</sup>

<sup>a</sup> University Children's Hospital, Basel, Switzerland

<sup>b</sup> Department of Pediatrics, University of Oulu, Finland

<sup>c</sup> National Institute for Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

<sup>d</sup> Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD, USA

<sup>e</sup> Department of Pediatrics, Wake Forest University Medical School, Winston-Salem, NC, USA

<sup>f</sup> Patterson Army Health Center, Fort Monmouth, NJ, USA

<sup>g</sup> Aventis Pasteur, Lyon, France

<sup>h</sup> Wyeth Pharmaceuticals, Collegeville, PA, USA

<sup>i</sup> Department of Medical Microbiology, University Medical Center, Nijmegen, The Netherlands

<sup>j</sup> Glaxo Smith Kline, Rixensart, Belgium

<sup>k</sup> Berna Biotech, Kusknacht, Switzerland

<sup>l</sup> Health Protection Agency, Centre for Emergency Preparedness and Response, Salisbury, United Kingdom

<sup>m</sup> Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

<sup>n</sup> Pediatric Infectious Diseases, Jordan University Hospital, Jordan

<sup>o</sup> University of Southern California and University of California Los Angeles Schools of Medicine, Kaiser Foundation Hospital, Panorama City, CA, USA

<sup>p</sup> Department of Infectious Diseases, Vilnius University, Lithuania

<sup>q</sup> Novartis Vaccines, Marburg, Germany

<sup>r</sup> Department of Pediatrics, LSU Medical School, New Orleans, LA, USA

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**Abbreviations:** AEFI, adverse event following immunization; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; LP, lumbar puncture; MMR, measles–mumps–rubella (vaccine); PCR, polymerase chain reaction; RBC, red blood cell; RFLP, restriction fragment-length polymorphism; WBC, white blood cell

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\* Corresponding author. Tel.: +41 61 685 6565.

E-mail address: [secretariat@brightoncollaboration.org](mailto:secretariat@brightoncollaboration.org) (J. Bonhoeffer).

<sup>1</sup> Brighton Collaboration homepage: <http://www.brightoncollaboration.org>.

## 1. Preamble

### 1.1. Need for developing case definitions and guidelines for aseptic meningitis as an adverse event following immunization

Aseptic meningitis is commonly defined as a syndrome characterized by acute onset of signs and symptoms of meningeal inflammation, cerebrospinal fluid (CSF) pleocytosis and the absence of microorganisms on Gram stain and/or on routine culture [1,2]. Aseptic meningitis is frequently caused by viral agents, particularly by enteroviruses [3]. In recent years, the use of polymerase chain reaction (PCR) for detection of viruses in CSF has become more common and the specific aetiology of aseptic meningitis can often be diagnosed in routine clinical practice [4,5]. Other known aetiologies are bacteria uncultivable on routine culture (*Mycobacterium tuberculosis*, *Treponema pallidum*, *Borrelia* species, etc.), *Chlamydia* species, *Mycoplasma* species, *Rickettsia* species, fungi, protozoa (toxoplasmosis, malaria, etc.) and other parasites, parameningeal infections, malignancies, sarcoidosis, immune diseases, drugs, foreign bodies and cysts in or adjacent to the central nervous system (CNS) [1,6–12]. Measles and mumps viruses were important causative agents of aseptic meningitis before introduction of measles and mumps vaccines [13].

Cases of aseptic meningitis have been reported after immunization with several live attenuated virus vaccines, including oral polio [14], combined measles–mumps–rubella (MMR), varicella, yellow fever [15] and smallpox vaccines [16]. Aseptic meningitis accompanying a radiculitis and myelitis has also occurred following administration of Semple-type inactivated rabies vaccine [17]. The increased risk of aseptic meningitis after MMR immunization has been well documented. Immunization with MMR containing the Urabe [18,19], Leningrad-Zagreb [20] and Hoshino [21] mumps strains results in a 5.5–38-fold increased risk of aseptic meningitis approximately 2–7 weeks following immunization. Outbreaks of aseptic meningitis have been documented following mass vaccination campaigns using MMR with the Leningrad-Zagreb or Urabe mumps strains [18,20]. The Jeryl-Lynn mumps strain has not been shown to increase the risk of aseptic meningitis [19,21–23]. There is a paucity of data on the Leningrad-3 mumps strain, a predecessor of the Leningrad-Zagreb strain [24,25].

Estimates of the incidence of aseptic meningitis associated with mumps vaccine have varied widely [20,22,24,26–30]. Discrepancies in estimated rates are likely due to differences in study design or case ascertainment, age-specific immunity or vaccine strains. Reported incidences have ranged from a frequency of 1:2041 for the Urabe strain [29] to 1 > 1,800,000 for Jeryl-Lynn [26]. In one further study, the incidence of aseptic meningitis after mass immunization with measles–rubella vaccine (i.e., without a mumps vaccine strain) has been reported to be low with an incidence of

1:867,000 doses [31]. Aseptic meningitis following immunization usually is benign and resolves without sequelae [32].

In the vaccine safety literature, aseptic meningitis has usually been defined as pleocytosis in the CSF and the absence of microorganisms on Gram stain and/or routine culture [19–21,23,33]. The cut-off value for pleocytosis in CSF has been presented in only a minority of studies with a range from five to ten leukocytes/ $\mu\text{L}$ . Additional tests such as fungal or mycobacterial culture, acid fast stain and bacterial antigen detection tests have been used variably to exclude other causes of aseptic meningitis [18,22]. Recent vaccine studies have used viral culture showing evidence of mumps virus or mumps-specific PCR to confirm MMR vaccine related cases [34,35].

In order to enable the standardized assessment and to improve comparability of cases of aseptic meningitis, an *Aseptic Meningitis Working Group* was initiated by the Brighton Collaboration to develop a case definition and guidelines for the collection, analysis and presentation of data for aseptic meningitis as an Adverse Event Following Immunization (AEFI) (listed in Sections 2 and 3 of this paper, respectively). The case definition and guidelines are intended to be applicable in diverse geographic, administrative and cultural regions, regardless of differences in the availability of resources and access to health care. Widespread use of this definition with its guidelines will enable data comparability and lead to a better understanding of the adverse event.

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

Following the process described in the overview paper in this volume of *Vaccine*, the Brighton Collaboration *Aseptic Meningitis Working Group* was formed in 2004 with 22 members from academia, public health, regulatory organizations and industry. The member composition and results of the web-based survey 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](http://www.brightoncollaboration.org/internet/en/index/working_groups.html).

To guide the decision-making for the case definition and guidelines, literature searches were conducted by a professional search person to identify citations addressing meningitis following immunization and meningitis diagnostics. Sources included the Cochrane Library, MEDLINE (1966–2003) and EMBASE (1980–2003). The literature searches resulted in 1693 articles. Based on a review of the title and abstract, 238 articles were retrieved for further evaluation. Selected articles were summarized to include information on the clinical signs and symptoms of aseptic meningitis and laboratory diagnostics performed, demographics of the vaccinee and information on the vaccine and study design.

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