Safety Platform for Emergency vACcines

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

Thrombocytopenia

Work Package: WP2 Standards and tools

V1.0 – February 8th, 2021

Authors: Barbara Law

Nature: Report | Diss. level: Public

TABLE OF CONTENTS

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

DOCUMENT INFORMATION

Master Service Agreement		Service order	SO2
Project acronym	SPEAC	Full project title	Safety Platform for Emergency Vaccines
CEPI Project Lead	Nadia Tornieporth / Jakob Cramer		
CEPI Project Manager	Brett Barnett		
CEPI Contract Manager	Nishat Miah		

Deliverable number	SO2 D2.5.2.1	Title	Transform Tier 1 AESI Tools
Work package number	WP2	Title	Standards and tools

Delivery date		Changes on due date ☑	Actual date	February 8th 2021
Status	Draft ☐ Final ☑	Old due date:	Version	1.0
Nature	Report ☑ Toolbox ☐ List ☐ Template ☐ Guidance ☐ Handbook ☐ Questionnaire ☐			
Dissemination Level	Public ☑ Confidential ☐			

SPEAC Project Lead	Robert Chen	E-mail: robert.chen@cepi.net
Scientific Coordinator	Miriam Sturkenboom	E-mail: miriam.sturkenboom@cepi.net

Reviewer 1	Wan-Ting Huang	E-mail: wan-ting.huang@cepi.net
Reviewer 2	Miriam Sturkenboom	E-mail: miriam.sturkenboom@cepi.net

Main Author(s)	Barbara Law	E-mail: barbara.law@cepi.net
WP Leader	Barbara Law	E-mail: barbara.law@cepi.net

Description of the deliverable	This deliverable collates into a single document the SPEAC Thrombocytopenia resources (Risk factors, background rates, ICD9/10-CM & MedDRA codes), tools (data abstraction & interpretation form, tabular summary of key case definition criteria and algorithm for level of certainty determination, pictorial level of certainty algorithm) and guidance (real time investigation, data collection, analysis and presentation). This guide can be used by stakeholders to assess the occurrence of thrombocytopenia in several settings including as an adverse event following immunization.
Key words	Thrombocytopenia, Brighton collaboration case definition, risk factors, background rates, ICD-9-CM, ICD-10-CM, MedDRA, case definition level of certainty.

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
SO2-D2.5.2.1 Transform Tier 1 AESI Tools	29 January 2021	V0.1	Barbara Law Marta Rojo Villaescusa	First draft
SO2-D2.5.2.1 Transform Tier 1 AESI Tools	31 January 2021	V0.1	Wan-Ting Huang	Review
SO2-D2.5.2.1 Transform Tier 1 AESI Tools	31 January 2021	V0.1	Miriam Sturkenboom	Review
SO2-D2.5.2.1 Transform Tier 1 AESI Tools	8 February 2021	V1.0	Barbara Law	Incorporate Reviewer comments/suggestions

DEFINITIONS & ACRONYMS

AESI	Adverse Events of Special Interest
BC	Brighton Collaboration
CEPI	Coalition for Epidemic Preparedness and Innovation
CI	Confidence Interval
CM	Clinical Modification (relates to numbered versions of ICD codes)
CUI	Concept Unique Identifier
ICD	International Classification of Diseases
ITP	Immune Thrombocytopenia
MedDRA	Medical Dictionary for Regulatory Activities
SPEAC	Safety Platform for Emergency Vaccines
UMLS	Unified Medical Language System

INTRODUCTION

1. Background

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

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

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

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

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

TABLE 1. AESI PRIORITIZED BY TIER

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

To simplify access to AESI specific tools and resources, companion guides to the Brighton AESI case definition are being prepared for each AESI. That is the purpose of this deliverable, which focuses on thrombocytopenia.

2. Objective of this deliverable

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

3. Methods

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

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

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

4. Results

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

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

5. Recommendations & discussion

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

The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used in order to assign level of certainty for all identified AEFI with features of thrombocytopenia. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

6. References

1. Wise RP, Bonhoeffer J, Beeler J et al. Thrombocytopenia: Case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25:5717-5724.
2. Rodeghiero F, Stasi R, Gernsheimer T et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood, 2009; 113:2386-2393.
3. McCrae K. Immune thrombocytopenia: no longer 'idiopathic'. Cleveland Clinic J Med 2011; 78:358-373. Doi:10.3949/ccjm.78gr.10005
4. Audia S, Mahévas, Samson M et al. Pathogenesis of immune thrombocytopenia. Autoimmunity Reviews 2017; 16:620-632.http://dx.doi.org/10.1016/j.autrev.2017.04.012.
5. Kistanguri G, McCrae KR. Immune thrombocytopenia. Hematol Oncol Clin North Am 2013; 27:495-520. Doi:10.1016/j.hoc.2013.03.001.
6. Onisâi M, Vlădăreanu AM, Spînu A, Gãman M, Bumbea H. Idiopathic thrombocytopenic purpura (ITP) – new era for an old disease. Rom J Intern Med 2019; 57(4): 273-283. Doi: 10.2478/rjim-2019-0014.
7. Frederiksen H, Christensen CF, Nørgaard M. Risk and prognosis of adult primary immune thrombocytopenia. Expert Rev Hematol 2012; 5(2): 219-228.
8. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood 2009; 113(25): 6511-6521.
9. Mead AJ, Newland AC, Provan D. Adult idiopathic thrombocytopenic purpura. Hematology 2003; 8(6): 345-357.
10. Rehman A. Immune thrombocytopenia in children with reference to low-income countries. Eastern Mediterranean Health Journal 2009; 15(3): 729-737.
11. Nugent DJ. Immune thrombocytopenic purpura of childhood. Hematology Am Soc Hematol Educ Program 2006(1): 97-103. https://doi.org/10.1182/asheducation-2006.1.97
12. Kamphuis MM, Paridaans NP, Porcelijn L et al. Incidence and consequences of neonatal alloimmune thrombocytopenia: A systematic review. Pediatrics 2014; 133(4): 715-721. Doi: 10.1542/peds.2013-3320.
13. Porcelijn L, von dem Borne AEG. Immune-mediated thrombocytopenias: basic and immunological aspects. Baillière's Clinical Haematology 1998; 11(2): 331-341.
14. Zitiello A, Grant GE, Ben Ali N, Feki A. Thrombocytopaenia in pregnancy: the importance of differential diagnosis during the COVID-19 pandemic. J Maternal-Fetal & Neonatal Medicine, 2020; https://doi.org/10.1080/1476058.2020.1786527
15. George JN, Raskob GE. Clinical decisions in ITP. Hospital Practice 1997; 32(9): 159-175. https://doi.org/10.1080/21548331.1997.11443569.
16. Cecinati V, Principi N, Brescia L et al. Vaccine administration and the development of idiopathic thrombocytopenic purpura in children. Human Vaccines and Immunotherapeutics 2013; 9(5):1158-1162. http://dx.doi.org/10.4161/hv.23601
17. Mantadakis E, Farmaki E, Buchanan GR. Thrombocytopenic purpura after measles-mumps-rubella vaccination: a systematic review of the literature and guidance for management. J Ped 2010; 156: 623-8.
18. O'Leary ST, Glanz JM, McClure DL et al. The risk of immune thrombocytopenic purpura after vaccination in children and adolescents. Pediatrics 2012; 129:248-255. Doi: 10.1542/peds.2011-1111.
19. IOM (Institute of Medicine). 2011. Adverse effects of vaccines: Evidence and Causality. Washington, DC: The national Academies Press.
20. Dudley MZ, Halsey NA, Omer SB et al. The state of vaccine safety science: systematic reviews of the evidence. Lancet ID 2020; published online April 9. https://doi.org/10.1016/S1473-3099(20)30130-4.
21. Watts RG. Idiopathic thrombocytopenic purpura: A 10-year natural history study at the Childrens Hospital of Alabama. Clin Pediatrics 2004;43:691–702 https://doi.org/10.1177/000992280404300802
22. Kurata Y, Fujimura K, Kuwana M, Tomiyama Y, Murata M. Epidemiology of primary immune thrombocytopenia in children and adults in Japan: apopulatio nbasedstudy and literature review.Int. J. Hematol. 93(3), 329–335 (2011).

23. Neylon AJ, Saunders PW, Howard MR, Proctor SJ, Taylor PR. On behalf of the Northern Region Haematology Group. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. Brit J Haematol. 2003; 122:966–974. [PubMed 12956768] 10.1046/j.1365-2141.2003.04547.x
24. Yong M, Schoonen WM, Li L, et al. Epidemiology of paediatric immune thrombocytopenia in the General Practice Research Database. Br J Haematol. 2010; 149(6):855–864. [PubMed: 20377590] https://doi.org/10.1111/j.1365-2141.2010.08176.x
25. Abrahamson PE, Hall SA, Feudjo-Tepie M, Mitrani-Gold FS, Logie J. The incidence of idiopathic thrombocytopenic purpura among adults: a population-based study and literature review. Eur. J. Haematol. 83(2), 83–89 (2009). https://doi.org/10.1111/j.1600-0609.2009.01247.x
26. Schoonen WM, Kucera G, Coalson J et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. Br. J. Haematol. 145(2), 235–244 (2009). https://doi.org/10.1111/j.1365-2141.2009.07615.x
27. Lilleyman JS. Intracranial hemorrhage in idiopathic thrombocytopenic purpura. Arch Dis Child 1994;71:251–253. https://doi.org/10.1177/000992280404300802
28. Bolton-Maggs PHB, Moon I. Assessment of UK practice for management of acute childhood idiopathic thrombocytopenic purpura against published guidelines. Lancet 1997;350:620–623. https://doi.org/10.1016/s0140-6736(97)04143-3
29. Sutor AH, Harms A, Kaufmehl K. Acute immune thrombocytopenia (ITP) in childhood: Retrospective and prospective survey in Germany. Semin Thromb Hemost 2001;27:253–267. https://doi.org/10.1055/s-2001-15255
30. Zeller B, Helgestad J, Hellebostad M, et al. Immune thrombocytopenic purpura in childhood in Norway: a prospective, population-based registration. Pediatr Hematol Oncol 2000; 17:551–558. https://doi.org/10.1080/08880010050122816
31. Zeller B, Rajantie J, Hedlund-Treutiger I, et al. Childhood idiopathic thrombocytopenic purpura in the Nordic countries: epidemiology and predictors of chronic disease. Acta Paediatr 2005; 94:178–184. https://doi.org/10.1111/j.1651-2227.2005.tb01887.x
32. Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. Blood 94(3), 909–913 (1999). https://doi.org/10.1182/blood.V94.3.909.415k02_909_913
33. Willame C, Dodd C, van der Aa L et al. Incidence rates of autoimmune diseases in European Healthcare databases: a contribution of the ADVANCE project. Drug Safety 2021, Jan 19. https://doi.org/10.1007/s40264-020-01031-1.
34. Zaki M, Hassanein AA, Khalil AF. Childhood idiopathic thrombocytopenic purpura: Report of 60 cases from Kuwait. J Trop Pediatrics 1990;36:10 –13.https://doi.org/10.1093/tropej/36.1.10
35. Becker BFH, Avillach P, Romio S, van Mulligen EM, Weibel D, Sturkenboom MCJM, Kors J. CodeMapper: Semi-automatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiology and Drug Safety, 2017 (8) 26: 998-1005. Doi:10.1002/pds.4245
36. McCray AT, Burgun A, Bodenreider O. Aggregating UMLS semantic types for reducing conceptual complexity. Studies Health Technology Information, 2001 84(Pt1): 216-20. PMID: 11604736; PMCID: PMC4300099.
37. Rogers F. Medical subject headings. Bull Med Libr Assoc, 1963. 51(1): 114-6. PMID: 13982385; PMCID: PMC197951.
38. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Safety, 1999. 0(2):109-17. Doi: 10.2165/00002018-199920020-00002.
39. Schuemie MJ, Jelier R, Kors JA. Peregrine: Lightweight gene name normalization by dictionary lookup. In: Proc of the Second BioCreative Challenge Evaluation Workshop., 2007. 131–133.

APPENDIX 1.
Thrombocytopenia Risk Factors

NOTE: In the published Brighton case definition of thrombocytopenia[1] the working group specifically refrained from using the acronym 'ITP' noting that in the current literature at the time (2007) it had several meanings: idiopathic thrombocytopenia, idiopathic thrombocytopenic purpura, immune thrombocytopenia and immune thrombocytopenic purpura. Further they provided two reasons for refraining from defining idiopathic thrombocytopenic purpura: first "the event observed is thrombocytopenia, with or without clinical manifestations" and second "the term ITP, understood as idiopathic thrombocytopenia, implies that no etiology of the observed thrombocytopenia could be established".[1] Since the case definition was published there has been some refinement of the meaning and causation of ITP. In 2009 an International Working Group on ITP recommended that the disease be designated as Immune Thrombocytopenia in recognition of the underlying immune pathogenesis.[2,3] Currently ITP is classified as primary and secondary with both involving one or more immune mechanisms that result in increased platelet destruction and/or decreased platelet production. Primary ITP matches that discussed by the Brighton working group where there is no identifiable etiology, and it is a diagnosis of exclusion. Secondary ITP is recognized as an autoimmune thrombocytopenia that occurs in the course of other diseases or follows an exogenous immune stimulus (infection, drug, vaccine). [3-5] Finally, there are also non-immune causes of thrombocytopenia that need to be considered and ruled out. The risk factor table below applies to all causes of thrombocytopenia: Primary ITP, secondary ITP and non-immune thrombocytopenia since it is unlikely that the classification will be apparent when first seen. Where possible, the risk factors for each of these three different scenarios are identified.

TABLE 1. RISK FACTORS [2-20]

Age	• Adults[7-9]: primary ITP more common than in children and incidence as well as severity increases with age; chronic ITP more frequent (>12 months);
	• Children[5,10,11:] most common form is secondary ITP, following a viral infection in 2/3 of cases, with the majority having spontaneous resolution in <6 months[5]
	• Neonates: two forms of ITP
	  ○ Neonatal alloimmune ITP results from maternal alloimmunization versus paternal platelet antigens absent from maternal platelets (analogous to Rh disease). A systematic review[12], of 6 studies of neonatal thrombocytopenia with nearly 60,000 newborns tested, found a pooled prevalence of severe thrombocytopenia (platelet count <50,000X10^9/Liter) of 0.0015 (95% CI of 0.0012-0.0018) translating to about 150 cases/100,000 neonates. Of these 27% of cases (24 in total) were caused by neonatal alloimmune thrombocytopenia. 6(25%) cases had accompanying intracranial hemorrhage.
	  ○ Neonatal thrombocytopenia may also occur as a result of maternal ITP during pregnancy if there are IgG anti-platelet antibodies that can cross the placenta.[13]

Gender	• Adult females – increased frequency until age 60; then similar in males and females [5]
	• Pregnancy – Thrombocytopenia may be seen in 6-11.6% of pregnancies for a variety of causes with distribution of: [14]
	  ○ Gestational thrombocytopenia (59% of cases): benign condition seen mainly at the end of pregnancy during 2nd and 3rd trimesters. Counts quickly normalize after delivery.
	  ○ Hemolysis-Elevated Liver enzymes-Low Platelets (HELLP) syndrome (12% of cases): observed primarily from 27-37 weeks gestation and may occur as a form of severe preeclampsia.

	○ ITP (11% of cases): main cause of isolated thrombocytopenia seen in 1st and early 2nd trimester and may result in neonatal thrombocytopenia if anti-platelet antibodies cross the placenta.[13] ○ Preeclampsia (10% of cases)
Genetics	• Primary ITP[4]: Most studies are of small cohorts so data not definitive but noted that ITP cohorts tend to have polymorphisms of several genes including MHC, Fc gamma receptor, transcription factors, chemokines, pro/anti-inflammatory cytokines and their receptors; human platelet antigens • Non-immune Congenital thrombocytopenia[6]: several syndromes (Absent Radius, DiGeorge, Wiskott-Aldrich, Bernard-Soulier, congenital megakaryocytic thrombocytopenia). Would expect there to be a family history for same.
Season	• Childhood ITP has a higher frequency in autumn and winter, reflecting the association with prior viral infections[5,10,11]
Geography	• Limited data but childhood disease pattern similar in high-and low-income countries.[10]
Diseases[3-11,15]	• Secondary ITP ○ Autoimmune disease: SLE, Evans / Sjogren's / antiphospholipid syndromes ○ Hematologic malignancy: non-Hodgkin lymphoma, chronic lymphocytic leukemia ○ Primary immune deficiency: common variable immune deficiency, autoimmune lymphoproliferative syndrome ○ Vitamin B9 or B12 deficiency • Non-immune thrombocytopenia ○ Decreased production: bone marrow replacement (proliferative disorders), bone marrow failure (aplastic anemia primary or secondary) ○ Increased consumption ▪ Hypersplenism ▪ Giant hemangioma (Kasabach-Merritt Syndrome)
Infection [3-11,15] Associated with secondary ITP	• Secondary ITP ○ Viral: most commonly Hepatitis C; also, HIV, CMV ○ Helicobacter pylori • Non-immune thrombocytopenia: ○ Infection associated consumptive coagulopathy – DIC (Dengue, bacterial sepsis)
Medication	• Reduced production due to bone marrow myelosuppression: anticancer drugs, valproic acid • Secondary ITP: many drugs may cause thrombocytopenia. Listing them is beyond the scope of this guide, however, when investigating thrombocytopenia that follows immunization, all concomitant medication, especially newly added drugs, should be reviewed for any possible association with thrombocytopenia
Vaccine	• Vaccine-related thrombocytopenia is considered a secondary ITP.[16] • MMR is the only vaccine for which there is a proven attributable risk of thrombocytopenia. Across 12 studies the median risk was calculated to be 1/38,500 doses (range 1/25,000-1/1.1 million doses)[17] The incidence is lower and disease course less severe than that observed with wild type infection. • One managed care data study involving a cohort of 1.8 million children found a possible association with Hepatitis A vaccine in 7- to 17-year-old children and with Varicella and TdaP in 11–17-year-old children but noted that further studies were needed to confirm the association.[18] • Institute of Medicine 2011[19] reviewed evidence for a link between VZV vaccine and thrombocytopenia as well as D/T/aP vaccines and ITP and concluded that, for both, evidence

	was inadequate to accept or reject a causal relationship. Although several other vaccines were reviewed (Influenza, Hepatitis A, Hepatitis B, Meningococcus, Human papillomavirus) no studies involving thrombocytopenia or ITP were mentioned. They did not review MMR and thrombocytopenia because they had already concluded that there the evidence supported a causal association in a prior publication not cited here since references 15 and 16 are more updated reviews with the same conclusion. • An updated review[20] of evidence published since 2011 IOM report for the same vaccines reviewed by IOM had similar conclusions regarding a proven association between MMR vaccine and ITP (attributable risk of 1-3 cases / 100,000 doses of vaccine) and lack of association with other vaccines routinely given to children in the United States. • Risk window for thrombocytopenia as a vaccine product related reaction: Following MMR immunization a median of 12-25 days (range 1-83 days) has been observed and the increased relative risk for hospitalization extends from 15-28 days.[1] In general a six-week period following immunization (from d1 to 42) is commonly used for studies of secondary ITP associated with immunization. [16-18]

APPENDIX 2.
Thrombocytopenia Background Rates

2.1 Thrombocytopenia Background Rates

TABLE 1. THROMBOCYTOPENIA BACKGROUND RATES[21-33]

Variation in rates dependent in part on case definition used for thrombocytopenia (as platelets/Liter), shown in brackets next to citation number and coded as follows: **A:** <150,000; **B**: <100,000; **C:** <50,000; **D:** <30,000; **E:** searched used ICD code for primary thrombocytopenia only, with no platelet count threshold; **F:** searched using broad-based READ code; no platelet count threshold: **G:** prospective cohort followed for ITP diagnosis – not defined; **H:** pediatrician diagnosis of ITP; **I:** Pediatrician diagnosis of ITP but also had to have evidence of mucocutaneous bleeding and no other diagnosis.

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs					
USA (Alabama) [21 (E)]	1993-2003	0-18	4.0 (409)		
ASIA					
Japan[22 (B)]	2004-2007	≤14 ≥15 All ages	1.91 (929) 2.20 (6845) 2.16 (7774)	2.01 (505) 1.68 (2538) 1.72 (3043)	1.79 (424) 2.69 (4307) 2.58 (4731)
EUROPE					
UK[23 C)]	1993-1999	**≥16**	**1.6 (245)**		
UK[24 (A)]	1990-2005	<2 2-5 6-12 13-17 **All <18**	6.8 [4.9-9.2] (43) 7.2 [5.9-8.8] (101) 3.0 [2.4-3.8] (74) 2.4 [1.7-3.3] (39) **4.2 [3.7-4.8] (257)**	8.7 [5.8-12.6] (28) 9.7 [7.5-12.2] (69) 2.6 [1.8-3.7] (33) 2.1 [1.3-3.3] (18) 4.7 [3.9-5.5] (148)	4.9 [2.7-8.1] (15) 4.7 [3.2-6.6] (32) 3.4 [2.5-4.7] (41) 2.7 [1.7-4.1] (21) 3.7 [3.0-4.4] (109)
UK[25 (F)]	1992-2005	18-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89 90-99 **All ≥18**	 **3.9 [3.6-4.1] (840)**	0.6 1.6 1.3 1.8 3.0 3.9 10.5 9.3 10.8 **3.2 [2.8-3.5] (336)**	4.9 3.6 3.5 3.0 4.2 5.5 6.4 9.2 8.1 **4.5 [4.2-4.9] (504)**
	1992-1998	**All ≥18**	**4.5 [4.1-4.8]**	**3.8 [3.3-4.3]**	**3.6 [3.0-4.2]**
	1999-2005	**All ≥18**	**2.9 [2.5-3.2]**	**3.2 [2.8-3.5]**	**5.1 [4.6-5.7]**
UK[26 (A)]	1990-2005	<18 18-64 65-100	4.2 [3.7-4.7] (257) 2.9 [2.7-3.2] (534) 7.4 [6.6-8.1] (354)	4.7 [3.9-5.5] (148) 2.0 [1.7-2.3] (188) 7.8 [6.6-9.0] (157)	3.7 [3.0-4.4] (109) 3.8 [3.4-4.2] (346) 7.1 [6.1-8.0] (197)

		All ages	**3.9 [3.7-4.1] (1145)**	**3.4 [3.1-3.7] (493)**	**4.4 [4.1-4.7] (652)**
	1990-1994	All ages	3.1 [2.6-3.5] (187)	2.5 [2.0-3.1] (76)	3.6 [2.9-4.2] (111)
	1995-1999	All ages	3.3 [3.0-3.7] (312)	2.6 [2.2-3.1] (121)	4.0 [3.5-4.6] (191)
	2000-2005	All ages	4.7 [4.3-5.1] (646)	4.4 [3.9-4.8] (296)	5.0 [4.5-5.5] (350)
UK[27] (G)	1980-1994	0-14	4.8 (70)		
UK[28] (H)	1995-1996	1.2-15	3 (427)		
Germany[29] (D)	1996-1997	0.1-16	2.16 (323)		
Norway[30] (H)	1996-1997	<15	5.3 (92)		
Denmark[31] (B)	1973-1984	16-<60 ≥60 **≥16**	1.58 2.94 **1.94**	1.56	2.30
	1985-1995	16-<60 ≥60 **≥16**	2.27 1.94 **3.33**	2.43	4.20
	1973-1995	16-<60 ≥60 **≥16**	1.94 [0.59-2.29] 4.62 [3.72-5.52] **2.68 [2.33-3.03] (221)**	**2.06 [1.62-2.50] (82)**	**3.28 [2.74-3.82] (139)**
Nordic Countries[32] (D) Denmark Finland Norway Iceland Sweden **All combined**	1998-2000	**0-14**	 3.9 (109) 5.6 (152) 5.6 (74) 2.5 (5) 4.0 (166) **4.8 (506)**		
European ADVANCE (Accelerated Development of Vaccine benefit-risk Collaboration in Europe) Project[33] (A)					
All country data combined	2003-2014	0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All age**s	20.77 [19.54-22.07] 16.22 [15.30-17.19] 7.15 [6.82-7.49] 9.31 [8.95-9.68] 12.39 [12.11-12.67] 23.76 [23.36-24.17] 53.30 [52.57-54.04] 21.76 [21.57-21.96]		
Denmark (Aarhus University Hospital and Staten Serum Institute)	2003-2014 for all	0-1 2-4 5-14 15-24 25-44 45-64	22.3 [20.08-24.6] 14.9 [13.47-16.51] 5.3 [4.85-5.80] 4.9 [4.58-5.44] 7..9 [7.49-8.28] 15.9 [15.37-16.54]		

		≥65 **All ages**	35.7 [34.63-36.8] **13.9[13.66-14.20](10,020)**		
Italy (Agenzia regionale di sanità)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	26.5[22.92-30.5] 26.1 [23.19-29.47] 10.6 [9.56-11.74] 8.7 [7.73-9.69] 9.5 [8.95-10.07] 19.9 [19.1-20.74] 47.5 [46.13-48.91] **21.9 [21.41-22.31]**		
Italy (Val Padana)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	22.9 [14.05-37.44] 28.0 [19.43-40.23] 6.7 [4.49-9.99] 3.3 [1.81-5.92] 6.5 [5.15-8.26] 11.7 [9.81-13.87] 22.0 [19.09-25.24] **12.1 [11.05-13.23](474)**		
Italy (Pedianet)		0-1 2-4 5-14 **All 0-14**	2.5 [0.62-9.86] 1.9 [0.48-7.73] 3.4 [1.61-7.10] **2.8 [1.56-5.07](11)**		
Spain (Base de Datos para la Ivestigación Farmacoepidemiológica en Atención Primaria)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	29.3 [25.56-33.63] 20.6 [17.84-23.83] 15.8 [14.38-17.38] 22.9 [21.63-24.3] 30.2 [29.11-31.34] 66.4 [64.50-68.37] 130.3 [126.9-133.78] **50[49.17-50.78](14796)**		
UK (Royal College of General Practitioners Research and Surveillance Centre)		0-1 2-4 5-14 15-24 25-44 45-64 ≥65 **All ages**	15.5 [12.04-20.06] 14.9 [11.86-18.76] 4.6 [3.68-5.77] 9.8 [8.42-11.43] 13.9 [12.81-15.13] 24.2 [22.67-25.78] 64.0 [60.91-67.20] **23.8[22.99-24.58](3447)**		
UK (The Health Improvement Network)		0-1 2-4 5-14 15-24 25-44 45-64	14.5 [12.63-16.57] 11.1 [9.69-12.66] 5.1 [4.59-5.70] 6.3 [5.72-6.96] 9.5 [9.07-10.03] 17.7 [17.01-18.33]		

		≥65 **All ages**	45.5 [44.17-46.83] **17.3 [16.92-17.6](9923)**		
Middle East					
Kuwait[34 (I)]	1981-1986	1-14	12.5 (60)		

APPENDIX 3

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

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

- Key elements of Case Definition (CD)
  - There are only two levels of certainty (1, 2) based on platelet count (150 X 10^9/L), whether or not a peripheral smear was done to rule out clumping as a cause of thrombocytopenia and clinical evidence of spontaneous bleeding. The working group chose the threshold of 150 rather than 100 based on the former being the most commonly used reference value in the reviewed hematologic literature.[1]
  - The working group deliberately avoided defining idiopathic thrombocytopenia or idiopathic thrombocytopenic purpura because the observed event is thrombocytopenia with or without clinical manifestations. Labelling an event ITP was considered to imply that a causality association with the vaccine was already excluded. The case definition aims to assist in studying whether and to what extent immunizations may cause thrombocytopenia. That said, since the 2007 publication of the case definition the understanding of ITP has been refined as Immune ThrombocytoPenia[2], with primary ITP (no defined cause) and secondary ITP (which includes vaccine-associated ITP as well as several other conditions).[3-6] See the Risk Factors table in Appendix 1.

- Duration of Surveillance for thrombocytopenia
  - Reports of thrombocytopenia should be collected throughout the study period regardless of the time elapsed between immunization and the adverse event. If not feasible the study periods during which such data are being collected should be clearly defined.
  - Occurrence of thrombocytopenia should be monitored at a predefined frequency. For early phase clinical trials, it is recommended to monitor at days 1, 7, 14, 21 and 28 following immunization.

- Recommendations for real time assessment
  - Appendices 5, 6 & 7 use different formats to summarize the key laboratory and clinical data needed to meet the case definition. All contain checklists for evidence of spontaneous clinical bleeding noted in the case definition.
  - Laboratory investigations
    - All platelet counts should be presented by date
    - Method of measurement should be specified (e.g. automated hematology analyzer, cell count slide or other)
    - Review of a blood smear is recommended to exclude pseudo-thrombocytopenia due to platelet aggregations in the test tube
    - Additional laboratory examinations are not required for the case definition but may help in causality assessment including:
      - Bone marrow cytology and histology
      - Anti-platelet antibodies
      - Serum cytokine levels
      - Surgical and/or pathological findings and diagnoses
  - The case definition is focused on establishing thrombocytopenia and as such does not contain exclusion criteria for non-immune causes of thrombocytopenia. Nor is distinguishing primary from secondary ITP necessary to meet the case definition. Such studies, however, may be helpful in assessing vaccine-associated causality given the many other causes of thrombocytopenia. These should be considered when investigating cases and expert consultation (e.g. hematology, immunology, infectious disease) may be helpful.

- Data Collection Guidelines
  - Therapeutic intervention: note type, duration and date.
  - Hospitalization if applicable: note type, duration and date.
  - Any re-occurrence of thrombocytopenia after the initial onset and recovery should be noted.
  - Provide a detailed description of the final outcome at the last observation (with date):
    - Recovery to pre-immunization health status
    - Resolution of symptoms
    - Return to normal platelet count
    - Development of: (NOTE: the definitions below have evolved[2,3,6] and may differ from the published case definition)
      - Persistent ITP (lasting from 3 to 12 months)
      - Chronic ITP (lasting >12 months)
      - Refractory ITP (no response to splenectomy or relapse post-surgery)
    - Death
    - Describe any other outcome
  - Provide details of medical confirmation of the event (contact information of diagnosing physician or identify as site investigator/other site personnel as appropriate.

- Data Analysis Guidelines
  - Classify each case into one of four categories:
    - Meets level 1 as specified in the case definition
    - Meets level 2 as specified in the case definition
    - Reported case of thrombocytopenia with insufficient evidence to meet the case definition
    - Not a case of thrombocytopenia
  - Determine time to onset as number and % of events occurring on day of immunization and specified intervals following immunization: day 1-6, day 7-13, day 14-20 or >20 days.
  - For duration of thrombocytopenia: number of consecutive days (or weeks, months or years) with a platelet count <150 X 10^9/L.
  - If thrombocytopenia occurs intermittently: include first episode and the one with the lowest platelet count. Also the frequency and pattern of re-occurrence should be analyzed.
  - Group degree of thrombocytopenia as number and % subjects with counts (X 10^9/L): <10, >10-20, >20 to 50, >50-100, >100-<150.
  - If detailed analysis in the increments noted above is not possible, at a minimum use the overall number of subjects with a platelet count <150 X 10^9/L as a basis for analysis of incidence and prevalence.
  - If few cases are reported in the trial, platelet count values over time can be presented individually.

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

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

TABLE 1. CONCEPTS FOR THROMBOCYTOPENIA AND THROMBOCYTOPENIC PURPURA

UMLSConcept		Diagnostic Coding System Term and Codes			
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM
C0040034	Thrombocytopenia	Thrombocytopaenia	10043551		
		Thrombocytopenia	10043554		
		Thrombocytopenias	10043555		
		Thrombocytopenia, unspecified	10043560	287.5	D69.6
		Thrombopenia	10043569		
C0154301	Acquired thrombocytopenia	Secondary thrombocytopenia	10039884	287.4	D69.5
C0392386	Decreased platelet count	Low platelets	10024922		
		Platelet count decreased	10035528		
		Platelet count low	10035529		
		Platelets decreased	10035545		
		Reduced platelet count	10038213		
		Thrombocyte count decreased	10043546		
C0398650	Immune thrombocytopenic purpura	Immune thrombocytopenic purpura	10074667	287.31	D69.3
		Idiopathic purpura	10021243		
		Idiopathic thrombocytopenic purpura	10021245		
		ITP	10023095		
		Werlhof's syndrome	10051064		
C0857305	Thrombocytopenic purpura	Thrombocytopaenic purpura	10043552		
		Thrombocytopenia purpura	10043558		
		Thrombocytopenic purpura	10043561		
		Purpura thrombocytopenic	10037561		
C0701157	Primary thrombocytopenia	Primary thrombocytopenia	10036735	287.3	
		Primary thrombocytopenia NOS			D69.49
C0477317	Other primary thrombocytopenia	Other primary thrombocytopenia		287.39	D69.49
C0272278	Congenital thrombocytopenia	Congenital thrombocytopenia			D69.42
C0270236	Neonatal thrombocytopenia due to idiopathic maternal thrombocytopenia				P61.0
C0270237	Neonatal thrombocytopenia due to isoimmunization				P61.0
C0158991	Transient neonatal thrombocytopenia	Transient neonatal thrombocytopenia	10044394	776.1	P61.0

APPENDIX 5
Thrombocytopenia Data Abstraction and Interpretation Form for Medical Chart Review

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

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

Four tables are included in the form.

- Table 1 is a guide to likely sources of information for the key case definition clinical and laboratory criteria.
- Table 2 is the main data abstraction form. Use it to record data from the chart and based on the evidence to assign a value to each case definition criterion. Space is limited and additional paper can be used as appropriate to capture key clinical and laboratory data.
- Table 3 should be used to summarize the criterion values as determined once table 2 is completed.

Table 4 is the key to determine the level of certainty based on the summary data in Table 3. It follows the logic of the Brighton case definition.

TABLE 1. Thrombocytopenia key case definition criteria: likely and actual sources of information

Criterion	Criterion category	Likely sources of information	Actual sources of Information
A	Platelet count	• Laboratory results – CBC, peripheral smear	
B	Blood smear exam		
C	Clinical signs & symptoms of bleeding	• Outpatient clinic / emergency room record(s) • Hospital admitting history & physical exam; discharge summary • Hematology consultation / other consultations	

TABLE 2. Data abstraction form

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

1.Criterion	2. Results	3.BCCD Criteria Value Determination
Criterion A **Decreased Platelet count**	**Lowest recorded platelet count:** ____ X 10^9 / Liter How was the platelet count done: ___not recorded ___automated hematology analyzer ___cell count slide	**A = 'YES'** IF **count <150X10^9/L** **A = 'NO'** IF **count ≥ 150X10^9/L** **A = 'UNKNOWN'** IF **no count done OR results unknown**
Criterion B **Blood smear confirms low platelet count**	**Peripheral blood smear:** __DONE* __Not Done __Unknown if Done/no results * If DONE, describe the results below:	**B = 'YES'** IF **reduced platelet numbers with no clumping seen** **B = 'NO'** IF **normal platelet numbers or clumping seen** **B = 'UNKNOWN'** IF **smear not done or results unavailable**
Criterion C **Clinical symptoms and/or Signs indicate spontaneous bleeding**	**__C1.** ≥ 1 symptom/sign in the table confirmed to be present. Check all that apply __Bruising | __Epistaxis | __Hematuria | __Hematemesis __Purpura | __Petechiae | __Hematoma | __Hematochezia __ Hemorrhagic oozing of skin lesion | __Occult bleeding from rectum __Conjunctival bleeding | __Intracranial bleeding __Vaginal bleeding (unless menstruating) __Other (describe): **__C2.** No clinical evidence of spontaneous bleeding **__C3.** No documentation of any symptoms/signs of spontaneous bleeding	**C = 'YES'** IF **C1 is checked** **C = 'NO'** IF **C2 is checked** **C = 'UNKNOWN'** IF **C3 is checked**

TABLE 3. Based on information in Table 2, check correct Criterion Value and record Final Value

1. Criterion	2. Criterion Value Options			3. Final Criterion Value
A	___YES	___NO	___UNKNOWN	A =
B	___YES	___NO	___UNKNOWN	B =
C	___YES	___NO	___UNKNOWN	C =

TABLE 4. Based on the values for the Criteria in table 3 above, use the formulae in the table below to determine thrombocytopenia level of certainty

Level of Diagnostic Certainty	
1	A = YES AND [B OR C = YES]
2	A = YES AND [B = NO OR UNKNOWN] AND [C = NO OR UNKNOWN]
3	Not applicable
4	Reported thrombocytopenia with insufficient evidence to meet the case definition
5	A = NO

APPENDIX 6

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

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

TABLE 1. STEP 1: USE AVAILABLE CLINICAL DATA TO ASSIGN VALUES FOR CRITERIA IN THE TABLE. YES' OR 'MET' MEANS CRITERION AS DESCRIBED IS DOCUMENTED TO BE PRESENT; 'NO' MEANS IT IS DOCUMENTED TO BE ABSENT; 'UNKNOWN' MEANS THERE WAS NO DOCUMENTATION OF CLINICAL FINDINGS OR A TEST WAS NOT DONE OR IT IS UNKNOWN IF THE TEST WAS DONE OR TEST RESULTS ARE UNAVAILABLE. 'NOT MET' CAN EQUAL 'NO' OR 'UNKNOWN' AS DEFINED ABOVE.

<table>
<tr><th>1.Data Category</th><th colspan="2">2.Results</th><th>3.BCCD Criteria Value Determination</th></tr>
<tr><td>Clinical Criteria</td><td colspan="2">Results</td><td>BCCD Criterion Rules</td></tr>
<tr><td>Criterion A
Decreased Platelet count</td><td colspan="2">Lowest recorded platelet count: _____ X 10^9 / Liter
How was the platelet count done: ___not recorded
___automated hematology analyzer ___cell count slide</td><td>A = 'YES' IF count <150X10^9/L
A = 'NO' IF count ≥ 150X10^9/L
A = 'UNKNOWN' IF no count done OR results unknown</td></tr>
<tr><td>Criterion B
Blood smear confirms low platelet count</td><td colspan="2">Peripheral blood smear: _DONE* _Not Done __Unknown
* If DONE, describe the results below: if DONE</td><td>B = 'YES' IF reduced platelet numbers with no clumping seen
B = 'NO' IF normal platelet numbers or clumping seen
B = 'UNKNOWN' IF smear not done or results unavailable</td></tr>
<tr><td>Criterion C
Clinical symptoms and/or Signs indicate spontaneous bleeding</td><td colspan="2">__C1. ≥ 1 symptom/sign in the table confirmed to be present. Check all that apply
<table>
<tr><td>__Bruising</td><td>__Epistaxis</td><td>__Hematuria</td><td>__Hematemesis</td></tr>
<tr><td>__Purpura</td><td>__Petechiae</td><td>__Hematoma</td><td>__Hematochezia</td></tr>
<tr><td colspan="2">__ Hemorrhagic oozing of skin lesion</td><td colspan="2">__Occult bleeding from rectum</td></tr>
<tr><td colspan="2">__Conjunctival bleeding</td><td colspan="2">__Intracranial bleeding</td></tr>
<tr><td colspan="4">__Vaginal bleeding (unless menstruating)</td></tr>
<tr><td colspan="4">__Other (describe):</td></tr>
</table>
__C2. No clinical evidence of spontaneous bleeding
__C3. No documented evidence for presence/absence of symptoms/signs of spontaneous bleeding</td><td>C = YES IF C1 checked
C = NO IF C2 checked
C = UNKNOWN IF C3 checked</td></tr>
</table>

TABLE 2. STEP 2: APPLY CRITERION VALUES FROM CHECKLIST ABOVE TO FORMULAE BELOW TO DETERMINE LEVEL OF CERTAINTY (LOC)

LOC	
Level 1	**A = YES AND [B OR C = YES]**
Level 2	**A = YES AND [B = NO OR UNKNOWN] AND [C = NO OR UNKNOWN]**
Level 4	Reported thrombocytopenia with insufficient evidence to meet the case definition
Level 5 (Not a case)	**A = NO**

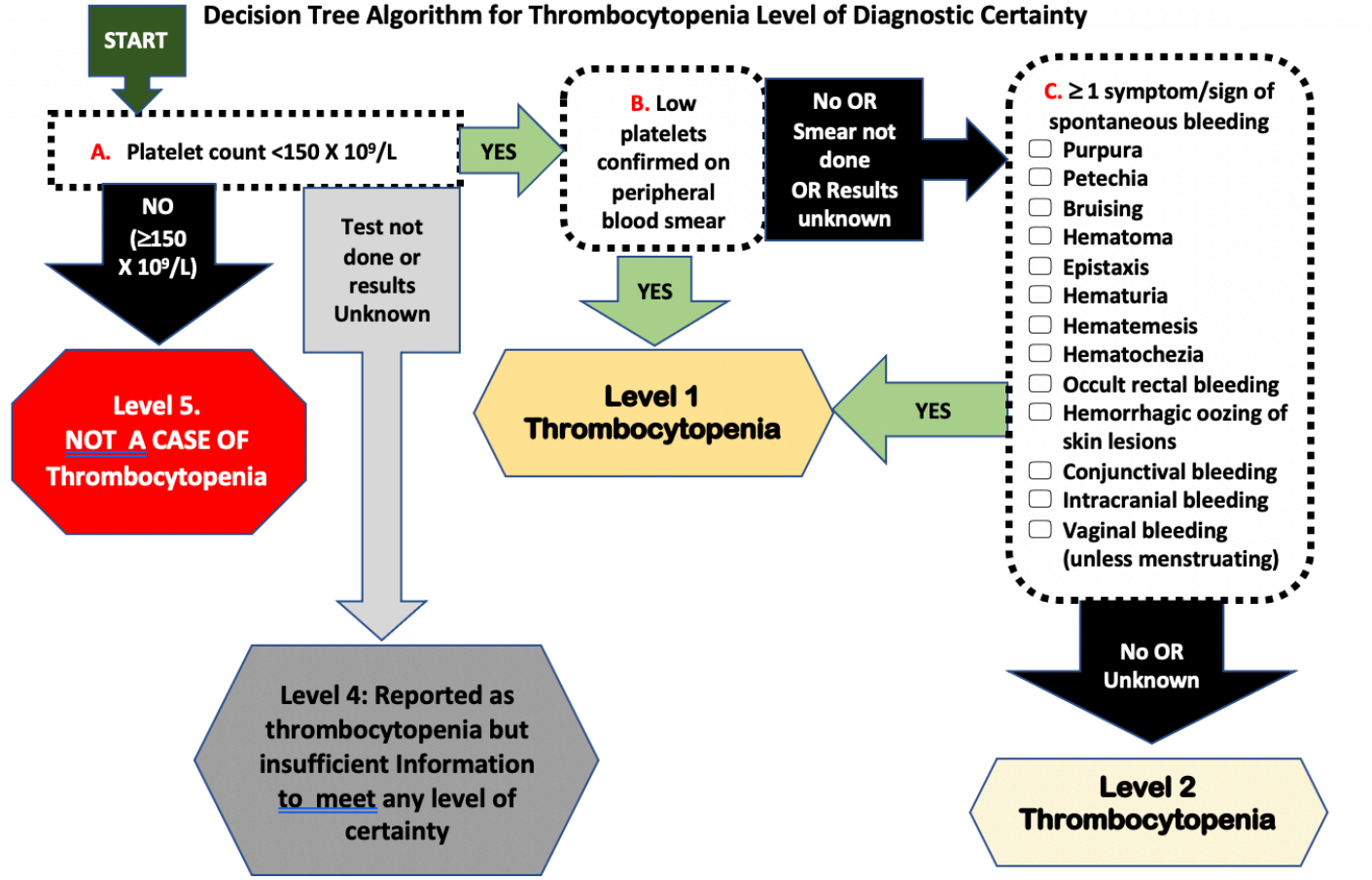
THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

APPENDIX 7

Thrombocytopenia Pictorial Level of Certainty Algorithm

7.1 Thrombocytopenia Pictorial level of certainty algorithm

Use available clinical history, examination and laboratory investigation results to determine level of diagnostic certainty for Thrombocytopenia.



APPENDIX 8.

Methodology: Brief Summary

8.1. Thrombocytopenia Risk Factors [1-20]

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

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

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

The published Brighton Case definition[1] for thrombocytopenia was reviewed for evidence related to associated risk factors. In addition, review articles published after the Brighton case definition were retrieved and reviewed in depth regarding known risk factors for acute thrombocytopenia.[2-8]

8.2. Thrombocytopenia Background Incidence [21-34]

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

("Purpura, Thrombocytopenic, Idiopathic"[Mesh:noexp] OR "Thrombocytopenia"[Mesh:noexp] OR "ITP"[ti] OR "Werlhof's Disease"[ti] OR "Werlhofs Disease"[ti] OR "Werlhof Disease"[ti] OR "morbus werlhof"[ti] OR "thrombocytopenic"[ti] OR "thrombocytopenia"[ti] OR "thrombocytopenias"[ti] OR "thrombopenia"[ti] OR "thrombopenias"[ti] OR "macrothrombocytopenia"[ti] OR "macrothrombocytopenias"[ti])) AND ("Incidence"[Mesh:noexp] OR "incidence"[tiab]) AND English[lang] AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT]) AND ("Meta-Analysis"[Publication Type] NOT ("animals"[Mesh:noexp] NOT "humans"[Mesh:noexp]) NOT ("Coronavirus"[Mesh:noexp] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti]) NOT ("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR trial[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti]).

Articles had to meet the following criteria:

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

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all nonoverlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for thrombocytopenia were extracted. Thrombocytopenia incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a single medical reviewer (BL). Screened in articles were then used for data abstracted (by MRV) for inclusion in the background rate table. When additional studies were found during review of papers, these were included as well. The spreadsheet with all extracted background incidence data is available on the Brighton Collaboration website.

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

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

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

8.4. Thrombocytopenia ICD-9/10-CM and MedDRA Codes[35-39]

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper[35] builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.[36] Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.[37,38] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[39] Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMED-CT, MeSH, ICPC-2 and Read-CTv3.

CodeMapper has three screens.

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

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

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

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

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

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

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

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

In some cases, lettered or numbered values were assigned to a given criterion. Rules to assign these values to the criterion were embedded within the data abstraction table or the tabular checklist depending on the specific tool, further described in results below.
Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition. Two types of algorithm were developed for each case definition. For one, formulae based on the logic in the case definition were put into tables with each row representing a level of certainty. For the second a more visual decision tree algorithm was developed. Both however, were based on the logic inherent in the published case definition.

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