



CEPI | Brighton Collaboration

# **Thrombocytopenia Companion Guide - Updated**

V2.1 – Sept 13, 2025

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# DOCUMENT INFORMATION

Master Service Agreement	SPEAC 2.0	Service order	SO1
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CEPI Project Lead	Rebecca Chandler		
CEPI Project Manager	Thomas Cole		
CEPI Contract Manager	Dorota Zdanekwicz		

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Nature	Report <input checked="" type="checkbox"/> Toolbox <input type="checkbox"/> List <input type="checkbox"/> Template <input type="checkbox"/> Guidance <input type="checkbox"/> Handbook <input type="checkbox"/> Questionnaire <input type="checkbox"/>			
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SPEAC Project Lead		
Scientific Coordinator		

Reviewer 1		
Reviewer 2		

Main Author(s)	Barbara Law, Hammad Ali	E-mail: <a href="mailto:barbara.law@cepi.net">barbara.law@cepi.net</a> ,
WP Lead/Co-Lead	Barbara Law / Hammad Ali	<a href="mailto:drhammadali@gmail.com">drhammadali@gmail.com</a>

Description of the deliverable	This deliverable updates the previous Companion Guide for Thrombocytopenia ( ) as follows: SNOMEDCT codes added; Background incidence and Risk Factor sections updated (to July 2024) and expanded section added with evidence for vaccine association with thrombocytopenia or ITP; data abstraction and interpretation form modified to match versions created for ABC Tool and RedCAP forms; order of annexes changed and references changed accordingly; glossary added to data abstraction form annex 5. This guide can be used by stakeholders to assess the occurrence of thrombocytopenia and ITP 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, SNOMEDCT, 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
SPEAC 2.0 D2.4.1	2025	V2.0	Barbara Law Hammad Ali Ariel Zadok Dale Nordenberg Marta Rojo Villaescusa Matthew Dudley Miriam Sturkenboom	Change order of annexes as follows: 1 = Code terms (was 4) 2 = Background incidence (was 2) 3 = Risk factors (was 1) 4 = Caveats and guidance for real time investigation (was 3) 5 = Data abstraction form and algorithms for levels of certainty (was 5, 6 and 7)  Renummer references to match the new order of annexes  Add SNOMED-CT codes  New material added to Background incidence and Risk Factors based on scoping literature review.
SPEAC 2.0 D2.4.1	4 June 2025	V2.0	Wan-Ting Huang	Review
SPEAC 2.0 D2.4.1	16 July 2025	V2.0	Miriam Sturkenboom	Review
SPEAC 2.0 D2.4.1	13 Sept 2025	V2.1	Barbara Law	Modify Risk Factor Table 3.1 to include all possible Risk Factor categories in order to facilitate digital transformation for Risk Factor dashboard. Previously, categories with no evidence for

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
				<p>risk factor were left out. New format includes all categories and notes 'no evidence found' as appropriate.</p> <p>Add List of Tables and Figures to Table of Contents</p>

## DEFINITIONS & ACRONYMS

ABC	Automated Brighton classification
aOR	Adjusted Odds Ratio
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
BC	Brighton Collaboration
CBC	Complete blood count
CD	Case definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CG	Companion guide
CI	Confidence Interval
CM	Clinical Modification (relates to numbered versions of ICD codes)
CMV	Cytomegalovirus
CUI	Concept Unique Identifier
DTaP	Diphtheria – Tetanus – acellular Pertussis vaccine
EBV	Epstein Barr Virus
GePaRD	German pharmacoepidemiological research database
	International Classification of Diseases
HiB	Hemophilus influenzae type b
HPV	Humanpapillomavirus
HPV4	Humanpapillomavirus quadrivalent vaccine
ICD	International Statistical Classification of Diseases and Related Health Problems
ICU	Intensive care unit
IPV	Inactivated polio vaccine
IQR	Interquartile range
IRR	Incidence rate ratio
ITP	Immune Thrombocytopenia
L	Liter
lang	Language
LOC	Level of diagnostic certainty
MedDRA	Medical Dictionary for Regulatory Activities

MERS	Middle east respiratory syndrome
MIV	Monovalent 2009 H1N1 vaccine
mm <sup>3</sup>	Cubic millimeter
MMR	Measles mumps rubella vaccine
MMRV	Measles mumps rubella varicella vaccine
OR	Odds ratio
PDAT	Publication date
PCV	Pneumococcal conjugate vaccine
PCV7	Pneumococcal conjugate vaccine with 7 capsular types
PCV10	Pneumococcal conjugate vaccine with 10 capsular types
PCV13	Pneumococcal conjugate vaccine with 13 capsular types
PPSV23	Pneumococcal polysaccharide vaccine with 23 capsular types
ptyp	Publication type
RF	Risk factor
RR	Relative risk
RV1	Monovalent rotavirus vaccine
RV5	Pentavalent rotavirus vaccine
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2 (cause of COVID-19)
SCCS	Self-controlled case series
SD	Standard deviation
SNOMEDCT	Systematized nomenclature of medicine-clinical terms
SPEAC	Safety Platform for Emergency Vaccines
TCP	Thrombocytopenia
Tdap	Tetanus – diphtheria – acellular pertussis vaccine
tiab	Title-abstract
TIV	Trivalent inactivated seasonal influenza vaccine
TMP/SMX	Trimethoprim/sulfasoxisole
UMLS	Unified Medical Language System
VZV	Varicella zoster virus

# 1. INTRODUCTION

## 1.1 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. Having identified relevant AESI, SPEAC then works to ensure tools and resources are available to facilitate a standard approach to global vaccine safety research and pharmacovigilance activities.

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, SNOMEDCT 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 relevant to the Brighton case definition.
  - b. Rules for creating new variables relevant to the case definition criteria, if needed.
  - c. Tabular formulae for determining Brighton Level of Diagnostic Certainty (LOC) based on the final value of each case definition criterion (YES, NO or UNKNOWN).
  - d. Pictorial algorithm showing the path to each LOC (1-5) based on criterion values. This contains all the information needed to determine LOC and thus can be used as a stand-alone tool.
  - e. Glossary of terms relevant to the case definition.

Initially these resources and tools were developed as separate documents but starting in 2020 they were pulled together into a single 'Companion Guide' for each published Brighton Collaboration Case Definition. The Thrombocytopenia case definition was first published in 2007[1]. The first Guide for Thrombocytopenia was finalized February 8, 2021. In November 2022, SPEAC began a new contract with CEPI as SPEAC 2.0. A new key feature was to embark on Digital Transformation of tools and resources developed as part of the original SPEAC project from 2019 through October 2022. The original data abstraction forms, tabular checklist and level of certainty algorithms published in V1.0 of the Companion Guides have been revised as part of the digital transformation process.

Another initiative of SPEAC 2.0 was to extend and update the original guide background rate and risk factor sections based on a more thorough literature review than was done for the first versions of the Guides.

## 1.2 Objective of this deliverable

To update the Companion guide for Thrombocytopenia to incorporate changes made to harmonize across all guides: language, order of annexes and provision of SNOMEDCT codes (in addition to MedDRA, ICD-9-CM and ICD-10-CM); to update the data abstraction forms and algorithms so they match what are being used for Digital Transformation including the Automated Brighton Classification (ABC Tool) and other digital data collection tools; to provide newly published data



for thrombocytopenia background incidence and risk factors; and to expand the section on vaccines as a risk factor for thrombocytopenia or ITP.

## 2. Methods

The methods for developing each of the guide resources and tools are briefly described in Annex 6 of this Guide along with links to source documents which have more detailed methodology. More detail regarding the literature review done to capture newly published evidence on thrombocytopenia background incidence and risk factors as well as a new section related to all published evidence on vaccine – thrombocytopenia / ITP associations is presented below.

A scoping literature review was done using two different search strategies.

The search strategy to update the background incidence and risk factor section from the first guide was as follows:

```
("Purpura, Thrombocytopenic, Idiopathic"[Mesh] OR "Thrombocytopenia"[Mesh] OR "Purpura"[Mesh] OR
"ITP"[tiab] OR "Werlhof's Disease"[tiab] OR "Werlhofs Disease"[tiab] OR "Werlhof Disease"[tiab] OR "morbus
werlhof"[tiab] OR "thrombocytopenic"[tiab] OR "thrombocytopenia"[tiab] OR "thrombocytopenias"[tiab] OR
"thrombopenia"[tiab] OR "thrombopenias"[tiab] OR "macrothrombocytopenia"[tiab] OR
"macrothrombocytopenias"[tiab] OR "platelet deficiency"[tiab] OR "platelet deficiencies"[tiab] OR "thrombocyte
deficiency"[tiab] OR "thrombocyte deficiencies"[tiab] OR "purpura"[tiab] OR "purpuras"[tiab] OR "TTS"[tiab])
AND ("Incidence"[Mesh:noexp] OR "incidence*"[tiab] OR "attack rate*"[tiab] OR "person time rate*"[tiab] OR
"background rate*"[tiab] OR "Epidemiology"[Mesh:noexp] OR "epidemiology"[tiab] OR "etiology"[Subheading] OR
"etiology"[tiab] OR "pathogenesis"[tiab] OR "causes"[tiab] OR "causality"[tiab] OR "Risk Factors"[Mesh] OR "risk
factor*"[tiab] OR "population at risk"[tiab] OR "populations at risk"[tiab] OR "risk score*"[tiab] OR "health
correlate*"[tiab])
AND ("2006/01/01"[PDAT]: "3000/12/31"[PDAT])
AND English[lang]
AND ("Meta-Analysis"[ptyp] OR "Systematic Review"[ptyp])
NOT ("animals"[Mesh] NOT "humans"[Mesh])
```

The search strategy to identify articles looking at evidence for vaccine association with thrombocytopenia or ITP was as follows:

```
("Vaccines"[Mesh] OR "vaccine"[tiab] OR "vaccines"[tiab] OR "Vaccination"[Mesh] OR "vaccination"[tiab] OR
"vaccinations"[tiab] OR "vaccinate"[tiab] OR "vaccinated"[tiab] OR "Immunization"[Mesh] OR
"immunization"[tiab] OR "immunizations"[tiab] OR "immunisation"[tiab] OR "immunisations"[tiab] OR
"immunize"[tiab] OR "immunized"[tiab] OR "immunise"[tiab] OR "immunised"[tiab])
AND ("Purpura, Thrombocytopenic, Idiopathic"[Mesh] OR "Thrombocytopenia"[Mesh] OR "Purpura"[Mesh] OR
"ITP"[tiab] OR "Werlhof's Disease"[tiab] OR "Werlhofs Disease"[tiab] OR "Werlhof Disease"[tiab] OR "morbus
werlhof"[tiab] OR "thrombocytopenic"[tiab] OR "thrombocytopenia"[tiab] OR "thrombocytopenias"[tiab] OR
"thrombopenia"[tiab] OR "thrombopenias"[tiab] OR "macrothrombocytopenia"[tiab] OR
"macrothrombocytopenias"[tiab] OR "platelet deficiency"[tiab] OR "platelet deficiencies"[tiab] OR "thrombocyte
deficiency"[tiab] OR "thrombocyte deficiencies"[tiab] OR "purpura"[tiab] OR "purpuras"[tiab])
AND ("2004/01/01"[PDAT]: "3000/12/31"[PDAT])
AND English[lang]
NOT (Comment[ptyp] OR Editorial[ptyp] OR Letter[ptyp] OR News[ptyp] OR Newspaper Article[ptyp])
NOT ("animals"[Mesh] NOT "humans"[Mesh])
```

NOT ("vaccine-induced prothrombotic immune thrombocytopenia"[tiab] OR "VIPIT"[tiab] OR "vaccine-induced immune thrombotic thrombocytopenia"[tiab] OR "VITT"[tiab] OR "Thrombotic Thrombocytopenia Syndrome"[tiab] OR "TTS"[tiab])

The 'background incidence and risk factor' search was conducted on July 19, 2024 and 'vaccine association' search was conducted on July 23, 2024. The results of each search were uploaded into separate COVIDENCE files. Two investigators (Done by authors BL, HA – author initials in parentheses hereafter) screened by title/abstract first, and subsequently by full text review. For each screen any conflicts were resolved to reach consensus on the final list of included articles for data abstraction. Additional articles were found via hand search of the included articles citation lists.

All articles related to background incidence were further screened by one investigator (MRV) to identify articles that had original incidence data. Citations included in all reviews and meta-analyses were obtained to ensure only original data would be captured. A standard excel spreadsheet was used to extract the incidence data. Subsequently the excel file was reviewed by a different investigator (BL) to update the background incidence table.

Data extraction for all articles related to general risk factors (not including vaccine as a risk factor) was done by one investigator (BL) using a word document to capture key findings.

Data extraction for all articles related to possible or proven vaccine-associations was done by Putnam Inizio Advisory using a formatted excel spreadsheet created by WP2 (HA, BL). The extracted data were reviewed by one WP2 investigator (HA) and summary tables prepared for presentation in the Guide. A brief summary of the key findings by vaccine from the tables was prepared by another WP2 investigator (BL) to include in the main guide risk factor table.

PRISMA summaries for each of the two literature reviews were prepared.

### 3. Results

Both search strategies were run in July 2024 (by MD). Figures 1 and 2 show the literature search results for incidence/non-vaccine risk factors and vaccine risk factors respectively, following PRISMA guidelines<sup>1</sup>.

<sup>1</sup> <https://www.prisma-statement.org/>

Figure 1. PRISMA diagram for articles retrieved for incidence and non-vaccine risk factors.

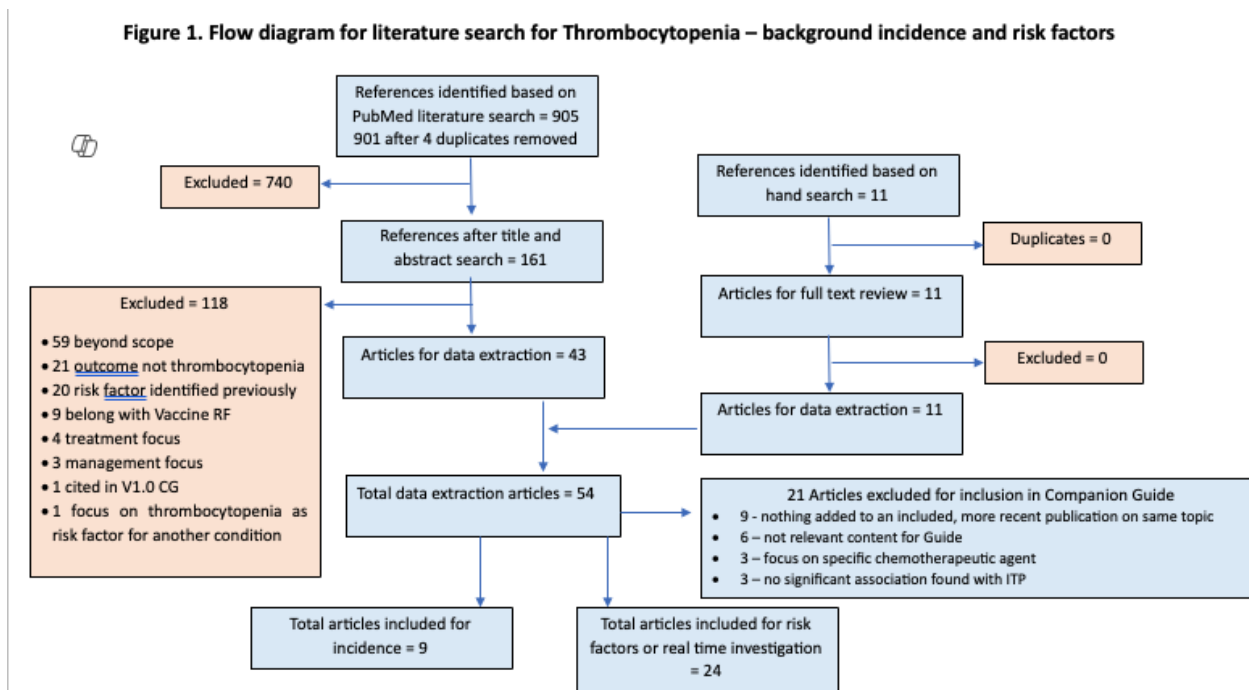
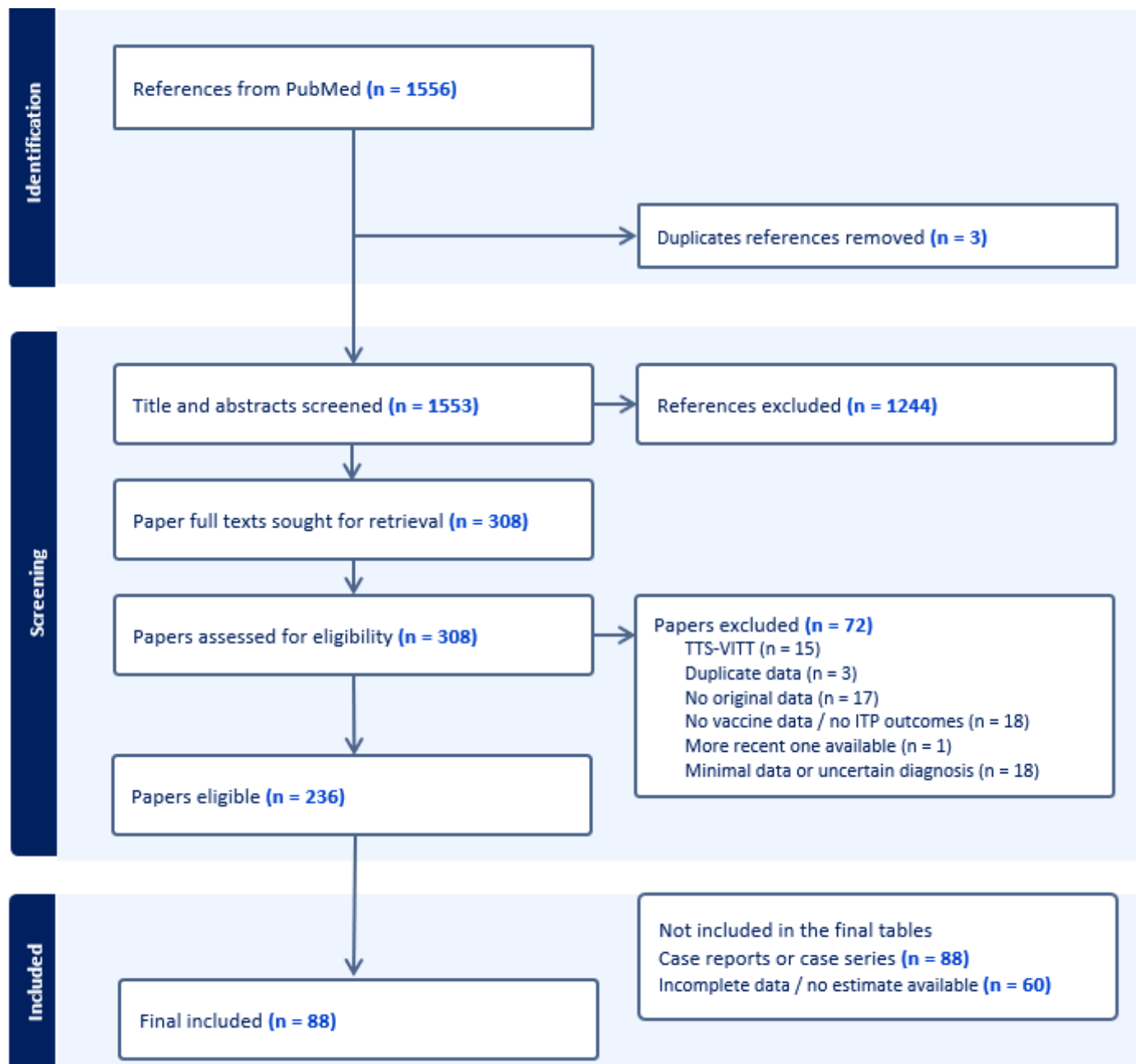


Figure 2. PRISMA diagram for articles retrieved for vaccine-related risk factors.



**TABLE 1.** Summary of the changes from V1 to V2 of the Thrombocytopenia Companion Guide

CHANGE CATEGORY	GUIDE VERSION 1 (V1.0)	GUIDE VERSION 2 (V2.0)
<b>1. Order of Annexes</b>	1. Risk Factors; 2. Background rates; 3. CD caveats; 4. Diagnostic codes; 5. Data abstraction form; 6 Tabular algorithm; 7. Pictorial algorithm; 8. Methods	1. Diagnostic codes; 2. Background rates; 3. Risk factors; 4. CD caveats; 5. Data abstraction form and algorithms to determine level of certainty; 6. Methods. Reference order updated to match the new order of annexes
<b>2. Diagnostic codes</b>	MedDRA, ICD-9-CM, ICD-10-CM	Same as V1.0 AND added SNOMEDCT codes
<b>3. Background incidence</b>	Incidence provided from 14 studies: 1 USA, 1 Japan, 6 UK, 1 Germany, 1 Norway, 1 Denmark, 1 5 Nordic countries, 1 multiple European countries, 1 Kuwait.	13 of 14 studies kept; 1 V1.0 UK study removed because it had incidence of intracranial hemorrhage complicating ITP rather than all ITP[2] 9 new studies added (3 US, 1 Denmark, 1 Sweden, 1 France, 1 Turkiye, 1 updated multi-European countries, 1 multiregion- Europe/Japan/US. For all studies in table, a second table added summarizing key aspects of methodology.
<b>4. Risk Factors</b>	1 Table of Risk factors based on Age, Sex, Genetics, Season, Geography, Comorbidities, Infection, Medication and Vaccine.	New evidence added to all sections except Season and Geography; 2 new categories added (Iatrogenic, Food). 7 new tables of evidence on vaccine-association with thrombocytopenia / ITP were added.
<b>5. Data collection form</b>	Single data form used to collect information AND to define new criterion variables if needed.	Step 1 – data collection form only Step 2 – new criterion variables defined as needed
<b>6. CD criterion values</b>	Summary table for all criterion values (Y=YES, N=NO, U=UNKNOWN)	Same as in V1 but now labelled as Step 3 rather than a numbered table.
<b>7. Level of Certainty (LOC) algorithms</b>	Tabular algorithm with formulae to determine LOC based on criterion values in the summary table.	Same as in V1 but now labelled as Step 4 rather than a numbered table.
<b>8. Tabular Checklist</b>	Annex 6	Deleted as now all checklists and algorithms presented in one annex (5)
<b>9. Pictorial Level of Certainty Algorithm</b>	Annex 7	
<b>10. Glossary of Terms</b>	Not provided	Table of terms specific to thrombocytopenia provided at end of annex 5. Terms yellow highlighted in the data form to alert user to presence of glossary.

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

1. Thrombocytopenia Diagnostic Codes: ICD-9CM, ICD-10CM, MedDRA, SNOMEDCT
2. Thrombocytopenia Background Rates
3. Thrombocytopenia Risk Factors
4. Thrombocytopenia Case Definition key caveats for diagnosis, data analysis and presentation
5. Thrombocytopenia Data Abstraction & Interpretation Form with algorithms for assessing level of certainty and glossary of terms.
6. Summary of methods. Also provides links, as appropriate to the original deliverable documents with more detailed methodology.

## Recommendations & discussion

This guide brings together many resources and tools related to the AESI of thrombocytopenia, several of which have been updated based on a scoping literature review. These include: ICD-9/10-CM SNOMEDCT and MedDRA codes for data entry or database searching; updated section on risk factors, in particular evidence for vaccine-thrombocytopenia/ITP association; updated section on background rates; key caveats of the published case definition and guidance for real time investigation; a simplified data abstraction form and algorithms for assigning level of diagnostic certainty that matches what is available in the online ABC tool and redcap forms; and a glossary of terms for thrombocytopenia.

SPEAC recommends that the tools be used in order to assign level of certainty for all identified AEFI with features of thrombocytopenia or ITP. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

## ANNEX 1

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

All codes in the table were derived from codemapper as described in Annex 6.[3-7]

**TABLE 1.1 THROMBOCYTOPENIA AND THROMBOCYTOPENIC PURPURA – NARROW TERMS**

UMLSConcept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0154301	Acquired thrombocytopenia	Secondary thrombocytopenia	10039884	287.4	D69.5	154826009
C0242584	Autoimmune thrombocytopenia	Immune thrombocytopenia	10083842			
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		
C0477317	Other primary thrombocytopenia	Other primary thrombocytopenia		287.39	D69.4 D69.49	
C0040034	Thrombocytopenia	Primary Immune thrombocytopenic purpura				128091003
		Primary thrombocytopenia				267534000
		Secondary autoimmune thrombocytopenia				128092005
		Secondary thrombocytopenia				154826009
		Immune thrombocytopenia				2897005
		Thrombocytopenic purpura				302873008
		Acquired thrombocytopenia				74576004



TABLE 1.2 THROMBOCYTOPENIA AND THROMBOCYTOPENIC PURPURA – BROAD TERMS

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0040034	Thrombocytopenia	Thrombocytopaenia	10043551			
		Thrombocytopenia	10043554			
		Thrombocytopenias	10043555			
		Thrombocytopenia, unspecified	10043560	287.5	D69.6	
		Thrombopenia	10043569			
		Thrombocytopenic disorder				302215000
		Isolated thrombocytopenia				724637001
		Acquired thrombocytopenia				74576004
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			
		Platelet count below reference range				415116008
		Platelet count below reference range at birth				441458001
C0154300	Purpura and other hemorrhagic conditions			287	D69	



## ANNEX 2

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### Thrombocytopenia Background Rates

**TABLE 2.1. THROMBOCYTOPENIA BACKGROUND RATES** (See Table 2.2 for methodology used in the incidence studies)

Country	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs					
USA (Alabama) [8]	1993-2003	0-18	4.0 (409)		
USA [9]	1991-2000	<18	2.7 {259}		
USA [10]	2012-2015	0-4	8.1	9.4	6.7
		5-17	3.6	3.3	3.9
		18-49	4.3	2.8	5.8
		50-64	5.9	5.8	6.0
		≥65	13.7	15.0	12.7
		All ages	6.1	5.5	6.7
USA [11]	2011-2016	<2	14.8 [13.9-15.8] (891)		
		2-<5	12.1 [11.4-13.0] (910)		
		5-<10	7.1 [6.6-7.5] (982)		
		10-<15	6.7 [6.3-7.1] (990)		
		15-<18	7.7 [7.0-8.4] (441)		
		≤18	8.8 [8.5-9.1] (4214)	9.0 [8.6-9.3] (2196)	8.6 [8.2-9.0] (2018)
ASIA					
Japan [12]	2004-2007	≤14	1.91 (929)	2.01 (505)	1.79 (424)
		≥15	2.20 (6845)	1.68 (2538)	2.69 (4307)
		All ages	2.16 (7774)	1.72 (3043)	2.58 (4731)
EUROPE					
UK [13]	1993-1999	≥16	1.6 (245)		
UK [14]	1990-2005	<2	6.8 [4.9-9.2] (43)	8.7 [5.8-12.6] (28)	4.9 [2.7-8.1] (15)
		2-5	7.2 [5.9-8.8] (101)	9.7 [7.5-12.6] (69)	4.7 [3.2-6.6] (32)
		6-12	3.0 [2.4-3.8] (74)	2.6 [1.8-3.7] (33)	3.4 [2.5-4.7] (41)
		13-17	2.4 [1.7-3.3] (39)	2.1 [1.3-3.3] (18)	2.7 [1.7-4.1] (21)
		All <18	4.2 [3.7-4.8] (257)	4.7 [3.9-5.5] (148)	3.7 [3.0-4.4] (109)
		≥18		3.1 [2.7-3.4] (345)	4.6 [4.2-5.0] (543)

		18-64 ≥65		2.0 [1.7-2.3] (188) 7.8 [6.6-9.0] (157)	3.8 [3.4-4.2] (346) 7.1 [6.1-8.0] (197)
UK [15]	1992-2005	18-19		0.6	4.9
		20-29		1.6	3.6
		30-39		1.3	3.5
		40-49		1.8	3.0
		50-59		3.0	4.2
		60-69		3.9	5.5
		70-79		10.5	6.4
		80-89		9.3	9.2
		90-99		10.8	8.1
		All ≥18	3.9 [3.6-4.1] (840)	3.2 [2.8-3.5] (336)	4.5 [4.2-4.9] (504)
	1992-1998	All ≥18	2.9 [2.5-3.2]	2.1 [1.7-2.6]	3.6 [3.0-4.2]
	1999-2005	All ≥18	4.5 [4.1-4.8]	3.8 [3.3-4.3]	5.1 [4.6-5.7]
UK [16]	1990-2005	<18	4.2 [3.7-4.7] (257)	4.7 [3.9-5.5] (148)	3.7 [3.0-4.4] (109)
		≥18	3.8 [3.6-4.1] (888)	3.1 [2.7-3.4] (345)	4.6 [4.2-5.0] (543)
		18-64	2.9 [2.7-3.2] (534)	2.0 [1.7-2.3] (188)	3.8 [3.4-4.2] (346)
		65-100	7.4 [6.6-8.1] (354)	7.8 [6.6-9.0] (157)	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 [17]	1995-1996	1.2-<16	3 (427)		
Germany [18]	1996-1997	0.1-1.9		5.84 [4.14-7.55] (45)	3.42 [2.08-4.77] (25)
		2-3.9		4.90 [3.38-6.41] (40)	3.49 [2.17-4.81] (27)
		4-5.9		3.68 [2.40-4.95] (32)	3.14 [1.94-4.35] (26)
		6-7.9		2.58 [1.57-3.59] (25)	2.93 [1.83-4.04] (27)
		8-9.9		1.53 [0.76-2.30] (15)	1.08 [0.41-1.75] (10)
		10-11.9		0.54 [0.07-1.01] (5)	1.80 [0.92-2.69] (16)
		12-13.9		0.87 [0.27-1.47] (8)	0.80 [0.21-1.40] (7)
		14-15.9		0.42 [0.01-0.84] (4)	0.89 [0.27-1.51] (8)
		16-16.9		0.42 [0.00-1.00] (2)	0.22 [0.00-0.65] (1)
		All <17	2.16 [1.92-2.40] (323)	2.29 [1.95-2.63] (176)	2.02 [1.69-2.34] (147)
Norway [19]	1996-1997	<15	5.3 (92)		

Denmark [20]	1973-1995 Platelets <100x10 <sup>9</sup>	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)
	1973-1995 Platelets <50x10 <sup>9</sup>	16-<60 ≥60 ≥16	1.61 [1.29-1.93] 4.07 [3.22-4.92] 2.25 [1.92-2.57]	1.78 [1.37-2.19]	2.71 [2.22-3.20]
Denmark [21]	1959-1969	≤15	3.19 (433)		
Sweden [22]	1964-1968	All ages		4.5	7.4
		≥14		4.2	8.1
Nordic Countries [23] Denmark Finland Norway Iceland Sweden All combined	1998-1999	0-14	3.9 (86) 5.6 (112) 5.6 (52) 2.5 ( 3) 4.0 (132) 4.8 (385)		
France [24]	2009-2011	<18 yrs ≥18 yrs ≥75 yrs All ages	2.83 [2.63-3.00] 2.94 [2.84-3.05]  2.92 [2.83-3.01] (3771)	9.0 [8.21-9.95] 2.77 [2.64-2.90]	6 [not provided] 3.03 [2.90-3.16]
Turkiye [25]	2000-2012	≥ 16 yrs	2.92 [1.57-4.27] (216)	1.5 [0.15-1.85] (159)	4.42 [2.04-6.8]
European ADVANCE (Accelerated Development of Vaccine benefit-risk Collaboration in Europe) Project[26]					
All country data combined	2003-2014	0-1	20.77 [19.54-22.07]		
		2-4	16.22 [15.30-17.19]		
		5-14	7.15 [6.82-7.49]		
		15-24	9.31 [8.95-9.68]		
		25-44	12.39 [12.11-12.67]		
		45-64	23.76 [23.36-24.17]		
		≥65	53.30 [52.57-54.04]		
		All ages	21.76 [21.57-21.96]		
Denmark (Aarhus University Hospital and Staten Serum Institute)	2003-2014 for all	0-1	22.3 [20.08-24.6]		
		2-4	14.9 [13.47-16.51]		
		5-14	5.3 [4.85-5.80]		

		15-24	4.9 [4.58-5.44]		
		25-44	7..9 [7.49-8.28]		
		45-64	15.9 [15.37-16.54]		
		≥65	35.7 [34.63-36.8]		
		All ages	13.9[13.7-14.2](10,020)		
Italy (Agenzia regionale di sanità)		0-1	26.5[22.92-30.5]		
		2-4	26.1 [23.19-29.47]		
		5-14	10.6 [9.56-11.74]		
		15-24	8.7 [7.73-9.69]		
		25-44	9.5 [8.95-10.07]		
		45-64	19.9 [19.1-20.74]		
		≥65	47.5 [46.13-48.91]		
		All ages	21.9 [21.41-22.31]		
Italy (Val Padana)		0-1	22.9 [14.05-37.44]		
		2-4	28.0 [19.43-40.23]		
		5-14	6.7 [4.49-9.99]		
		15-24	3.3 [1.81-5.92]		
		25-44	6.5 [5.15-8.26]		
		45-64	11.7 [9.81-13.87]		
		≥65	22.0 [19.09-25.24]		
		All ages	12.1 [11.05-13.23](474)		
Italy (Pedianet)		0-1	2.5 [0.62-9.86]		
		2-4	1.9 [0.48-7.73]		
		5-14	3.4 [1.61-7.10]		
		All 0-14	2.8 [1.56-5.07](11)		
Spain (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria)		0-1	29.3 [25.56-33.63]		
		2-4	20.6 [17.84-23.83]		
		5-14	15.8 [14.38-17.38]		
		15-24	22.9 [21.63-24.3]		
		25-44	30.2 [29.11-31.34]		
		45-64	66.4 [64.50-68.37]		
		≥65	130.3 [126.9-133.78]		
		All ages	50 [49.17-50.78](14796)		
UK		0-1	15.5 [12.04-20.06]		
		2-4	14.9 [11.86-18.76]		

(Royal College of General Practitioners Research and Surveillance Centre)		5-14 15-24 25-44 45-64 ≥65 All ages	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 ≥65 All ages	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] 45.5 [44.17-46.83] 17.3 [16.92-17.6](9923)		
European ACCESS (The vACCine covid0-19 monitoring readinESS project)[27]					
		All ages for all settings (countries) shown below			
Spain (SIDIAP, FISABIO, BIFAPO) UK (CPRD) Netherlands (PHARMO) Denmark (Danish registries) Italy (ARS) France (SNDS) Germany (GePaRD)	2017-2019 for all except Denmark (2010-2013)	GP only (Italy, Spain, UK)	38.99 [7.23-70.76]		
		Inpatients only (Netherlands)	18.01 [16.31-19.70]		
		Inpatient & emergency (Italy)	29.55 [26.03-33.08]		
		GP & in/out-patient (Spain, Netherlands)	92.09 [42.47-141.71]		
		In-&out-patient (Denmark, France)	63.16 [0.00-147.83]		
Middle East					
Kuwait [28]	1981-1986	1-14	12.5 (60)		
Multiple Global Regions					
Australia, France, Germany, Japan, Netherlands, Spain, UK, USA[29]	2017-2019	1-5		17 [12-23]	12 [8-19]
		6-17		8 [3-19]	9 [4-21]
		18-34		8 [2-23]	14 [6-36]
		35-54		10 [3-35]	15 [5-43]
		55-64		19 [6-57]	18 [6-53]
		65-74		30 [9-105]	25 [8-82]
		75-84		41 [10-170]	30 [8-110]



		≥85		56 [15-210]	36 [11-118]
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TABLE 2.2. Methodology used for incidence studies in Table 2.1

Study	Case definition	Study Type / data source	Case Ascertainment / Validation	Excluded secondary ITP	Incident cases included
<b>Watts 2004 [8]</b>	Not stated	Retrospective / Alabama hospital	ICD 287.3 code for ITP / validated by medical chart review	Yes, based on known diagnoses	Acute (76%) and chronic (24%)
<b>Glanz 2008 [9]</b>	Spontaneous bleeding + ≥1 platelet count ≤50 X 10 <sup>9</sup> /L + normal RBC/WBC indices	Retrospective / 8 managed care organizations participating in US CDCP Vaccine Safety Datalink project.	ICD-9 287.0-287.9 / validated by medical chart review	Excluded cases with known cause of thrombocytopenia (prior drugs, infection, pregnant, neonate, sepsis, AIDS, leukemia).	Acute (77%) and chronic (23%)
<b>Weycker 2020 [10]</b>	Not stated	Retrospective / US healthcare claims	Diagnostic codes / no validation	No	Acute and chronic proportion unknown
<b>Shaw 2020 [11]</b>	Not stated	Retrospective / US healthcare claims	ICD-9 and ICD-10 codes / no validation	No	48.3% acute, 32.4% lasted 3-12 months; 15.9% >12 months.
<b>Kurata 2011 [12]</b>	Platelet count <100 x 10 <sup>9</sup> /L	Retrospective / Japanese national registry	Registered ITP diagnosis; registry included patient characteristics, hemorrhagic symptoms, drug therapy, lab tests	Yes, based on known diagnoses	Acute and chronic Proportion unknown
<b>Neylon 2003 [13]</b>	Platelet count <50 x 10 <sup>9</sup> /L	Prospective / England North health region	New ITP Cases registered & validated by Hematologists	Partially; excluded known causes except infection-related	Acute (67%) and chronic (33%)
<b>Yong 2010 [14]</b>	Not stated	Retrospective / UK-GPRD	≥1 diagnostic code for ITP; validation done for random sample of 150 cases	No but identified cases with prior infection (20.2%), immunization(8.6%), hematologic malignancy (1.6%). Noted that none had other related medical conditions or drug exposures	Unable to distinguish acute from chronic ITP
<b>Abrahamson 2009 [15]</b>	Not stated	Retrospective / UK - GPRD	≥1 diagnostic code for auto-immune or idiopathic ITP / no validation	Not specified	Not specified
<b>Schoonen 2009 [16]</b>	Not stated	Retrospective / UK – GPRD	≥1 diagnostic code for ITP; validation on random sample totalling 122 cases of which 93 confirmed	Yes based on presence of codes for selected co-morbid conditions within 6 months before or after ITP diagnosis or relevant drugs within 60 prior days	Unable to distinguish acute from chronic ITP

<b>Bolton-Maggs 1997 [17]</b>	Not stated	Prospective / surveillance questionnaire sent to pediatricians and hematologists	Survey for physician diagnosis	Not clearly stated	Acute (78%) and chronic (22%; 1/3 later found to have underlying disorders).
<b>Sutor 2001 [18]</b>	Platelet count $<30 \times 10^9/L$ + acute bleeding	Questionnaire: retrospective to German hospitals / prospective, monthly to MDs for ITP cases	Survey for physician diagnosis	Yes – excluded neonatal, chronic, oncologic, acute infectious and familial thrombocytopenia; did not exclude prior infection or drug exposure.	Not clearly stated
<b>Zeller 2000 [19]</b>	Not stated; all cases had platelets $\leq 59 \times 10^9/L$ at presentation	Prospective / registration of new cases by Norwegian pediatricians	Survey for pediatrician diagnosis	Yes – other causes of thrombocytopenia to be ruled out by the pediatrician	82% acute, 18% chronic
<b>Frederiksen 1999 [20]</b>	Platelet count $<100 \times 10^9/L$ + no other hematologic disorder	Retrospective / Diagnostic codes for ITP	Diagnostic codes for ITP; not validated	Yes – excluded other hematologic disorders or comorbid conditions causing thrombocytopenia	Not stated
<b>Cohn 1976 [21]</b>	Platelet count $<150 \times 10^9/L$	Retrospective / questionnaire to Danish pediatricians and medical departments	Diagnoses from pediatric and medical departments; medical charts reviewed to validate	Primary and some but not all secondary ITP*	Not clearly stated; 15% of 360 followed for $\geq 1$ year thrombocytopenic.
<b>Bottiger 1972 [22]</b>	Not defined; all cases had counts $\leq 100 \times 10^9/L$	Retrospective / computer registry plus spontaneous AE reports	Cases registered from Uppsala region supplemented by spontaneous reports verified by medical record review	No – all cases counted with 47% primary and the remainder with an identified cause including drugs	38% acute, 45% chronic
<b>Zeller 2005 [23]</b>	Platelet count $<30 \times 10^9/L$	Prospective / registration of new cases in pediatric departments	Survey questionnaire of for new ITP MD diagnosis	58% had prior infection; 7% had prior vaccination. Other causes not mentioned	38% acute, 45% chronic ITP, 17% uncertain
<b>Moulis 2014 [24]</b>	Not stated	Retrospective / French healthcare national database	Diagnostic codes for ITP; not validated	Specified % secondary ITP by age: 0-1 yrs: 1.23%; 2-12yrs: 2.11% 13-17yrs: 4.24%; 18-29yrs: 10.1% 30-49yrs: 14.62%; 50-69yrs: 20.95%; $\geq 70$ yrs: 21.15%	66.7% chronic ITP among adults; 35.7% chronic ITP among children
<b>Koylu 2015 [25]</b>	Platelet count $<100 \times 10^9/L$	Retrospective / Single hospital in Turkiye	Diagnostic codes for ITP; validated with medical chart review	Yes; only included Primary ITP	Not stated
<b>Willame 2021 [26]</b>	Not stated	Retrospective / multiple European country electronic databases	Diagnostic codes for ITP; not validated	Not stated	Not stated

<b>Willame 2023 [27]</b>	Not stated	Retrospective/ multiple European country electronic databases	Diagnostic codes for thrombocytopenia; not validated	Not stated	Not stated
<b>Zaki [28]</b>	Mucocutaneous bleeding + thrombocytopenia (no defined count)	Retrospective / single hospital in Kuwait	Hospital diagnostic codes; yes by medical record review	Excluded diseases known to cause low platelet counts. All cases had bone marrow aspiration to rule out leukemia and marrow hypoplasia	68.3% acute ITP, 31.7% chronic ITP
<b>Li 2021[29]</b>	Not stated	Retrospective / country specific electronic databases	Diagnostic codes or problem lists from electronic health records; not validated	Not stated	Not stated

\* Included congenital, neonatal, drug or infection-induced thrombocytopenia; also included cases of Hemolytic uremic syndrome and Kassabach Merritt syndrome; excluded cases with associated malignancy, myelofibrosis, hypo- or aplastic anemia, SLE or congenital heart disease.

## ANNEX 3

### 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. [30, 31] 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). [31-34] 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. Finally, it must be remembered that thrombocytopenia could be erroneous due to platelet clumping in the presence of EDTA which is the anticoagulant used in routine blood counts. [32] This is why the Brighton case definition requires either a peripheral smear (to detect clumping as the cause of a low count) or evidence of spontaneous bleeding to reach level 1 of diagnostic certainty.

**TABLE 3.1. RISK FACTORS**

<b>Age</b>	<ul style="list-style-type: none"> <li>Adults [35-37]: primary ITP more common than in children and incidence as well as severity increases with age; chronic ITP more frequent (&gt;12 months);</li> <li>Children [33, 38, 39]: most common form is secondary ITP, following a viral infection in 2/3 of cases, with the majority having spontaneous resolution in &lt;6 months [33]</li> <li>Neonates: two forms of ITP               <ul style="list-style-type: none"> <li>Neonatal alloimmune ITP results from maternal alloimmunization versus paternal platelet antigens absent from maternal platelets (analogous to Rh disease). A systematic review [40], of 6 studies of neonatal thrombocytopenia with nearly 60,000 newborns tested, found a pooled prevalence of severe thrombocytopenia (platelet count &lt;50,000X10<sup>9</sup>/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.</li> <li>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. [41] A meta-analysis of 21 studies (retrospective cohort design for all but 1) involving 1951 mothers with ITP and 1844 offspring done in 11 different countries (7 Turkiye, 3 Japan, 2 Israel, 2 Iran and 1 each: Netherlands, France, Egypt, Iran, India, Thailand, Korea) found a pooled estimate for neonatal thrombocytopenia of 24% (95% confidence interval 16.7-33.1) for infants born to a mother with ITP. [42]</li> </ul> </li> </ul>
<b>Sex</b>	<ul style="list-style-type: none"> <li>Adult females – increased frequency until age 60; then similar in males and females [33]</li> </ul>
<b>Genetics</b>	<ul style="list-style-type: none"> <li>Primary ITP [34]: Most studies are of small cohorts so data not definitive but noted that ITP cohorts tend to have polymorphisms of several genes including those listed below. Since the Audia study, several new meta-analyses have been done related to the significance of specific polymorphisms and they are cited below:               <ul style="list-style-type: none"> <li>MHC</li> <li>Fc gamma receptor (FCGR): Li et al did a meta-analysis of 17 studies that examined the association between FCGR polymorphisms that were missense mutations, all of which could affect the binding of Fc gamma receptors with immunoglobulins. They found 2 polymorphisms that were significantly associated with childhood ITP (FCGR2A H131R, FCGR3A F158V) and 1 that was significantly associated with adult-onset ITP (FCGR3A F158V). Detailed results which involved 4 different genetic models and subgroup analyses is beyond the scope of the guide, but can be found in the publication.[43]</li> <li>Transcription factors,</li> <li>Chemokines:</li> <li>Pro/anti-inflammatory cytokines and their receptors: Interleukin 27 rs181206 T&gt;C polymorphism [44], Interferon gamma +874 T/A polymorphism [45], TNF-alpha-308 G&gt;A polymorphism, most notably among Caucasians [46]</li> <li>Human platelet antigens.</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>Non-immune Congenital thrombocytopenia [47]: several syndromes (Absent Radius, DiGeorge, Wiskott-Aldrich, Bernard-Soulier, congenital megakaryocytic thrombocytopenia). Would expect there to be a family history for same.</li> <li>May-Hegglin anomaly is a rare autosomal dominant genetic disorder that may present like ITP. It is distinguished from that by the presence of blue inclusion bodies in leukocytes (but not platelets). [48]</li> </ul>
Pregnancy	<ul style="list-style-type: none"> <li>Thrombocytopenia may be seen in 6-11.6% of pregnancies for a variety of causes with distribution of: [49]               <ul style="list-style-type: none"> <li>Gestational thrombocytopenia (59% of cases): benign condition seen mainly at the end of pregnancy during 2<sup>nd</sup> and 3<sup>rd</sup> trimesters. Counts quickly normalize after delivery. A meta-analysis of 46 studies involving ≥30 women with uncomplicated pregnancies, looked at changes in platelet counts during each trimester, at delivery and 4-8 weeks postpartum. There was a trend for gradual decrease in platelets as pregnancy progressed but only 23 studies followed counts longitudinally and results were inconsistent. The authors concluded that additional studies were needed to establish a normal range of platelet counts during pregnancy, consistent with gestational thrombocytopenia. [50]</li> <li>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.</li> <li>ITP (11% of cases): main cause of isolated thrombocytopenia seen in 1<sup>st</sup> and early 2<sup>nd</sup> trimester and may result in neonatal thrombocytopenia if anti-platelet antibodies cross the placenta. [49] In cases that don't respond to therapy, consider looking for the May-Hegglin anomaly – see Genetic risk factors below. The Hussein study was focused on pregnant women. [48]</li> </ul> </li> <li>Preeclampsia (10% of cases)</li> </ul>
Pre-/Peri-/Postnatal Condition	<ul style="list-style-type: none"> <li>Maternal alloimmunization versus paternal platelet antigens absent from maternal platelets (analogous to Rh disease) – see neonate in 'Age' above.</li> <li>Maternal ITP – see neonate in 'Age' above.</li> </ul>
Social/Culture	No evidence found
Occupation	No evidence found
Season	<ul style="list-style-type: none"> <li>Childhood ITP has a higher frequency in autumn and winter, reflecting the association with prior viral infections [33, 38, 39]</li> </ul>
Geo-Location	<ul style="list-style-type: none"> <li>Limited data but childhood disease pattern similar in high-and low-income countries. [38]</li> </ul>
Environment	No evidence found
Diet	<ul style="list-style-type: none"> <li>A single case report of thrombocytopenia in a 70-year-old man after ingesting ice cream with walnuts provided convincing evidence for a causal association between walnut ingestion and ITP: acute onset of ITP after consumption with spontaneous recovery; other causes of thrombocytopenia excluded; re-exposure to walnuts resulted in a repeated episode of ITP; detection of walnut-dependent platelet antibodies in his serum. [51]</li> </ul>
Behavior	No evidence found
Comorbidity	<ul style="list-style-type: none"> <li>Secondary ITP can be associated with [31, 33, 47, 52]               <ul style="list-style-type: none"> <li>Autoimmune disease: systemic lupus erythematosus, Evans syndrome, Sjogren's syndrome, antiphospholipid syndrome, autoimmune lymphoproliferative syndrome</li> <li>Hematologic malignancy: non-Hodgkin lymphoma, chronic lymphocytic leukemia, large granular T-lymphocyte leukemia</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>○ Primary immune deficiency: common variable immune deficiency, autoimmune lymphoproliferative syndrome</li> <li>○ Solid organ or stem-cell transplantation; in a review of autoimmune cytopenias following pediatric stem cell transplantation the pooled incidence of ITP from 10 studies was 0.76% (Standard Error 0.18%) [53]</li> <li>○ Vitamin B9 or B12 deficiency</li> <li>● Non-immune thrombocytopenia can be associated with:           <ul style="list-style-type: none"> <li>○ Decreased production: bone marrow replacement (proliferative disorders), bone marrow failure (aplastic anemia primary or secondary)</li> <li>○ Increased consumption               <ul style="list-style-type: none"> <li>▪ Hypersplenism</li> <li>▪ Giant hemangioma (Kasabach-Merritt Syndrome)</li> </ul> </li> </ul> </li> </ul>
<b>Iatrogenic/Injury/Trauma</b>	<ul style="list-style-type: none"> <li>● ECMO (extracorporeal membrane oxygenation) A meta-analysis of 21 studies involving 7,190 patients found a pooled estimate for the prevalence of thrombocytopenia in patients receiving ECMO to be 21% (95% CI 12.9-29.0). [54]</li> <li>● Complication of critical care (multifactorial causation): a scoping review of 70 studies, published from 1983-2019, involving 215,098 patients calculated the range of incidence of thrombocytopenia expressed as number of cases/100 admissions based on type of ICU: Any (25 studies) - 8-56; Coronary/cardiac ICU (3 studies): 8-47; Medical ICU (6 studies): 26-44; Surgical ICU (3 studies): 15-41; Mixed Medical/Surgical ICU (7 studies): 8-46. [55]</li> </ul>
<b>Infection</b>	<ul style="list-style-type: none"> <li>● Secondary ITP: many microbes have been associated with ITP, as noted below. [52, 56] Citations focusing on specific pathogens are also provided in the list below.           <ul style="list-style-type: none"> <li>○ Viruses: most commonly Hepatitis C [56], HIV [56], CMV. Also:               <ul style="list-style-type: none"> <li>▪ Chikungunya, Coronaviruses: SARS-CoV, MERS, SARS-CoV-2 [57]; Dengue, EBV, Hepatitis B, measles, mumps, pandemic Influenza A – H1N1, Parvovirus B19, rubella, VZV, Zika,</li> <li>▪ SFTSV (Severe fever with thrombocytopenia syndrome) virus causes an emerging infectious disease seen in east and central China.[58]</li> </ul> </li> <li>○ Bacteria: Anaplasmosis, Borreliosis (relapsing fever), Brucellosis, Ehrlichiosis, Helicobacter pylori [56], Rickettsia, Tuberculosis - disseminated,</li> <li>○ Parasites: Babesiosis, Leishmaniasis [59], Malaria [60, 61], Toxoplasmosis</li> </ul> </li> <li>● Non-immune thrombocytopenia:           <ul style="list-style-type: none"> <li>○ Infection associated consumptive coagulopathy – DIC (Dengue, bacterial sepsis)</li> </ul> </li> </ul>
<b>Medication</b>	<ul style="list-style-type: none"> <li>● Reduced production due to bone marrow myelosuppression: anticancer drugs, valproic acid</li> <li>● 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. The studies cited below were based on meta-analyses or antiplatelet antibody testing.</li> </ul>

- Thrombocytopenia was identified as a complication of linezolid (anti-bacterial used to treat multidrug resistant gram positive bacterial infections) among children [62] and adults [63]. The meta-analysis by Shi et al included 9 studies with 758 children with a pooled incidence of thrombocytopenia of 0.68% (95% CI 0.05-8.47%). Zhang et al included 40 studies involving 6454 patients. Overall incidence of linezolid-associated thrombocytopenia was 37% with a range by study from 13.9% to 60.5%. This study focused on identifying risk factors for linezolid-associated thrombocytopenia and several were found suggesting the impact of co-morbidities, including: advanced age, lower body weight, concurrent renal or liver dysfunction, treatment duration and need for renal replacement therapy.
- A meta-analysis of 29 large placebo controlled RCTs provided pooled estimates for the risk ratio (95% Confidence Interval) of thrombocytopenia following specific anti-platelet Glycoprotein IIb/IIIa inhibitors [64]:
  - Abciximab 2.93 (2.43-3.52)
  - Tirofiban: 2.79 (1.17-6.63)
  - Eptifibatide 1.05 (0.86-1.29)
- A systematic review of reports of drugs causing ITP assessed the validity and reliability of laboratory testing for drug-dependent platelet antibodies which in turn was considered evidence for drug-induced ITP [65]; While 153 drugs were implicated only 36 met all validity criteria for lab testing; of these **16 were considered definite** because results were confirmed by 2 or more independent laboratories whereas *20 were probable because positive test from single lab only*. These included, by drug class:
  - Analgesics: *acetaminophen* ,
  - Antianxiety: *diazepam, lorezepam* ,
  - Antiarrhythmic: *amiodarone*,
  - Anticlotting: **heparin** (including unfractionated heparin, low-molecular-weight heparin, polysulfated chondroitin sulphate, other glycosaminoglycans)
  - Anticonvulsant: **carbamazepine**, *phenytoin* ,
  - Antidepressant: **mirtazapine**,
  - Antidiabetic: *rosiglitazone*,
  - Antihistamine: *tranilast*
  - Antimicrobial: **TMP/SMX, vancomycin, penicillin, rifampin, ceftriaxone, quinine, quinidine, suramin; ampicillin, cefamandole, ciprofloxacin, piperacillin, sulfisoxazole, ethambutol,**
  - Antiplatelet: **glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide)**; *roxifiban* ,
  - Antipsychotic: *haloperidol* ,
  - Calcium channel blockers: *amlodipine*,
  - Chemotherapeutic agents: **oxaliplatin**,
  - Diuretic: *furosemide*.
  - Histamine-2 Blocker: *ranitidine*,
  - NSAIDs: **ibuprofen**, *naproxen* ,
  - Miscellaneous: *gold*



	<ul style="list-style-type: none"> <li>A meta-analysis of ITP as a complication of alemtuzumab treatment for multiple sclerosis included 15 studies with 1729 patients and 37 cases of secondary ITP for a pooled incidence of 2.43% (95% CI 1.76-3.21%). [66]</li> </ul>
Vaccine	<p>Vaccine-related thrombocytopenia is considered a secondary ITP. [67] The evidence for an association between specific vaccines and ITP and/or thrombocytopenia is summarized here, with a focus on the findings from epidemiologic studies. Temporal associations based on pharmacovigilance data or published case reports / series are only included if there were no epidemiologic studies for a given vaccine. More detailed evidence including pharmacovigilance data is presented in Tables 3.2 to 3.8. A spreadsheet with extracted data from all included articles is also available at the SPEAC website and Zenodo. A digital dashboard providing graphic summaries of the results is also available on the Safety Intelligence dashboard for thrombocytopenia.</p> <ul style="list-style-type: none"> <li><b>Measles containing vaccines (M, MR, MMR, MMRV – see Table 3.2)</b> A significant association was found for MMR vaccines in 7 self-controlled case series studies [68-74], 1 case control study [75] and 5 cohort studies.[71, 76-79] Estimated attributable risk for ITP within 6 weeks following MMR was: 1 case per 39,500 doses (95% CI 1 case per 30,500 to 48,500 dose) [74] and 1 in 32,300 doses.[79] MMRV was studied in 1 SCCS and 1 Cohort study: no association with ITP was found in the SCCS study [69] whereas the Cohort study found an Odds Ratio (95%CI) of 11.3 (1.9-68.2). [76]</li> <li><b>COVID-19 vaccines (See Table 3.3):</b> <ul style="list-style-type: none"> <li>The <b>adenoviral vector ChAdOx1</b> vaccine stood out as having a significant association with thrombocytopenia or ITP in the majority of studies (6 of 11): Of 6 SCCS studies, 4 found no significant association [80-83] and 2 found an association with thrombocytopenia: A Scandinavian study found a relative risk for thrombocytopenia within 0 – 28 days of vaccination of 4.29 (95% CI 2.96 – 6.20); [84] and a UK study found an Incidence Risk Ratio at 8 to 14 days after vaccine of 1.33 (1.19 – 1.47). [85] A single UK Case-Control study found an increased risk of ITP within 0 – 27 days after vaccination: RR 5.77 (2.41 – 13.83). [82] Of 3 cohort studies, 1 done in Denmark [86] found no significant association; a significant association with thrombocytopenia but not ITP was found in a Spanish study: [87] Standardized Incidence Ratio (SIR) of 1.28 (1.19-1.38); the same study analyzed UK cases and found a significant association for both thrombocytopenia [SIR for dose 1 of 1.43 (1.38 – 1.49), for dose 2 of 1.47(1.38 – 1.57)] and ITP after dose 1 [1.28 (1.19 – 1.38)]. A third study done in UK found a significant association with thrombocytopenia within 1 – 28 days of vaccination [Hazard ratio 1.71 (1.35 – 2.16)].[88] A fourth cohort study calculated attributable risk per million doses: among those aged 15-39 years 11.3 (7.3-13.8) and among those aged 14-64 years: 10.1 (7.2-11.9). [89]</li> <li>The most studied COVID-19 vaccine was <b>Pfizer’s mRNA BNT162b2</b>, examined in 10 SCCS [80-85, 90-93], 3 Case-Control [82, 92, 94] and 3 Cohort studies.[87, 88, 95] Significant associations were found in: one UK SCCS study where the IRR was 2.8 (1.21-6.49) for ITP occurring in the interval from 0 to 7 days following the first dose of vaccine; [93] and one Cohort study for thrombocytopenia [87] done in both Spain [SIR: dose 1, 1.49 (1.43 – 1.54); dose 2, 1.40 (1.35 – 1.45)] and UK [SIR: dose 1, 1.27 (1.21 – 1.34); dose 2 1.33 (1.25 – 1.40)]. ITP was examined in both countries and no association was found after either dose.</li> <li><b>Moderna’s mRNA-1273</b> was assessed in 3 SCCS, 2 focused on ITP as an outcome [90, 93] and 1 on thrombocytopenia. [84] None found a significant association. Several studies analyzed the 2 mRNA vaccines together, none of which found a significant association: 2 SCCS [96, 97] and 4 Cohort. [96, 98-100]</li> </ul> </li> </ul>

- The **inactivated Coronavac vaccine** was assessed in 2 SCCS, [80, 92] 1 Case-Control [92] and 1 Cohort study. [95] and no significant association was found.
- **COVID-19 vaccines given to individuals with pre-existing ITP** (See Table 3.4): 1 Case-Control and 10 Cohort studies done in Netherlands, UK, Qatar, Italy, USA, Israel and China followed 1372 (range of 64-360/study) patients with known chronic ITP to look for evidence of relapse of disease (new drop in platelets or bleeding event) following COVID-19 vaccination (different vaccines and doses studied – see Table 3.4 for specific details). All studies found evidence for relapse in a % of patients.
- **HPV vaccines (See Table 3.5)**: 2 Case-control found no association between HPV vaccine and ITP. [69, 101] 1 UK Cohort study looked at incidence trends for thrombocytopenia before and after the introduction of HPV vaccine programs and found no significant change. [102] The only study, done in Columbia, which found an increased risk of ITP at 360 days following the 1<sup>st</sup> dose of quadrivalent HPV vaccine (OR 2.54 (1.28 – 5.02). [103] There was no rationale for using such a long post immunization interval in the study and a noted limitation of the study was lack of access to records of risk factors such as family history, ethnicity, or other socio-demographic characteristics that could influence development of disease.
- **Pneumococcal vaccines (See Table 3.6)**: Two SCCS studies done in infants found no association between pneumococcal conjugate vaccine and thrombocytopenia. [69, 104] Two SCCS studies involving senior adults (≥64 years) found no association between pneumococcal polysaccharide vaccine and thrombocytopenia [105] or ITP. [106] 2 cohort studies found no increased risk of thrombocytopenia after PCV13 vaccine relative to PCV7 in infants [107] or pneumococcal polysaccharide 23 vaccine in ≥ 65 year olds. [108]
- **Influenza vaccines (See Table 3.7)**: Among 2 SCCS [69, 109], 1 RCT [110], 2 Case-Control [111, 112] and 3 Cohort [113-115] studies, only one found an increased risk for ITP following influenza vaccine. This was a German case-control study which defined cases as in- or outpatients with confirmed ITP and controls from similar settings but with diseases other than ITP. The odds ratio for influenza vaccine induced ITP was 4.0 (1.5-9.6). [112]
- Table 3.8 provides evidence for association with thrombocytopenia or ITP following vaccines other than those listed above. These include:
  - **DTaP vaccines**: no significant association between DTaP and ITP was found in 1 SCCS, [69] 1 case-control, [111] , and 2 Cohort [116, 117] studies.
  - **VZV vaccine**: one SCCS study done in Taiwan found no association with ITP [118]
  - **Meningococcal C conjugate vaccine**: one SCCS study done in UK found no association with ITP [70]
  - **Hepatitis A vaccine**: one SCCS study in US [69] found an increased risk for ITP following vaccine in 7 to 17 years olds [2 ITP cases; IRR 23.14 (3.59 – 149.3) but no increased risk among 12-23 month olds (4 ITP cases) or 2 – 6 year olds (1 ITP case).
  - **HZ vaccine**: one case control study found no significant increased risk for thrombocytopenia [119]
- In 2011 the Institute of Medicine 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. As noted above no evidence for an association was found in 4 studies of DTaP and 1 study of VZV vaccine. Although several other vaccines were reviewed (Influenza, Hepatitis A, Hepatitis B, Meningococcus, Human papillomavirus) no studies involving thrombocytopenia or

	<p>ITP were mentioned. Our review found possible increased risk following Hepatitis A vaccine and Influenza vaccine – each based on only one study and no increased risk for Meningococcal C conjugate vaccine based on only 1 study. Further studies of all would be needed to establish a causal association.</p> <ul style="list-style-type: none"> <li>The literature review identified a total of 108 cases of thrombocytopenia or ITP following vaccination, based on 84 published single case reports and 8 case series with 2 to 4 cases each. Summarized here are vaccines with no other evidence for an association. Clearly these are temporal associations only. Included are: 2 case reports following Rabies vaccine [120, 121] and single cases for each of the following vaccines: TBE[122], OPV[123] and HBV[124]</li> <li>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.<sup>CD</sup> In general a six-week period following immunization (from day 1 to 42) is commonly used for studies of secondary ITP associated with immunization. [67, 69, 125]</li> </ul>
Other	No Evidence Found

**TABLE 3.2** Studies reporting on risk of thrombocytopenia after vaccination with measles containing vaccines, by study type

Author, year, Journal	Location	Study Years	Age Group	Number of TCP / ITP cases	Specific Vaccine	Risk Estimate	Risk estimate value*	Relevant Additional Study Details
SCCS (n=7)								
Perez-Vilar 2018[68]	Multiple countries <sup>1</sup>	2010 – 2014	9-23 months	ITP: 183	MMR	Adjusted IRR (95% CI)	5.6 (2.7–11.9)	Case ascertainment: ICD9/10 codes Risk period = 8-35days Non-risk period = 43-84 days
O’Leary 2012[69]	USA	2000 – 2009	6 weeks-17 years	ITP: 197	MMR	IRR (95% CI) 12-19 months 4-6 years	5.48 (1.61-18.64) 3.06 (0.42-22.30)	Case ascertainment: ICD-9 codes ITP cases after MMR: - In 12-19 month olds=6 - In 4-6 years olds=2 ITP cases after MMRV in 12-19 month olds=4
					MMRV	IRR (95% CI) 12-19 months	2.87 (0.78-10.56)	
Andrews 2007[70]	UK	1999 – 2003	1-17 years	ITP: 108	MMR	Relative incidence (95% CI) in toddlers and children	6.91 (1.81 - 26.4)	Case ascertainment: ICD-10 codes Outcome: number of hospital admissions for purpura Risk period = 0-41 days ITP cases after MMR=6

Andrews 2012[71]	England, Denmark	1996 – 2007	12-23 months	TCP: 55	MMR	Pooled relative incidence (95% CI)	1.98 (1.41 - 2.78)	Case ascertainment: ICD-10 (D69.3) or ICD-8 (287.10) codes Risk period = 0-42 days Pooled data used meta-analysis of each country's individual SCCS Relative Incidence estimates
Whitaker 2018[72]	UK	1991 – 1994	366-730 days	ITP: 35	MMR	Relative incidence (95% CI)	3.23 (1.53 - 6.79)	Risk period = 0-42 days
Campos 2017[73]	USA	-	12-23 months	ITP: 35	MMR	Relative incidence	3.5	Risk period = 30 days
France 2008[74]	USA	1991 – 2000	12-23 months	ITP: 20	MMR	IRR (95% CI)  Attributable risk with 42 days of vaccination	5.38 (2.72-10.62)  1 case per 39,500 (30,500–48,500) doses	Case ascertainment: 2 platelet counts ≤50,000/uL or 1 count plus associated ICD-9 code (287.0-287.9) Risk Period = 0-42 days ITP cases: 18 acute and 2 chronic
Case Control (n=1)								
Bertuola 2010[75]	Italy	1999 – 2007	1month-18 years	ITP: 14	MMR	OR (95% CI)	2.4 (1.2-4.7)	
Cohort study (n=5)								
Klein 2015[76]	USA	2000 – 2012	12-23 months	-	MMRV	OR of ITP (95% CI)	11.3 (1.9-68.2)	Case ascertainment: Two platelet counts of <50,000 within 7 days of each other
				-	MMR+V	OR of ITP (95% CI)	10 (4.5-22.5)	
Andrews 2012[71]	Denmark	1996 – 2007	12-23 months	TCP: 38	MMR	Relative incidence	1.85 (1.23–2.78)	Case ascertainment: ICD10 (D69.3) or ICD8 (287.10) code Risk period = 0-42 days
Rajantie 2007[77]	Multiple countries <sup>2</sup>	-	0-14 yrs	ITP: 24	MMR	Risk of ITP	1 / 30,000 inoculations	ITP cases = 24 Study n = 506
Svanstrom 2010[78]	Denmark	1995 – 2007	*	ITP: 529	MMR	Information component	Nothing significant for any interval assessed (0-13, 14–27, 28-41, 42-55, 56-69 or 70-83 days)	Case ascertainment: ICD-10 Study n = 918,831 *Children born from Jan 1, 1995, to Dec 31, 2007
Miller 2001	UK	1991 – 1994	12-23 months	ITP: 9	MMR	1.Absolute risk of admission for ITP	1. 1 in 22,300 doses	Case ascertainment: ICD 9 code (278.3)

[79]						2. Attributable risk of ITP 3. Relative incidence of admission for ITP	2. 1 in 32,300 doses 3. 3.27 (1.49-7.16)	Risk period = 0-42 days
Pharmacovigilance Studies (n=5)								
Soriolo 2024[126]	Italy	2007 – 2022	0-12 years	TCP: 18	MMRV	Reporting rate per 10,000 during study period	0.22	Case ascertainment for thrombocytopenia: BC MMRV doses= 813,956 MMR-V doses= 340,357
				TCP: 2	MMR+V		0.05	
Meng 2017[127]	China	2009 - 2014	8 months - $\geq$ 8 years	TCP: 2	MR	Annual incidence rate, per million doses	0.3	Measles containing doses = 9.9 million
					Measles alone		0.8	
Nakayam 2007[128]	Japan	1994 – 2004	-	ITP Measles: 5 Mumps: 1 Rubella: 4	Measles Mumps Rubella	Calculated incidence rate, per million doses	Measles = 1.37 Mumps = 1.0 Rubella = 0.65	Measles = 3.64 million doses Rubella = 4 million doses Mumps = 1.53 million doses
Shu 2011[129]	China	2007-2008	7 years	ITP: 1	Measles	Incidence of ITP, per million doses	0.07	Case ascertainment: bleeding tendency and platelets $<100,000/\text{mm}^3$ . Measles doses= 14.3 million
Khetsuriani 2010[130]	Georgia	2008 - 2009	6 – 27 years	TCP: 1	MR	Calculated incidence rate, per million doses	2.03	MR doses= 493,000

<sup>1</sup> 16 countries - Albania, Argentina, Australia, Chile, China, Colombia, Costa Rica, Honduras, India, Iran, Peru, Singapore, South Africa, Spain, Uganda, Uruguay

<sup>2</sup> Nordic countries

~ Confidence intervals are included if they were reported in the paper

\* Bold values represent statistically significant data

**TABLE 3.3** Studies reporting on risk of thrombocytopenia after vaccination with COVID-19 vaccines, by study type

Author, year, Journal	Location	Study Years	Age Group	Number of TCP or ITP Cases	Specific Vaccine	Risk Estimate	Risk estimate value*	Relevant Additional Study Details
SCCS (n=12)								
AbRahman, 2023[80]	Malaysia	2021 and 2022	18+ years	TCP: 344	1 <sup>st</sup> dose: 1. BNT162b2 2. Coronavac 3. ChAdOx1 2 <sup>nd</sup> dose: 1. BNT162b2 2. Coronavac 3. ChAdOx1	IRR (95% CI)	1 <sup>st</sup> dose: 1. 0.83 (0.68-1.02) 2. 0.78 (0.57-1.08) 3. 1.36 (0.67-2.78) 2 <sup>nd</sup> dose: 1. 0.96 (0.79-1.16) 2. 0.92 (0.68-1.23) 3. 1.45 (0.68-3.10)	Case ascertainment: ICD-10 Risk period = 1- 21 days
Joy 2023[81]	UK	2020 - 2022	≥16 years	TCP: 104 ITP: 15 TCP: 175 ITP: 18	BNT162b2 ChAdOx1	IRR (95% CI)	TCP = 0.79 (0.64-0.98) ITP = 1.26 (0.68-2.82) TCP = 1.47 (0.59-3.63) ITP = 1.38 (0.73-2.61)	Case ascertainment: ICD-10, SNOMED clinical terms Risk period = 0-27 days Vaccinated n = 12.3 million
Shoaibi 2023[90]	USA	2020 - 2021 2021 - 2022	≥65 years	ITP: 1. 668 2. 417 ITP: 1. 49 2. 39	Primary series 1. BNT162b2 2. m-RNA-1273 Booster 1. BNT162b2 2. m-RNA-1273	IRR (95% CI)	Primary series: 1. 1.12 (0.94-1.33) 2. 1.08 (0.86-1.37) Booster 1. 1.17 (0.66-2.04) 2. 1.54 (0.82-2.91)	Risk period = 1-42 days Primary series doses = 3,360,981 Booster doses = 6,156,100
Yamin 2023[91]	Israel	2021 – 2022	≥12 years	TCP: 7 TCP: 24 TCP: 6	BNT162b2 1 <sup>st</sup> monovalent booster BNT162b2 2 <sup>nd</sup> monovalent booster BNT162b2 1 <sup>st</sup> , 2 <sup>nd</sup> or 3 <sup>rd</sup> bivalent booster	Risk difference for events per 100,000 people (95% CI)	2.6 (0.7-4.7) 0.3 (–3.0-3.8) 0.0 (–5.7-5.7)	Case ascertainment: ICD-9 Risk period = 28 days 1 <sup>st</sup> monovalent booster= 1,073,110 2 <sup>nd</sup> monovalent booster= 394,251 1 <sup>st</sup> , 2 <sup>nd</sup> or 3 <sup>rd</sup> bivalent booster= 123,084

Sing 2022[92]	Hong Kong	2018 – 2021	≥16 years	TCP: 975	BNT162b2 1 <sup>st</sup> dose	IRR (95% CI)	0-13d 0.96 (0.72–1.28) 14-27d 1.00 (0.74-1.35)	Case ascertainment: Platelet counts <150 x10 <sup>9</sup> /L Risk period = 27 days
				TCP: 1,166	Coronavac 1 <sup>st</sup> dose		0-13d: 1.04 (0.80–1.34) 14-27d: 1.18 (0.93- 1.50)	
Takeuchi, 2022[96]	Japan	2020 – 2021	≥18 years	ITP: Dose 2: 3	BNT162b2 or mRNA-1273	Within-subject IRRs (95% CI)	4.47 (0.74–27.18)	Case ascertainment: ICD-10 codes Risk period = 21 days
DagBerild 2022[84]	Norway, Finland & Denmark	2020 – 2021	<65 years	TCP: 40	ChAdOx1	Rate Ratio (95% CI)	4.29 (2.96-6.20)	Case ascertainment: ICD-10 codes Risk period = 28 days
				TCP: 172	BNT162b2		1.04 (0.88-1.23)	
				TCP: 13	mRNA-1273		0.86 (0.48-1.55)	
Simpson 2021[82]	UK	2020 – 2021	≥16 years	ITP: 27	ChAdOx1,	Adjusted risk ratio (95% CI)	1.28 (0.68-2.41)	Case ascertainment: Read codes Risk period = 28 days
				ITP: 13	BNT162b2		0.58 (0.21-1.61)	
Torabi 2022[93]	UK	2020 – 2021	≥16 years	ITP: <10	BNT162b2 Dose 1	IRR (95% CI)	Only significant result 0-7 days = 2.8 (1.21-6.49)	Risk period = 0-28 days Intervals analyzed in days = 0-7, 0-14, 8-14, 15-21, 22-28 ChAdOx1 and mRNA-1273 included in study but no significant results
Simpson 2022[83]	UK	2020 – 2021	16-30 Years	TCP: 13 ITP: 9	BNT162b2	IRR (95% CI)	TCP 0.95 (0.65-1.38) ITP 1.68 (0.80-3.52)	Risk period =27 days
				TCP: 6 ITP: 34	ChAdOx1		TCP 0.84 (0.62-1.13) ITP 1.15 (0.61-2.15)	
Hippisley- Cox 2021[85]	UK	2020 – 2021	≥ 16 years	TCP: 1,480	ChAdOx1	IRR (95% CI)	8-14 d = 1.33 (1.19- 1.47)	Risk period = 28 days Intervals analyzed in days = -28--1, 0, 1-7, 8-14, 15-21, 22-28. Only significant risk estimates shown
				TCP: 1,010	BNT162b2		No significant results	
Dorajoo 2023[97]	Singapore	2020 – 2022	≥5 years	ITP: 17	mRNA Dose 1	Adjusted RR (95% CI)	0.88 (0.54-1.45)	Case ascertainment: BC Risk period = 42 days Vaccines: BNT162b2 or mRNA-1273
				ITP: 12	mRNA Dose 2		0.64 (0.36-1.14)	
				ITP: 17	mRNA Booster		0.92 (0.56-1.52)	
Case Control (n=3)								
Sing 2022[92]	Hong Kong	2018 – 2021	≥16 years	TCP: 107	BNT162b2	Odds ratio (95% CI), compared to control	Dose 1: 0.89 (0.72-1.09) Dose 2: 0.86 (0.70-1.06)	Case ascertainment: Platelet counts <150 x10 <sup>9</sup> /L
				TCP: 166	Coronavac,		Dose 1: 1.05 (0.89-1.24) Dose 2: 0.76 (0.62-0.93)	

Barda 2021[94]	Israel	2020 – 2021	27 to 53 years	TCP: 56	BNT162b2	Risk Ratio (95% CI), compared to unvaccinated	0.94 (0.63-1.27)	Case ascertainment: ICD-10 and short free-text phrases that accompany diagnoses Risk period = 42 days Vaccinated n = 923,123
Simpson 2021[82]	UK	2020 – 2021	≥16 years	ITP: 23 TCP: 46	ChAdOx1,	Adjusted RR (95% CI), compared to unvaccinated	ITP: 5.77 (2.41-13.83) TCP: 1.42 (0.86-2.37)	Case ascertainment: Read codes Risk period = 0-27 days Vaccinated n: <ul style="list-style-type: none"><li>ChAdOx1=1.71 million</li><li>BNT162b2=0.82 million</li></ul>
				ITP: 13 TCP: ≤5	BNT162b2		ITP: 0.54 (0.10-3.02) TCP: 0.67 (0.32-1.43)	
Cohort study (n=13)								
Harris 2023[98]	USA	2020 – 2021	Mean (SD): 76.7 (7.7) years	ITP: 1,543	mRNA-1273	Adjusted RR (95% CI), compared with BNT162b2	0.96 (0.90-1.03)	Case ascertainment: ICD-10 codes Risk period = 1-28 days Vaccinated n = 2,997,492
DeSilva 2023[99]	USA	2020 – 2022	16 to 49 years	ITP: 66	mRNA*	Adjusted rate ratio (95% CI) compared to unvaccinated	1.14 (0.79–1.65)	Risk period = 1-42 day Vaccinated n = 40,208 * Vaccine: Pfizer BioNTech or Moderna
Choi 2023[131]	Australia	2021 – 2022	20-97 years	ITP: 50	ChAdOx1,	ITP incidence, per 100,000	2.72	Case ascertainment: Standard international consensus definitions
					BNT162b2		0.28	
Peng 2023[95]	Hong Kong	2020 – 2022	Mean (SD): 54.25 (18.33) years	ITP: 308	BNT162b2 or CoronaVac	aHR (95% CI)	0.45 (0.29-0.70)	Vaccinated n = 3,168,131 aHR: fully vaccinated vs non- vaccinated
Burn 2022[87]	Spain	2020 – 2021	45 to 75 years	ITP Dose 1: 97 Dose 2: 61 TCP: Dose 1: 3186 Dose 2: 2749	BNT162b2	Standardised incidence ratio (95% CI), compared to background population	ITP: Dose 1: 1.03 (0.84–1.26) Dose 2: 0.69 (0.53–0.88) TCP: Dose 1: 1.49 (1.43–1.54) Dose 2: 1.40 (1.35–1.45)	Case ascertainment: Diagnostic codes or a measurement of a platelet count between 10,000 and 150,000 platelets/microliter. Vaccinated n = 2,613,774
				ITP: 12	ChAdOx1		ITP: 0.48 (0.27–0.85)	



				TCP: 754			TCP: 1.28 (1.19-1.38)	
Burn 2022[132]	UK	2020 – 2021	-	-	BNT162b2,	Standardised incidence ratio (95% CI)	ITP: Dose 1: 1.28 (0.83-1.96) Dose 2: 0.79 (0.41-1.52) TCP Dose 1: 1.27 (1.21-1.34) Dose 2: 1.33 (1.25-1.40)	Case ascertainment: Diagnostic codes or a measurement of a platelet count between 10,000 and 150,000 platelets/microliter.  Number of doses: • BNT162b2= 1,832,841 • ChAdOx1= 3,768,517
					ChAdOx1		ITP: Dose 1: 1.79 (1.33-2.39) Dose 2: 1.04 (0.52-2.07) TCP: Dose 1: 1.43 (1.38-1.49) Dose 2: 1.47 (1.38-1.57)	
Takeuchi 2022[96]	Japan	2020 – 2021	Mean (SD): 69.0 (16.5) years	-	BNT162b or mRNA-1273	IRD (95%CI), adjusted/ 100,000 person day	Dose 1: -0.04(-0.06-0.01) Dose2: 0.08(-0.06-0.21)	Case ascertainment: Cases diagnosed using ICD-10 codes 1 <sup>st</sup> dose: 136,667 2 <sup>nd</sup> dose: 127,322
Hviid 2022[86]	Denmark	2020 – 2021	Media n (IQR) 44 (32, 54) years	-	AZD1222	Risk difference (95% CI) compared to no vaccination	2.39 (-1.09–5.87)	Case ascertainment: ICD-10 Risk period = 28 days Vaccinated n = 121,152
Whiteley 2022 [88]	UK	2020 – 2021	≥18 years	-	ChAdOx1-S,	Fully adjusted Hazard ratio in <70-year-olds	1.71 (1.35-2.16)	Case ascertainment: Specialist clinician-verified SNOMED-CT and ICD-10 Vaccinated n = 46 million Risk period = 28 days
					BNT162b2		1.00 (0.75-1.34)	
Andrews 2022[89]	UK	2020 – 2021	15+ years	-	ChAdOx1	Attributable risk, per 1 million doses (95% CI)	15-39 years = 11.3 (7.3- 13.8) 40-64 years = 10.1 (7.2- 11.9)	Case ascertainment: ICD-10 Vaccinated n = 27,378,384

Pottegard 2021[133]	Denmark, Norway	2021	18-65 years	TCP: 17	ChAdOx1	Incidence rate per 1000 person years	Denmark=0.15 Norway=0.38	Vaccinated n = 281,264
Klein 2021[100]	USA	2020 – 2021	Mean, years = 49	-	BNT162b2, mRNA-1273	Adjusted RR (95% CI)	1.12 (0.65-1.97)	Risk period = 21 days Comparison period: 22-42 days Vaccinated n = 6.2 million Comparison period: 22-42 days
Mericililer 2023[134]	Multiple	2010 – 2023	Mean (SD) = 52.2 (19.1) years	ITP: 24	mRNA	Event rate per 10,000 doses	0.07	Vaccinated n = 3,177,285
Pharmacovigilance Studies (n=9)								
Kim 2024[104]	South Korea	2020 – 2023	12 – 17 years	ITP: 52	Any COVID-19 vaccine	Adjusted ROR for COVID-19 vaccine vs all other vaccines	1.12 (0.59-2.09)	Vaccinated n = 80,018
Kim 2023[135]	South Korea	2020 – 2021	≥ 18 years	TCP: 20	JNJ-78436735, mRNA-1273 and BNT162b2	Odds ratio (95% CI)	2.01 (1.11-3.61)	Vaccinated n = 6,829 Odds ratio for Type 2 diabetes patients versus non-diabetic
Jacobs 2023[136]	USA	1990 – 2022	Mean (SD): 53.3 (20.5) years	ITP: 141	BNT162b2	Rate of ITP per 10,000 doses	0.039	
				ITP: 126	mRNA-1273		0.055	
				ITP: 25	JNJ-78436735		0.133	
Wong 2023[137]	USA	2020 – 2022	≥ 65 years	ITP: 1526	mRNA-1273	RR observed vs expected	1.14	Risk period = 42 days Number of doses: • mRNA-1273 = 15,761,718 • BNT162b2=15,896,042 • Ad26 COV2.S = 576,698
				ITP: 1670	BNT162b2		1.26	
				ITP: 62	Ad26 COV2.S		1.34	
Yan 2022[138]	USA	2010 – 2021	≥ 18 years	TCP: 509	BNT162b2,	Reporting odds ratio (95% CI)	1.24 (1.11-1.40) <sup>1</sup>	Vaccinated n: • BNT162b2= 445,926 • Ad26 COV2.S=167,457
				TCP: 267	Ad26 COV2.S		1.66 (1.45-1.90) <sup>2</sup>	

				ITP: 70	mRNA-1273		3.32 (2.49-4.42) <sup>3</sup>	<ul style="list-style-type: none"> <li>mRNA-1273=535,126</li> <li><sup>1</sup> BNT162b2 compared to other 2</li> <li><sup>2</sup> Ad26COV2.S compared to other 2</li> <li><sup>3</sup> mRNA-1273 compared to other 2</li> </ul>
Woo 2022[139]	USA	2021	Mean (SD): 54.6 (15.55) years	TCP: 100	Ad26 COV2.S	Crude reporting rate per 100,000 doses administered	0.61	Risk period: 28 days Number of doses: 16,292,911
Moulis 2022[140]	France	2020 – 2021	16 - 98 Years	ITP: 70	BNT162b2,	Rate per 1,000,000 doses administered (95% CI)	1.22 (0.97-1.54)	-
				ITP: 5	mRNA-1273		0.71 (0.30-15.60)	
				ITP: 47	ChAdOx1-S		6.12 (4.63-8.04)	
				ITP: 1	Ad26COV2		1.19 (0.02-0.67)	
Welsh 2021[141]	USA	2020 – 2021	22 - 82 years	TCP: 28	Pfizer or Moderna	Reporting rate per million doses (for both vaccines)	0.80	Case ascertainment: BC LOC 1-3 Number of doses <ul style="list-style-type: none"> <li>Pfizer = 18,841,309</li> <li>Moderna = 16,260,102</li> </ul>
Mesina 2023[142]	Philippine s	2021 – 2022	≥12 years	TCP: 16 ITP: 11	All COVID-19 vaccines	Rate per 10,000 vaccine doses	TCP: 0.0017 ITP: 0.0007	-
Kragholm 2021[143]	Denmark	2020 – 2021	≤ 65 Years	-	Oxford- AstraZeneca PfizerBioNTech/ Moderna	Odds ratio (95% CI)	Male: 0.49 (0.14–1.79) Female: 1.99 (1.05–3.76)	Vaccinated n <ul style="list-style-type: none"> <li>Oxford-AstraZeneca = 11,689</li> <li>PfizerBioNTech + Moderna = 16,509</li> </ul> Odds ratio for TCP after Oxford versus Pfizer/Moderna

~ Confidence intervals are included if they were reported in the paper

\* Bold values represent statistically significant data

**TABLE 3.4** Studies reporting on risk of relapse or exacerbation of thrombocytopenia after vaccination with COVID-19 vaccines, by study type

Author, year, Journal	Location	Study Years	Age Group	Number of participants with pre-existing ITP	Specific Vaccine	Risk Estimate	Risk estimate value*	Relevant Additional Study Details
<b>Case Control (n=1)</b>								
Visser 2022[144]	Netherlands	2021	Mean (SD) = 55.2 (16.8)	218	BNT162 b2, ChAdOx 1-S, mRNA-1273	ITP exacerbation % (95% CI)	13.8% (9.5-19.1)	Case ascertainment: Definition based on 5th official meeting of the European Hematology Association Scientific Working Group on Thrombocytopenias
<b>Cohort study (n=8)</b>								
Woolley 2022[145]	UK	2021	19-78 years	211	BNT162 b2 or mRNA-1273 or ChAdOx 1	Incidence of ITP relapse	6.6%	-
						Incidence of newly diagnosed ITP	1.4%	
Stefani 2024[146]	Netherlands & UK	-	Median (IQR), years = 36 (44)	124 (Primary or secondary)	BNT162 b2, ChAdOx 1, mRNA-1273	Relapse rate	After 1 <sup>st</sup> dose = 4.2% After 2 <sup>nd</sup> dose = 9.1% After 3 <sup>rd</sup> dose = 2.9%	Case ascertainment: Relapse was defined within 30 days following vaccination, as either a drop in platelet >50% with a nadir count <30 × 10 <sup>9</sup> /L, or as a drop in platelets <50% with a nadir count <30 × 10 <sup>9</sup> /L associated with a new bleeding event.
Qasim 2023[147]	Qatar	2019 – 2021	Mean (SD), years = 40 (13)	67	BNT162 b, mRNA-1273	% of ITP relapse cases after vaccination	Within 3 months=9% Within 6 months=15% >6 months=12%	-
Auteri 2023[148]	Italy	2020 – 2022	-	360	mRNA-BNT162 b2,	% relapse after <30 days	After 1 <sup>st</sup> dose = 3.3% After 2 <sup>nd</sup> dose = 4.6% After 3 <sup>rd</sup> dose = 5.4%	Case ascertainment: New diagnoses of ITP = inf-ITP or vax-ITP when they occurred within 30 days of SARS-CoV-

					mRNA-1273, ChAdOx1-S			2 infection or vaccination, respectively. ITP relapse = drop in PLT count within 30 days from vaccination, compared to PLT count before vaccination that required a rescue therapy OR a dose increase of an ongoing therapy OR a PLT count $<30 \times 10^9/L$ with $\geq 20\%$ decrease from baseline. Risk period $<30$ days
Lee 2022 [149]	USA & UK	2020 – 2021	Mean (SD), years = 63 (19.7)	117	BNT162b2	ITP exacerbation %	After 1 <sup>st</sup> dose = 17.1% After 2 <sup>nd</sup> dose = 20%	-
Aharoni 2022[150]	Israel	-	Mean (SD), years = 54 (21)	93	BNT162b2	% relapse (calculated)	After 1 <sup>st</sup> or 2 <sup>nd</sup> dose = 10.7% After 3 <sup>rd</sup> dose = 11.6%	Case ascertainment: Clinical exacerbation of ITP defined as a reduction in platelet count requiring initiation or escalation of ITP treatment and/or a new bleeding tendency that led to medical attention, within 3 months after vaccination.
Zhan 2023[151]	China	-	-	118 (cured and uncured)	-	OR (95% CI)	Platelet dropping event after vaccination = 9.697 (3.047-30.865) New bleeding events = 10.084 (2.718-37.411)	OR: comparing patients with time since ITP diagnosis of $<1$ year to those $>1$ year
Dainese 2022[152]	Italy	2019 – 2022	Mean (SD) = 62.39 (17.26) years	64 (Chronic ITP)	BNT162b, mRNA-127, ChAdOx1	Odds ratio for platelet reduction compared to COVID19 infection, p-value	1 <sup>st</sup> dose= 16.94, 0.009 2 <sup>nd</sup> dose=15.00, 0.022 3 <sup>rd</sup> dose=16.29, 0.02	Case ascertainment: ITP exacerbation defined as: 1. $>50\%$ drop in platelet vs baseline 2. $>20\%$ drop in platelet vs baseline AND nadir $<30 \times 10^9/L$ 3. Need for rescue medication

~ Confidence intervals are included if they were reported in the paper. \* Bold values represent statistically significant data

**TABLE 3.5.** Studies reporting on risk of thrombocytopenia after vaccination with HPV vaccines, by study type

Author, year, Journal	Location	Study Years	Age Group	Number of TCP or ITP Cases	Specific Vaccine	Risk Estimate	Risk estimate value*	Relevant Additional Study Details
<b>Case Control (n=2)</b>								
Grimaldi-Bensouda 2014[101]	France	2006 – 2011	14-26 years	ITP: 6	HPV4 (15% of cases vs 18% of controls)	Adjusted odds ratio (95% CI)	1.0 (0.4-2.6)	Case ascertainment: national disease registries 33 controls (age matched from GP practices with no history of ITP)
O’Leary 2012[69]	USA	2000 – 2009	6 week – 17years	ITP: 1	HPV	IRR (95% CI) 11-17 years	9.71 (0.87-108.92)	Case ascertainment: ICD-9 codes
<b>Cohort study (n=2)</b>								
Maldonado 2024[103]	Columbia	2012 – 2021	9-19 years	ITP within 180 days: Dose 1: 7 Dose 2: 6	HPV4	Odds Ratio (95% CI)	Dose 1: 1.12 (0.41-3.09) Dose2: 0.89 (0.37-2.12)	Case ascertainment: ICD-10 1 dose = 55,114 2 doses = 35,801 OR compared to unvaccinated Analysis done for ITP occurring within 180 days or 360 days of follow-up
				ITP within 360 days: Dose1: 15 Dose 2: 9			Dose 1: 2.54 (1.28-5.02) Dose 2: 0.85 (0.41-1.75)	
Cameron 2016[102]	UK	2004 – 2014	12-18 years	TCP cases Female: 10 Male: 12	HPV	2012 Incidence ratio (Observed/Expected * 100), 95% CI	Females = 65.8 (31.5-121.1) Males = 130.7 (67.5-228.3)	Case ascertainment: ICD- 10 codes Vaccinated n in 2012 Females = 206,323 Males = 216,88 IR not significant for 2012 or over time
<b>Pharmacovigilance Studies (n=1)</b>								
Harris 2014[153]	Canada	2007 – 2011	12-15 years	TCP cases 1	HPV4	Rate per 100,000 doses distributed	0.1	Doses=691,994

~ Confidence intervals are included if they were reported in the paper

\* *Bold values represent statistically significant data*

**TABLE 3.6.** Studies reporting on risk of thrombocytopenia after vaccination with pneumococcal vaccines, by study type

Author, year, Journal	Location	Study Years	Age Group	Number of TCP or ITP Cases	Specific Vaccine	Risk Estimate	Risk estimate value*	Relevant Additional Study Details
<b>SCCS (n=4)</b>								
Kim 2024[104]	South Korea	2018 – 2022	Infants	TCP: 128	PCV10 or PCV13	Adjusted IRR (95 % CI)	1.22 (0.94-1.58)	Case ascertainment: ICD-10 codes Risk period = 1-28 days
Yoon 2024[105]	South Korea	2022 – 2023	≥65 years	TCP: 35	PPSV23	IRR (95 % CI)	1.18 (0.6-2.35)	Case ascertainment: ICD-10 codes Risk period = 13 days
Sato 2024[106]	Japan	2015 – 2020	≥64 years	ITP: 53	PPSV23	IRR* (95 % CI)	0.89 (0.12-6.4)	Case ascertainment: ICD-10 codes Risk period = 28, 42 days * Incidence rate during risk period / Incidence rate during control period for 28 or 42 days
O’Leary 2012[69]	USA	2000 – 2009	6 weeks-17 years	TCP 6 weeks-11 months: 3 12-19 months: 2	PCV	IRR (95% CI) 6 weeks – 11 months 12 – 19 months	0.58 (0.15-2.18) 0.72 (0.14-3.97)	Case ascertainment: ICD-9 codes
<b>Cohort study (n=2)</b>								
Tseng 2013[107]	USA	2010 – 2012	1-24 months	-	PCV13	Relative risk, compared to PCV7	Platelet count ≤50,000 = 0.42 Platelet count ≤100,000 = 0.42	Case ascertainment: ICD-9 codes Risk period = 1-28 days Thrombocytopenia cases Platelet count ≤50,000) = 43,000 Count ≤100,000) =30,900

Tseng 2018[108]	USA	2011 – 2015	≥65 years	-	PCV13 and PPSV23	Unadjusted relative incidence (95% CI)	Comparing PCV13 and PPSV23 – Thrombocytopenia I (2 platelet counts of ≤50 000 within 7 d of each other) = 0.60 (0.31- 1.13) Thrombocytopenia I (2 platelet counts of ≤100 000 within 7 d of each other) = 0.71 (0.53- 0.94)	Risk period = 1-28 days Doses PCV13= 313,136 PPSV23= 232,591
Pharmacovigilance Studies (n=2)								
Wang 2024 [154]	China	2020 – 2023	1.5 – 6 months	TCP: 1	PCV13 – CRM197	Reporting odds ratio	0.03	Doses=947,555
Autret-Leca 2011[155]	France	2004 – 2007	1 - 108 months	ITP: 10	PCV7	Incidence/100,000 doses (95% CI)	0.13 (0.06–0.22)	

~ Confidence intervals are included if they were reported in the paper

\* Bold values represent statistically significant data

**TABLE 3.7.** Studies reporting on risk of thrombocytopenia after vaccination with influenza vaccines, by study type

Author, year, Journal	Location	Study Years	Age Group	Number of TCP or ITP Cases	Specific Vaccine	Risk Estimate	Risk estimate value*	Relevant Additional Study Details
SCCS (n=2)								
Lafaurie 2022[109]	France	2009 – 2018	≥65 years	ITP: 231	Influenz a	Adjusted IRR	0.91 (0.79-1.05)	Risk period = 6 weeks
O'Leary 2012[69]	USA	2000 – 2009	6 week – 17 years	ITP: 1. 6-23 months=5	TIV	IRR (95% CI) 1. 6-23 months 2. 2-6 years 3. 7-17 years	1. 2.69 (0.81-8.88) 2. 1.86 (0.41-8.38) 3. 5.95 (0.54-65.96)	Case ascertainment: ICD-9 codes



				2. 2-6 years =3 3. 7-17 years=2				
RCT (n=1)								
Vaughn 2014[110]	Finland, Mexico, Poland, Taiwan	-	Mean (SD) = 44 (18.1)	TCP: 3	H5N1 / H1N1	Rate (95% CI) per 100,000 person-years	33.9 (7.0-99.1)	Vaccinated n = 16,160 Rate for adjuvanted vaccine recipient in multiple controlled trials
Case Control (n=2)								
Grimaldi- Bensouda 2012[111]	France	2008 – 2011	18-79 years	ITP: 43	Influenz a	aOR (95% CI)	0.7 (0.5-1.1)	Case ascertainment: Platelet counts below 100 x 10 <sup>9</sup> /L according to the consensual international criteria aOR for patients vaccinated in 12 months compared to no vaccination Total ITP cases found: 198
Garbe 2012[112]	Germany	2000 - 2009	≥18 years	ITP: 3	Influenz a	aOR (95% CI)	4.0 (1.5–9.6)	Case ascertainment: Guidelines of the American Society of Hematology
Cohort study (n=4)								
Nordin, 2014[114]	USA	2008- 2010	14-49 years	TCP: 13	MIV	Adjusted IRR (95% CI)	1.22 (0.65-2.28)	Vaccinated n MIV=9,349 TIV=7,979 IRR compared to unexposed group
				TCP: 8	TIV		1.42 (0.61-3.31)	
Nordin 2013[113]	USA	–	Mean (SD), years = 30.8 (5.6)	TCP: 80	TIV	Adjusted IRR (95% CI)	0.90 (0.68-1.19)	Vaccinated n = 75,906 ARR compared to unvaccinated
Huang 2012[115]	TAIWAN	2009 – 2010	-	ITP: 119	H1N1	Estimated to expected ratio, 95% CI	1.63 (0.91-3.00)	Case ascertainment: BC Risk period = 0-42 days

								Doses = 5,688,517
Mericliler 2023[134]	Global	2010 – 2023	Mean (SD) years = 52.2 (19.1)	ITP: 59	Influenza	Event rate per 10,000 doses	0.25	Vaccinated n = 2,355,057

~ Confidence intervals are included if they were reported in the paper

\* Bold values represent statistically significant data

**TABLE 3.8** Studies reporting on risk of thrombocytopenia after vaccination with other vaccines, by study type

Author, year, Journal	Location	Study Years	Age Group	Number of TCP or ITP Cases	Specific Vaccine	Risk Estimate	Risk estimate value*	Relevant Additional Study Details
SCCS (n=3)								
Liu 2020[118]	Taiwan	2004 – 2014	12-35 months	-	Varicella	Adjusted IRR (95% CI)	1.00 (0.76–1.33)	Case ascertainment: ICD-9- Clinical Modification Risk period = 42 days Vaccinated n = 1,194,189
Andrews 2007[70]	UK	1999 – 2003	28 days- 17 years	ITP: 108	Meningococcal C	Relative incidence, self control (95% CI)	In infants (28 days-1 year) = 1.81 (0.31-10.77) In toddlers and children (1-17 years) = 0.97 (0.41- 2.33)	Case ascertainment: ICD-10 codes Outcome: number of hospital admissions for ITP Risk period = 27 days
O’Leary 2012[69]	USA	2000 – 2009	6 weeks- 17 years	ITP: 1. 12-19 months=2 2. 4 – 6 yrs=2	DTaP	IRR (95% CI)	1. 1 (0.21-4.81) 2. 2.57 (0.53-12.37)	Case ascertainment: ICD-9 codes

				1. 12-23 months=1 2. 2-6 years=4 3. 7-17 years=2	Hepatitis A		1. 0.22 (0.03-1.82) 2. 1.14 (0.34-3.86) 3. 23.14 (3.59-149.3)	
				6 weeks – 11 months = 2	HiB		0.75 (0.16-3.63)	
Case Control (n=2)								
Lai 2015[119]	USA	2006 – 2014	Median, years =65	TCP: 9	Herpes Zoster	Odds ratio (95% CI) for cases vs controls	1.4 (0.65-0.9)	
Grimaldi-Bensouda 2012[111]	France	2008 – 2011	18-79 years	ITP: 18	DTPP (adult formulation)	Adjusted Odds ratio (95% CI) for patients vaccinated in 12 months compared to no vaccination	1.4 (0.8-2.4)	Case ascertainment: Platelet counts below 100 G/L according to the consensual international criteria. Total ITP 198
Cohort study (n=4)								
Li 2020[156]	China	2011 – 2017	-	TCP: 4	DTaP-IPV/Hib	Rate for thrombocytopenia per 100,000 vaccine doses	0.8	Doses=516,000
Layton 2018[116]	USA	2006 – 2014	Mean (SD), weeks = 11.2 (5.0)	TCP: 1. Dose 1: 108 2. Dose 2: 55 3. Dose 3: 50	DTaP + RV (RV5 or RV1)	Adjusted Hazard ratio (95% CI) vs DTaP alone	1. 0.66 (0.40-1.10) 2. 1.44 (0.66-3.15) 3. 0.97 (0.48-1.96)	Vaccinated n 1. 1,030,809 2. 821,546 3. 615,030
Kharbanda, 2016[117]	USA	2007 – 2013	14-49 years	TCP: 249	Tdap	Adjusted rate ratio (95% CI) compared to unvaccinated	0.85 (0.73-0.98)	Risk period = 42 days Vaccinated n = 53,885

Mericliler 2023[134]	Multiple	2010 – 2023	Mean (SD) years = 52.2 (19.1)	ITP: 51	Tdap/Td	Event rate per 10,000 doses	0.28	Vaccinated n = 1,817,211
Pharmacovigilance Studies (n=3)								
Shaum 2022[157]	Zimbabwe	2019	6-45 years	TCP: 3	Typhoid conjugate vaccine	Rate per 100,000 doses administered	0.94	Case ascertainment: BC Risk period = 42 days
Gao 2021[158]	China	2016 – 2020		ITP: 7	Bivalent OPV	Rate per 100,000 doses	0.08	Doses = 8,627,132
Chang 2013[159]	USA	2005 – 2007	9-38 years	TCP: 5	Tdap	Rate per 100,000 doses	0.02	Case ascertainment: BC Doses = About 20 million

~ Confidence intervals are included if they were reported in the paper. \* Bold values represent statistically significant data

## ANNEX 4

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

#### 4.1. Thrombocytopenia Case Definition 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 ( $150 \times 10^9/L$ ), 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[30], with primary ITP (no defined cause) and secondary ITP (which includes vaccine-associated ITP as well as several other conditions).[31, 33, 34, 47] See the Risk Factors table in Annex 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**
  - Annexes 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.
    - Thrombocytopenia is a criterion for Vaccine-Induced Thrombosis and Thrombocytopenia (VITT) and Thrombosis with Thrombocytopenia Syndrome (TTS). If there are other signs and symptoms such as severe headache that persists or more than 5 days or evidence suggesting thrombosis, or thromboembolism consideration the [case definition](#) and [companion guide](#) for VITT-TTS can be found here.
  - 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.
    - Thrombocytopenia is a criterion for Vaccine-Induced Thrombosis and Thrombocytopenia (VITT) and Thrombosis with Thrombocytopenia Syndrome (TTS). If there are other signs and symptoms such as severe headache that persists or more than 5 days or evidence suggesting thrombosis, or thromboembolism consideration the [case definition](#) and [companion guide](#) for VITT-TTS can be found here.
- **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[30, 31, 47] 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  $<150 \times 10^9/L$ .
    - 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 ( $\times 10^9/L$ ):  $<10$ ,  $>10-20$ ,  $>20$  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  $<150 \times 10^9/L$  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.

## ANNEX 5

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Thrombocytopenia Data Abstraction and Interpretation Form With Algorithms for Assessing Level of Certainty and Glossary of Terms



## 5.1. Thrombocytopenia Data Abstraction and Interpretation Form with algorithms for assessing level of certainty

The form is organized in a series of Steps presented as tables.

- Step 1 guides the collection of data needed to meet the case definition criteria for Thrombocytopenia. Depending on the specific criterion, data are collected using two formats:
  - i. as mutually exclusive answers of YES, NO or UNKNOWN to a series of questions
  - ii as a checklist of specific things that were noted to be present (i.e. YES) like signs or symptoms, or lab test results.

Relatively simple criteria used in the case definition may be defined directly in step 1. Others may require formulae to define – as done in Step 2.

- Step 2 uses some or all of the data entered in Step 1 to assign values (YES, NO or UNKNOWN) to selected case definition criteria, as necessary.
- Step 3 is a small tabular summary of the assigned value (YES, NO or UNKNOWN) for each criterion in the case definition.
- Step 4 provides a tabular algorithm to assign the Level of certainty that meets the case definition (Level 1, 2 or 3) or that does not meet the case definition (Levels 4 and 5).
- A Pictorial algorithm is presented that presents, in a single page, all the relevant criteria needed to meet the case definition and a flow diagram that shows the path to each level of diagnostic certainty depending on the criterion values.
- A Glossary of Terms is also included. Any terms defined in the glossary are yellow highlighted in the Step 1 data form.

Digital Transformation: For the digital version, in the Automated Brighton Classification (ABC) Tool users need to enter data into the online form for Step 1 only and an LOC will be provided (based on the information in Steps 2-4 which operate in the background of the Tool) along with a summary of the data entered. In addition, the pictorial algorithm will be provided so users can see how the LOC was derived based on data entered. In contrast, for the analog version, as here in the Companion Guide, users must complete all 4 steps in order to reach the LOC.

The data abstraction form (analog or digital versions) can be used in several settings:

- Epidemiologic research: As a case report form for data abstraction from a hospital/other institutional chart as part of epidemiologic studies or hypothesis testing studies for causal association between vaccine (s) and thrombocytopenia or ITP.
- Real world evidence studies: Guide data collection for case validation (all or a subset) in studies where electronic health data were used for case identification based on selected medical codes (ICD9/10, SNOMEDCT, MedDRA).
- Clinical vaccine trials: Serve as a supplement to a clinical trial case report form that does not capture information specific to thrombocytopenia or ITP; i.e., when thrombocytopenia or ITP is not part of solicited safety information in the clinical trial. In such settings it may also serve as a guide for the type of data to be collected and investigations to be done should generalized convulsive seizure occur as an unsolicited adverse event.
- Pharmacovigilance: Most AEFI report forms, including the CIOMS form, allow for free text to describe an adverse event but are not set up to collect specific information that would facilitate applying a standard Brighton case definition. In the event of a possible safety signal involving thrombocytopenia or ITP, the abstraction form could be used to gather the information needed to assess individual cases to see if they meet the Brighton case definition. In the absence of a signal, where thrombocytopenia or ITP is considered an AESI (such as in the COVID-19 pandemic campaign), the data abstraction form can be used to guide selection of critical criteria needed to meet the case definition, that could then be added to a special AEFI report form for use in a mass campaign setting.

**TABLE 5.1 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	<ul style="list-style-type: none"> <li>Laboratory results – CBC, peripheral smear</li> </ul>	
B	Blood smear exam		
C	Clinical signs & symptoms of bleeding	<ul style="list-style-type: none"> <li>Outpatient clinic / emergency room record(s)</li> <li>Hospital admitting history &amp; physical exam; discharge summary</li> <li>Hematology consultation / other consultations</li> </ul>	

**Step 1.** Complete the case data entry form choosing the most appropriate answer as defined below:

- 'YES' means there was written or verbal evidence that the criterion was present.
- 'NO' means there was written or verbal evidence that the criterion was not present.
- 'UNKNOWN' means there was uncertainty in interpreting whether the criterion was present or absent, OR nothing was documented about the criterion.
- Questions regarding criteria marked with an asterisk\* are integral to assigning level of diagnostic certainty.

#### Terms with a glossary definition

Criterion	Question	Possible Answers		
<b>Criterion A: Thrombocytopenia</b>				
A*	Platelet count was < 150 X 10 <sup>9</sup> / L (Litre)	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
<b>Criterion B: Peripheral blood smear confirms low platelet count</b>				
B0.1*	Was a peripheral blood smear done? If Yes complete B1 and B2.	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
B Peripheral smear report	Check the single most correct option below based on the peripheral blood smear report: <input type="checkbox"/> 1. Peripheral smear confirmed reduced number of platelets or no clumping of platelets seen <input type="checkbox"/> 2. Peripheral smear showed normal platelet numbers or there was clumping of platelets <input type="checkbox"/> 3. Peripheral smear done but report unavailable or report did not describe either platelet number or platelet clumping			
<b>Criterion C: Evidence of spontaneous bleeding</b>				
C0.1*	Were there any signs of spontaneous bleeding? Check any of the signs listed below in C, if present. If at least one is checked, answer YES for C0.1. If none checked answer 'NO or UNKNOWN' for C0.1.	<input type="checkbox"/> YES	<input type="checkbox"/> NO or UNKNOWN	
C. Evidence of spontaneous bleeding signs (Check all that were present)	<input type="checkbox"/> 1. Bruising <input type="checkbox"/> 5. Purpura. <input type="checkbox"/> 9. Bleeding into gums <input checked="" type="checkbox"/> 13. Hematemesis			
	<input checked="" type="checkbox"/> 2. Epistaxis <input type="checkbox"/> 6. Hematoma <input type="checkbox"/> 10. Intracranial bleeding <input type="checkbox"/> 14. Hemoptysis			
	<input type="checkbox"/> 3. Petechiae <input type="checkbox"/> 7. Conjunctival bleeding <input type="checkbox"/> 11. Hematuria – gross <input type="checkbox"/> 15. Hematochezia			
	<input checked="" type="checkbox"/> 4. Hemorrhagic oozing of skin lesions <input type="checkbox"/> 8. Vaginal bleeding (Don't check if menstruating) <input checked="" type="checkbox"/> 12. Hematuria – microscopic <input type="checkbox"/> 16. Occult rectal bleeding			

**Step 2.** Based on clinical data entered in Step 1, assign a value to criteria B and C using the rules in the Criterion Options column

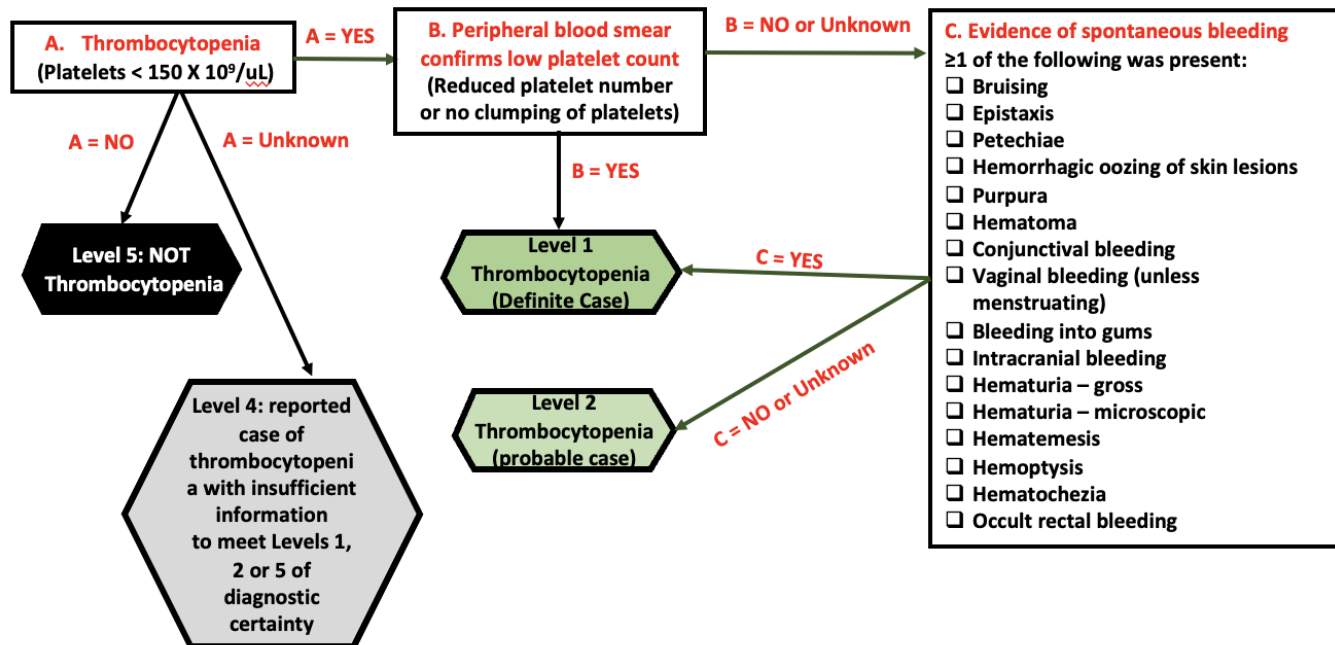
CRITERION		CRITERION VALUE: compare data entered in step 1 table to formulae in the YES, NO and UNKNOWN columns to determine FINAL VALUE for each criterion.					
CLINICAL CATEGORY	Name	FINAL VALUE (Circle/Highlight)			YES (Y) IF:	NO (N) IF:	UNKNOWN (U) IF:
Peripheral blood smear confirms low platelet count	B	Y	N	U	B = 1	B = 2	B0.1 = NO or UNKNOWN or B = 3
Evidence of spontaneous bleeding	C	Y	N	U	C0.1 = YES and ≥1 of C (1-16) checked	C0.1 = NO or UNKNOWN AND none of C (1-16) checked	

**Step 3.** Record the final value for A from step 1 and for B and C from step 2 in the table below.

Criterion	A	B	C
Final Value			

**Step 4.** Use the values of the thrombocytopenia criteria recorded in the Step 3 above to determine the level of certainty based on the formulae below. Start with Level 1 (criteria A, B, C). If Level 1 not met, then move to Level 2 (criteria A, B, C). If level 2 not met go to Level 5 (as there is no Level 3). If none of Levels 1, 2 or 5 are met, then assign Level 4.

Level of Certainty	THROMBOCYTOPENIA
Level 1	A = YES AND [ B OR C ] = YES
Level 2	A = YES AND [ B AND C ] = NO OR Unknown
Level 3	There is no Level 3
Level 4	Reported as a case of thrombocytopenia but fails to meet any level of certainty)
Level 5	A = NO (Normal platelet count)

**Figure 3.** Pictorial algorithm for determining THROMBOCYTOPENIA level of diagnostic certainty**TABLE 5.2** GLOSSARY OF THROMBOCYTOPENIA TERMS

Term	Definition
Epistaxis	nosebleed
Hematemesis	vomiting up blood
Hematochezia	passage of visible blood in feces / bowel movement
Hematoma	collection of blood, usually clotted, under the skin or in an organ or body cavity
Hematuria – gross	blood in the urine that is visible to the eye
Hematuria - microscopic	blood in the urine that is not visible to the eye; it is proven by microscopic examination that shows the presence of red blood cells or a positive dipstix test for blood
Hemoptysis	coughing up blood
Occult rectal bleeding	Blood in feces (bowel movement) that is not visible to the eye; it is detected by a positive fecal occult blood test
Peripheral blood smear	Examination of blood elements by microscope. Platelet counts done automatically by machine may give erroneous results if something caused the platelets to clump abnormally. These clumps aren't counted by the machine, but can be visualized under the microscope.
Petechiae	small ( $\leq 2\text{mm}$ ), non-blanching, reddish or purplish spots due to local bleeding in skin or mucous membranes (cellular layer that lines the mouth, tongue, eye and gastrointestinal tract )
Purpura	patches ( $> 2\text{mm}$ ) of purplish discoloration of skin or mucous membranes due to local bleeding

## ANNEX 6

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### Methodology: Brief Summary

## 6.1. Thrombocytopenia ICD-9/10-CM and MedDRA Codes[3-7]

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[38] 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. [39]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. [40, 41]A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition. [42]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](#).

## 6.2. Thrombocytopenia Background Incidence

What follows is the methodology used for V1.0 of the Companion Guide. It is kept here because most of the references found in that search have been kept for this guide. Details of the search done for the updated background incidence are provided in the Methods section on page 7.

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.

### 6.3 Thrombocytopenia Risk Factors

What follows is the methodology used for V1.0 of the Companion Guide. It is kept here because most of the references found in that search have been kept for this guide. Details of the search done for the updated background incidence are provided in the Methods section on page 7.

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 annexes 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.[24-30]

#### 6.4 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.

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

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

A data abstraction form was developed to capture information relevant to the Thrombocytopenia case definition criteria. The form uses a standard format developed to ensure harmonized approaches between paper forms (as here in the Companion Guide) and digital forms used online. The questions in the form are designed to enable one of three possible answers:

- 'YES' means there was written or verbal evidence that the criterion was present.
- 'NO' means there was written or verbal evidence that the criterion was absent or not present.
- 'UNKNOWN' means there was uncertainty in interpreting whether the criterion was present or absent OR nothing was documented about the criterion

Step 1 involves completing the data abstraction form. Most of the criteria used to determine Level of diagnostic certainty (LOC) are determined by the evidence provided in Step 1. However, for some criteria further manipulation of the data entered in Step 1 is needed to define one or more specific criteria. This is done in Step 2. A small summary table of all the final criterion values from the first two steps is done as Step 3. Step 4 involves a tabular algorithm that uses the values of the Case Definition Criteria (YES, NO or UNKNOWN) to determine the highest achievable LOC with Level 1 being the highest, most specific level (Definite Case). A one-page pictorial algorithm is created to show the stepwise pathway to each defined LOC based on the criterion values. This algorithm is designed for use as a stand-alone tool for LOC calculation since in addition to the pathway it also provides defines the data needed for each criterion.

A glossary of terms relevant to the case definition criteria was developed based initially on the published case definition. Where possible, the term definition was taken directly from the published case definition (often from the footnotes provided within each published case definition). If there was no definition in the Brighton publication, then an on-line search was done to obtain definitions based on available medical dictionaries or other on-line resources. The glossary is provided for use by data-abstractors without a medical background.



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