



CEPI | Brighton Collaboration

## AESI Case Definition Companion Guide

# Spontaneous Abortion and Ectopic Pregnancy

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## DOCUMENT INFORMATION

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

## DOCUMENT HISTORY

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SPEAC 2.0 D2.2.2 Spontaneous Abortion and ectopic pregnancy Companion Guide	2 June 2023	1.0	Sonali Kochhar	Incorporate Reviewer comments/suggestions

## DEFINITIONS & ACRONYMS

<b>AEFI</b>	Adverse Event Following Immunization
<b>AESI</b>	Adverse Events of Special Interest
<b>BC</b>	Brighton Collaboration
<b>CD</b>	Case Definition
<b>CEPI</b>	Coalition for Epidemic Preparedness and Innovation
<b>CI</b>	Confidence Interval
<b>CRL</b>	Crown-rump length
<b>CT</b>	Computed Tomography
<b>CUI</b>	Concept Unique Identifier
<b>D&amp;C</b>	Dilation and curettage
<b>GA</b>	Gestational Age
<b>GSD</b>	Gestational sac diameter
<b>ICD-9-CM</b>	International Classification of Diseases-9 <sup>th</sup> Revision-Clinical Modification
<b>ICD-10-CM</b>	International Classification of Diseases-10 <sup>th</sup> Revision-Clinical Modification
<b>LMIC</b>	Lower- or Middle-Income Country
<b>LOC</b>	Level of Certainty
<b>MedDRA</b>	Medical Dictionary for Regulatory Activities
<b>SPEAC</b>	Safety Platform for Emergency Vaccines
<b>UI</b>	Uncertainty interval/ confidence interval
<b>UMLS</b>	Unified Medical Language System
<b>US</b>	Ultrasound scan
<b>VAERS</b>	Vaccine Adverse Event Reporting System

## INTRODUCTION

### 1. Background

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

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

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

1. ICD9/10, MedDRA and SNOMEDCT codes for each AESI.
2. Tabular summaries of risk factors and background rates for each AESI.
3. Guidance on AESI real time investigation, data collection, analysis and presentation.
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 needed to meet the AESI CD, tabular guidance to assign values to each CD criterion and a tabular algorithm to determine level of certainty.
  - b. Glossary of terms used in the case definition
  - c. Pictorial decision tree algorithms that are stand-alone tools to determine the level of diagnostic certainty for each AESI.

All tools and resources noted above are compiled together into a companion guide for each Brighton AESI case definition. That is the purpose of this deliverable, which focuses on spontaneous abortion and ectopic pregnancy.

### 2. Objective of this deliverable

To collate SPEAC & BC tools and resources that have been developed for spontaneous abortion and ectopic pregnancy.

### 3. Methods

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

- Spontaneous abortion and ectopic pregnancy diagnostic codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM, MedDRA and SNOMEDCT Codes
- Spontaneous abortion and ectopic pregnancy background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Spontaneous abortion and ectopic pregnancy case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI developers
- Spontaneous abortion and ectopic pregnancy tabular checklist and level of certainty algorithms: SO2-D2.5.1.1-Tools for Tier 1 AESI Data Collection and Interpretation

The methods are briefly described in Appendix 6 of this guide along with links to source documents which have more detailed methodology. A new feature of this and future Companion Guides is that a systematic search was done for risk factors and background rates. The methods section in Appendix 6 has been amended to include the new approach and specific search strategy used.

## 4. Results

### 4.1 Systematic search for background incidence and risk factors

For risk factors, a total of 166 articles were retrieved as per the search strategy mentioned, of which 89 articles were screened out as they were non-contributory to risk factors and 13 focused on treatment, diagnosis or prevention or were duplicates. Of 64 articles screened in for full text review, further screening eliminated 20 publications that didn't provide risk factors. 27 additional published literature not found in the search was included after review of reference lists and through consultation with subject matter experts. 71 articles provided original source data, all of which were included.

All outputs are provided in separate appendices as shown below:

1. Spontaneous abortion and ectopic pregnancy Diagnostic Codes: ICD-9-CM, ICD-10-CM, MedDRA, and SNOMEDCT-US
2. Spontaneous abortion and ectopic pregnancy background rates
3. Spontaneous abortion and ectopic pregnancy risk Factors
4. Spontaneous abortion and ectopic pregnancy case definition glossary of terms
5. Spontaneous abortion and ectopic pregnancy case definition key caveats for diagnosis, data analysis and presentation plus recommendations for real time investigation.
6. Spontaneous abortion and ectopic pregnancy data abstraction and interpretation forms with algorithms for assessing level of certainty.
7. Summary of methods. Also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

## 5. Recommendations & discussion

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

The choice of tabular or pictorial algorithm is up to the user in terms of what is best suited to the situation and the assessor. SPEAC recommends that the tools be used to assign level of certainty for all identified AEFI with features of spontaneous abortion and ectopic pregnancy. This standard, harmonized approach will facilitate signal detection and assessment, epidemiologic studies of background incidence, hypothesis testing for causality and capacity to combine data across trials for meta-analyses.

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## APPENDIX 1

Spontaneous abortion and ectopic pregnancy diagnostic codes: ICD-9/10-CM,  
MedDRA and SNOMEDCT

### 1.1 Spontaneous Abortion and Ectopic Pregnancy Diagnostic Codes: ICD-9/10-CM, MedDRA and SNOMEDCT

TABLE 1.1. TERMS FOR Spontaneous Abortion

UMLS Concept		Diagnostic Coding System Name/Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0000786	Spontaneous abortion	Spontaneous abortion	10041687	634	O03	
		Abortion spontaneous	10000234			156071003 267294003
		Abortions spontaneous	10000235			
		Abortion spontaneous NOS	10000241			
		Spontaneous abortion NOS				156074006 198689000
		Spontaneous abortion unspecified				198631006
		Unspecified spontaneous abortion NOS				198643007
		Incomplete spontaneous abortion without complication				O03.4
		Complete or unspecified spontaneous abortion without complication				O03.9
		Genital tract and pelvic infection following incomplete spontaneous abortion				O03.0
		Genital tract and pelvic infection following complete or unspecified spontaneous abortion				O03.5
		Delayed or excessive hemorrhage following incomplete spontaneous abortion				O03.1
		Delayed or excessive hemorrhage following complete or unspecified spontaneous abortion				O03.6
		Embolism following incomplete spontaneous abortion				O03.2
		Embolism following complete or unspecified spontaneous abortion				O03.7
		Spontaneous abortion, fetus			761.8	
		Miscarriage	10027649			17369002
		Miscarriage of pregnancy	10027650			
		Miscarriage NOS				O03.9

UMLS Concept		Diagnostic Coding System Name/Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0156459	Unspecified spontaneous abortion without mention of complication	Unspecified spontaneous abortion without mention of complication				198642002
		Spontaneous abortion without mention of complication	10041698	634.9		
		Spontaneous abortion without mention of complication, unspecified	10041726	634.90		
C0729205	Spontaneous abortion, incomplete, without complication	Spontaneous abortion, without mention of complication, incomplete	10041716	634.91		
		Incomplete spontaneous abortion without complication			O03.4	
		Incomplete spontaneous abortion with no mention of complication				198653008
		Complete or unspecified spontaneous abortion without complication			O03.9	
C0156456	Miscarriage with complication	Miscarriage with complication				34614007
		Unspecified spontaneous abortion with complication NOS				198641009
		Spontaneous abortion with unspecified complication	10041697	634.8		
		Spontaneous abortion, with unspecified complication, unspecified	10041725	634.80		
		Abortion spontaneous complicated	10000238			
		Urinary tract infection due to incomplete miscarriage				10812041000119103
		Miscarriage with cerebral anoxia				12394009
		Miscarriage with laceration of cervix				127009
		Miscarriage with perforation of broad ligament				14136000
		Miscarriage with urinary tract infection				1469007
		Miscarriage with perforation of uterus				15809008
		Incomplete spontaneous abortion due to hemorrhage				16111000119105
		Miscarriage with laceration of bowel				16714009
Incomplete miscarriage with genital tract or pelvic infection				198644001		
Incomplete miscarriage with delayed or excessive hemorrhage				198645000		

Incomplete miscarriage with damage to pelvic organs or tissues				198646004
Complete miscarriage with genital tract or pelvic infection				198655001
Complete miscarriage with damage to pelvic organs or tissues				198657009
Miscarriage with afibrinogenemia				21360006
Miscarriage with heavy bleeding				275421004
Miscarriage with endometritis				30806007
Miscarriage complicated by genital-pelvic infection				373896005
Miscarriage with laceration of bladder				39199000
Miscarriage with acute necrosis of liver				40444006
Incomplete miscarriage with complication				413338003
Miscarriage with laceration of periurethral tissue				44814008
Miscarriage with cardiac arrest and/or cardiac failure				48739004
Miscarriage with defibrination syndrome				50770000
Miscarriage with perforation of periurethral tissue				51954003
Miscarriage with intravascular hemolysis				53183006
Miscarriage complicated by damage to pelvic organs and/or tissues				58990004
Miscarriage with salpingo-oophoritis				61568004
Miscarriage with electrolyte imbalance				64814003
Miscarriage with sepsis				67465009
Miscarriage with oliguria				72613009
Delayed hemorrhage due to and following miscarriage				737318003
Disorder of vein following miscarriage				737331008
Miscarriage with perforation of cervix				74369005
Miscarriage with laceration of uterus				7809009
Miscarriage with salpingitis				7910003
Miscarriage with perforation of bowel				8071005
Miscarriage with parametritis				83922009
Miscarriage with laceration of broad ligament				85331004
Miscarriage with perforation of bladder				85467007



	Miscarriage with laceration of vagina				85632001
	Miscarriage with pelvic peritonitis				85991008
	Miscarriage with perforation of vagina				87967003

UMLS Concept & Name		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10M	SNOMEDCT
C0269403	Miscarriage complicated by damage to pelvic organs and/or tissues	Miscarriage complicated by damage to pelvic organs and/or tissues				58990004
		Spontaneous abortion complicated by damage to pelvic organs or tissues	10041688	634.2		
		Spontaneous abortion complicated by damage to pelvic organs or tissues, unspecified	10041717	634.20		
C0156424	Spontaneous abortion, complicated by genital tract and pelvic infection, unspecified	Spontaneous abortion, complicated by genital tract and pelvic infection	10041692	634.0		
		Spontaneous abortion, complicated by genital tract and pelvic infection, unspecified	10041720	634.00		
C0156425	Spontaneous abortion, incomplete, complicated by genital tract and pelvic infection		10041711	634.01		
C0156427	Miscarriage complicated by delayed and/or excessive hemorrhage	Miscarriage complicated by delayed and/or excessive hemorrhage				2781009
		Spontaneous abortion complicated by delayed or excessive hemorrhage	10041690	634.1		
		Spontaneous abortion complicated by delayed or excessive haemorrhage	10041689			
C0156435	Miscarriage complicated by renal failure	Spontaneous abortion complicated by renal failure	10041694	634.3		
		Miscarriage complicated by renal failure				10697004
		Miscarriage with acute renal failure				57469000
		Miscarriage with renal tubular necrosis				11026009

		Miscarriage with uremia				11109001
		Incomplete miscarriage with renal failure				198647008
		Complete miscarriage with renal failure				198659007
<b>UMLS Concept &amp; Name</b>		<b>Diagnostic Coding System Term and Codes</b>				
<b>CUI</b>	<b>Name</b>	<b>Term</b>	<b>MedDRA</b>	<b>ICD9CM</b>	<b>ICD10CM</b>	<b>SNOMEDCT</b>
<b>C0156439</b>	Miscarriage complicated by metabolic disorder	Spontaneous abortion complicated by metabolic disorder	10041693	634.4		
		Spontaneous abortion complicated by metabolic disorder, unspecified	10041721	634.40		
		Miscarriage complicated by metabolic disorder				13384007
		Incomplete miscarriage with metabolic disorder				198648003
		Complete miscarriage with metabolic disorder				198660002
<b>C0156443</b>	Miscarriage complicated by shock	Spontaneous abortion complicated by shock	10041695	634.5		
		Miscarriage complicated by shock				34270000
		Miscarriage with septic shock				18613002
		Incomplete miscarriage with shock				198649006
		Complete miscarriage with shock				198661003
		Miscarriage with postoperative shock				47537002
<b>C0156447</b>	Miscarriage complicated by embolism	Spontaneous abortion complicated by embolism	10041691	634.6		
		Miscarriage complicated by embolism				43306002
		Miscarriage with amniotic fluid embolism				10058006
		Incomplete miscarriage with embolism				198650006
		Complete miscarriage with embolism				198663000
		Miscarriage with blood-clot embolism				55976003
		Miscarriage with septic embolism				59204004
		Miscarriage with air embolism				60265009
		Miscarriage with fat embolism				66131005
Miscarriage with pulmonary embolism				82153002		

C0156452	Unspecified spontaneous abortion with other specified complication	Spontaneous abortion with other specified complications	10041696	634.7		
		Spontaneous abortion with other specified complications, unspecified	10041724	634.70		
		Unspecified spontaneous abortion with other specified complication				198640005
<b>UMLS Concept &amp; Name</b>		<b>Diagnostic Coding System Term and Codes</b>				
<b>CUI</b>	<b>Name</b>	<b>Term</b>	<b>MedDRA</b>	<b>ICD9CM</b>	<b>ICD10CM</b>	<b>SNOMEDCT</b>
C0000814	Missed abortion	Missed abortion	10027704	632	O02.1	156087000
		Missed abortion				198616002
		Missed abortion				267187007
		Abortion missed	10000230			
		Missed miscarriage				16607004
C0015927	Fetal death	Fetal death	10016479			276507005 84122000
		Foetal death	10055690			
		Fetal demise	10076683			
		Foetal demise	10076696			
		Fetal death in utero	10016484			
		Foetal death in utero	10055691			
		Death fetal	10011908			
		Death foetal	10011909			
		Intrauterine fetal death				156184005
		Intrauterine death unspecified				199606000
		Intrauterine death NOS				199609007
		Intra-uterine death	10022747			
		Intrauterine death – delivered				199607009
		Intrauterine death with antenatal problem				199608004

Intrauterine death of one twin				237363008
Antenatal death				19960500176358005
Antepartum fetal death				237361005
Antepartum fetal death with continued labor				434671000124102
Antepartum fetal death with cessation of labor				434681000124104
Death intrauterine	10011911			
Fetal death from asphyxia AND/OR anoxia during labor				1762004
Fetal death from asphyxia AND/OR anoxia, not clear if noted before OR after onset of labor				17766007
Fetal death due to prelabor anoxia				206258000
Fetal death due to labor anoxia				206259008
Fetal intrapartum death				237362003
Fetal intrapartum death after first assessment				434631000124100
Fetal death from asphyxia AND/OR anoxia before onset of labor				44174001
Fetal death due to asphyxia				445862009
Fetal death due to anoxia				445868008
Fetal death due to asphyxia during labor				446035009
Fetal death due to termination of pregnancy				67313008

TABLE 1.2. TERMS FOR Ectopic Pregnancy

UMLS Concept & Name		Diagnostic Coding System Term and Codes					
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT	
C0032987	Ectopic pregnancy	Ectopic pregnancy	10014166	633	O00	156080003 34801009	
		Ectopic pregnancy NOS				156083001 198630007	
		Pregnancy ectopic	10036559				
		Other ectopic pregnancy			O00.8		
		Other ectopic pregnancy without intrauterine pregnancy			O00.80		
		Other ectopic pregnancy with intrauterine pregnancy			O00.81		
		Ectopic pregnancy, unspecified	10014169		O00.9		
		Unspecified ectopic pregnancy, without intrauterine pregnancy			O00.90		
		Unspecified ectopic pregnancy	10045857	633.9			
		Extrauterine pregnancy	10015865				
		Extra-uterine pregnancy	10015765				
		Eccyesis	10072039				
		Ovarian pregnancy				9899009	
		Ectopic pregnancy of left ovary				16836261000119107	
		Ectopic pregnancy of right ovary				16836351000119100	
		Ruptured ectopic pregnancy				17433009	
		Tubal pregnancy				79586000	
		Pregnancy of left fallopian tube				16836391000119105	
		Pregnancy of right fallopian tube				16836891000119104	
		Unruptured tubal pregnancy				237254009	
Ruptured tubal pregnancy				198620003			
Ruptured tubal pregnancy of left fallopian tube				16836571000119103			
Ruptured tubal pregnancy of right fallopian tube				16836431000119100			

		Miscarriage of tubal ectopic pregnancy				609525000	
		Miscarriage of left tubal ectopic pregnancy				16836811000119108	
		Miscarriage of right tubal ectopic pregnancy				16836851000119109	
		Abdominal pregnancy				82661006	
		Viable fetus in abdominal pregnancy				237253003	
		Delivery of viable fetus in abdominal pregnancy				198617006	
		Secondary abdominal pregnancy				276881003	
		Intraperitoneal pregnancy				17285009	
		Angular pregnancy				198627000	
		Cervical pregnancy				79290002	
		Comual pregnancy				87605005	
		Intraligamentous pregnancy				35656003	
		Intramural ectopic pregnancy of myometrium				786067000	
		Membranous pregnancy				198624007	
		Mesenteric pregnancy				198626009	
		Mesometric pregnancy				60000008	
		Combined pregnancy				31601007	
		Combined tubal and intrauterine pregnancy				442478007	
		Combined intrauterine and ovarian pregnancy				699240001	
<b>C0032994</b>	Pregnancy, Tubal	Tubal pregnancy	10044724	633.1		156082006 198619009	
		Tubal pregnancy NOS				198622006	
		Fallopian pregnancy				O00.1	
		Tubal pregnancy without intrauterine pregnancy				O00.10	
		Right tubal pregnancy without intrauterine pregnancy				O00.101	
		Left tubal pregnancy without intrauterine pregnancy				O00.102	
		Unspecified tubal pregnancy without intrauterine pregnancy				O00.109	
<b>C0000822</b>	Abortion tubal	Tubal abortion	10059036			198621004 77846006	

C0029604	Other ectopic pregnancy	Other ectopic pregnancy	10032027	633.8	O00.8	198623001
		Other ectopic pregnancy NOS				198629002
		[X]Other ectopic pregnancy				200481006
C1135239	Unspecified ectopic pregnancy without intrauterine pregnancy			633.90		
C1135240	Unspecified ectopic pregnancy with intrauterine pregnancy			633.91	O00.91	
C0032984	Pregnancy abdominal	Abdominal pregnancy	10000088	633.0	O00.0	156081004
		Abdominal pregnancy without intrauterine pregnancy			O00.00	
		Abdominal pregnancy with intrauterine pregnancy			O00.01	

## APPENDIX 2

### Spontaneous Abortion and Ectopic Pregnancy Background Rates



## 2.1 Spontaneous Abortion and Ectopic Pregnancy Background Rates

**TABLE 2.1. Spontaneous Abortion BACKGROUND RATES**

Country <sup>reference</sup>	Study years	Population (age in years)	Incidence rate per 100 pregnancies [95% confidence interval] (total cases)
All			
<b>AFRICA No incidence data found</b>			
<b>AMERICAs</b>			
USA, New York Albany Country <sup>7</sup> Prospective study of 16,800 women, all residents of Albany County, randomly selected from New York Dept of Motor Vehicles; defined pregnancy based on HCG levels using 3 different models; Early pregnancy loss not defined	1987-1988	22-35	17.4% [11.0-25.6] (20)
<b>ASIA</b>			
India <sup>8</sup> Cross-sectional, multicentre, and outpatient clinic-based epidemiological study of 2398 females with a past history of at least one spontaneous miscarriage at $\geq 20$ weeks of gestation. Locations included Mumbai, Bengaluru, Ahmedabad, Kolkata and Delhi. Outcome measured was loss of $\geq 3$ pregnancies of $\geq 20$ weeks' gestation.	Not specified	18-22 23-27 28-32 33+	9.38% 4.35% 6.64% 14.68%
<b>AUSTRALIA/OCEANIA No incidence data found</b>			
<b>EUROPE</b>			
England <sup>9</sup> Prospective study of 630 women; pregnancy viability assessed by abdominal ultrasound before end of 8 <sup>th</sup> week of gestation; repeated assessment if vaginal bleeding occurred; defined spontaneous abortion as expulsion of fetus before 20 weeks' gestation or weighing <500 gm.	1986-1988	Women of reproductive age	12% (50 of 407 pregnancies)

Sweden <sup>10</sup> , Goteborg Recruited 3 cohorts of women born in 1962, 1972 and 1982 via postal questionnaire. Repeated questionnaire every 5 years until 2001. Defined miscarriage as one occurring where MD or a conventional pregnancy test confirmed pregnancy.	1981-2001	19-39 years	12.2% (108 of 887 pregnancies)
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TABLE 2.2 Ectopic Pregnancy BACKGROUND RATES

Country <sup>reference</sup>	Study years	Population (age in years)	Incidence rate per 100 ,000 woman-years [95% confidence interval] (total cases)
			All
<b>AFRICA</b>			
Nigeria <sup>11</sup> Single center (University of Benin Teaching hospital). Ectopic pregnancy identified out of all deliveries during the study years and confirmed by retrospective chart review.	1994-1998	Reproductive Age from 15 to ≥41	Rate per 1000 pregnancies: <u>1.68 [0.61-3.12] (152)</u>
<b>AMERICAS No incidence rate studies found</b>			
<b>ASIA</b>			
India <sup>12</sup> Retrospective cross-sectional study from a single outpatient and inpatient medical center in Lucknow, Uttar Pradesh. No case definition specified.	2017-2020	18 - 40+	
India <sup>13</sup> Retrospective cohort study done in tertiary care hospital in Pondicherry. All ectopic pregnancy case records retrieved and reviewed.	2009-2015	18+	
China <sup>14</sup> Single center study with cases ascertained from an electronic database. Case definition not provided.	2011	15+	Rate per 100 pregnancies: 2.3%
	2020	15+	Rate per 100 deliveries: 4.28
<b>AUSTRALIA/OCEANIA</b>			
<b>EUROPE</b>			
Norway <sup>15</sup>	1970-74	15-19	0.1

Population based study in Norwegian country; case ascertainment using ICD8 and ICD9 codes for ectopic pregnancy; Medical records reviewed for patient information, diagnostics, date and type of operation, histologic examination of removed tissue.		20-24	0.5	
		25-29	0.7	
		30-34	0.9	
		35-39	0.3	
		40-44	0.2	
		15-44	0.4 (97)	
	1975-79		15-19	0.2
			20-24	0.8
			25-29	1.3
			30-34	1.0
			35-39	0.7
			40-44	0.04
		15-44	0.7 (167)	
	1980-84		15-19	0.1
			20-24	1.0
			25-29	1.8
			30-34	1.5
			35-39	1.0
			40-44	0.01
		15-44	0.9 (247)	
	1985-89		15-19	0.1
			20-24	1.1
			25-29	2.8
			30-34	3.0
		35-39	1.3	
		40-44	0.02	
	15-44	1.4(382)		
1990-93		15-19	0.2	
		20-24	0.9	
		25-29	2.7	
		30-34	3.6	

		35-39	1.9
		40-44	0.1
		15-44	1.6 (353)
Norway <sup>16</sup> Case ascertainment from hospital records of all country hospitals.	1976-1981	15-19	24 (21)
		20-24	107 (94)
		25-29	188 (158)
		30-34	133 (109)
		35-39	66 (40)
		40-44	17 (9)
		15-44	95 (431)
	1982-1987	15-19	10 (9)
		20-24	121 (105)
		25-29	244 (210)
		30-34	209 (172)
		35-39	85 (70)
		40-44	22 (14)
		15-44	117 (580)
	1988-1993	15-19	19 (17)
		20-24	114 (110)
		25-29	266 (238)
		30-34	302 (260)
35-39		184 (152)	
40-44		37 (31)	
15-44		154 (808)	

## APPENDIX 3

### Spontaneous Abortion and Ectopic Pregnancy Risk Factors

### 3.1 Spontaneous Abortion and Ectopic Pregnancy Risk Factors and Etiologies

TABLE 3.1 Spontaneous Abortion risk factors

Age	<ul style="list-style-type: none"> <li>• Young age (&lt; 25 years)<sup>17</sup></li> <li>• Advanced maternal age at pregnancy<sup>18</sup> (<math>\geq 30</math> years<sup>19</sup>, <math>\geq 40</math> years)<sup>20,21, 22</sup> <ul style="list-style-type: none"> <li>○ Risk increases with maternal age (OR*: 0.90 for women aged &lt;25, to 2.98 for women &gt; 40 years)<sup>23</sup></li> <li>○ Age <math>\geq 30</math> vs &lt; 30 years: OR: 1.683, 95% CI: 1.017-2.785)<sup>23</sup></li> </ul> </li> <li>• Significantly older age at menarche (first menstrual period)<sup>24</sup></li> </ul>
Maternal history	<ul style="list-style-type: none"> <li>• History of spontaneous abortion<sup>18,24</sup></li> <li>• Risk increases significantly with <math>\geq 2</math> prior spontaneous abortions<sup>22</sup> (OR: 2.30, 95% CI: 1.17-4.61)<sup>23</sup>, 1 prior spontaneous abortion not associated with an increased risk<sup>22</sup></li> <li>• Previous elective abortions<sup>18</sup></li> <li>• Previous infertility<sup>21</sup></li> <li>• Assisted contraception<sup>21</sup></li> <li>• Contraception occurring after a change in partner<sup>21</sup></li> <li>• Mental health disorder prior to pregnancy<sup>25</sup> <ul style="list-style-type: none"> <li>○ AOR**: 1.8; CI: 1.35-2.41</li> </ul> </li> <li>• Affective disorders (depression, dysthymia and mania)<sup>26</sup> <ul style="list-style-type: none"> <li>○ OR: 1.61; CI: 1.03–2.50</li> </ul> </li> <li>• Posttraumatic stress disorder<sup>21</sup> <ul style="list-style-type: none"> <li>○ OR:1.9, 95% CI: 1.3-2.9<sup>27</sup></li> </ul> </li> <li>• One or more negative life events in the 6 months preceding loss<sup>21</sup> <ul style="list-style-type: none"> <li>○ AOR: 2.6, 95% CI: 1.3-5.2<sup>28</sup></li> </ul> </li> <li>• <b>Stress</b> (with trend with number of stressful or traumatic events)<sup>21</sup></li> <li>• Conception within three to six months after delivery<sup>18</sup></li> <li>• Intrauterine device use<sup>18</sup></li> <li>• Difference between mean gestational sac diameter and crown-rump length<sup>19</sup> <ul style="list-style-type: none"> <li>○ mGSD-CRL &gt; 20.0 vs <math>\leq 11.7</math> mm: OR: 2.960, 95% CI: 1.397-6.273</li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>○ mGSD-CRL <math>\leq</math> 20.0 vs <math>&gt;</math> 20.0 mm: OR: 0.341, 95% CI: 0.172-0.676</li> <li>● Exposure to air pollutants such as particulate matter (PM10), carbon monoxide (CO)<sup>29</sup></li> <li>● Anaesthetic gas use (e.g., nitrous oxide)<sup>18</sup></li> <li>● Women with a family history of abortion<sup>24</sup></li> <li>○ RR***:1.96, 95% CI:1.22-3,14<sup>30</sup></li> </ul>
<b>Genetic makeup</b>	<ul style="list-style-type: none"> <li>● Chromosomal abnormalities are causative in approximately 50 percent of spontaneous abortions<sup>18,20</sup></li> <li>○ Abnormal chromosome number (aneuploidy) <sup>31,32</sup></li> <li>● Chromosome complements as percentages of karyotyped spontaneous abortions<sup>18</sup></li> <li>○ Autosomal trisomy – 19.5%</li> <li>○ Sex chromosome trisomy – 0.2%</li> <li>○ Mosaic trisomy – 1.8 %</li> <li>○ Double trisomy – 1.1 %</li> <li>○ Monosomy X – 6.1 %</li> <li>○ Mosaic monosomy (45, X /46, XX) – 0.5 %</li> <li>○ Triploidy total – 5.6 %</li> <li>○ Hypertriploidy – 0.4 %</li> <li>○ Tetraploidy- 2.0 %</li> <li>○ Hypertetraploidy- 0.4 %</li> <li>○ Balanced structural rearrangements- 0.3%</li> <li>○ Unbalanced structural rearrangements- 1.2 %</li> <li>○ Others (double anomalies)- 0.6 %</li> </ul>
<b>Ethnicity</b>	<ul style="list-style-type: none"> <li>● North African women<sup>23</sup></li> <li>○ OR:2.85, 95%CI:1.58-5.10</li> </ul>
<b>Social status</b>	<ul style="list-style-type: none"> <li>● Women in rural areas<sup>33</sup></li> <li>○ AOR: 1.68, 95% CI: 1.54- 1.84</li> <li>● Women with lower income<sup>33</sup></li> <li>○ AOR: 0.90, 95% CI: 0.84-0.97</li> <li>● Women with primary school education and below<sup>33</sup></li> <li>○ AOR: 0.90, 95% CI: 0.82–0.98</li> </ul>
<b>Occupation</b>	<ul style="list-style-type: none"> <li>● Agriculture and related workers<sup>33</sup></li> </ul>
<b>Behavior</b>	<ul style="list-style-type: none"> <li>● Smoking<sup>18, 20, 33</sup></li> <li>● Women who have ever regularly smoked cigarettes<sup>22, 33</sup></li> </ul>



	<ul style="list-style-type: none"> <li>• Regular or high alcohol use<sup>18, 33</sup></li> <li>• Cocaine use<sup>18</sup></li> <li>• Substance use disorder (dependence or abuse of alcohol or drugs (excluding tobacco)<sup>26</sup> <ul style="list-style-type: none"> <li>○ OR:1.44; CI: 1.01–2.06)</li> </ul> </li> <li>• Daily consumption of more than 150 mg of caffeine<sup>18,24</sup></li> </ul>
<b>Nutrition</b>	<ul style="list-style-type: none"> <li>• Obese (BMI <math>\geq 28</math> kg/m<sup>2</sup>) prior to pregnancy<sup>30</sup> <ul style="list-style-type: none"> <li>○ RR: 2.01, 95% CI: 1.1-3.68</li> </ul> </li> <li>• Overweight (BMI 24–27.9 kg/m<sup>2</sup>) prior to pregnancy<sup>30</sup> <ul style="list-style-type: none"> <li>○ RR: 1.71, 95% CI: 1.04-2.81</li> </ul> </li> <li>• Overweight (BMI <math>\geq 25</math> kg/m<sup>2</sup>)<sup>34</sup> <ul style="list-style-type: none"> <li>○ OR: 1.67; 95% CI: 1.25-2.25</li> </ul> </li> <li>• BMI (&gt; 24 vs <math>\leq 24</math> kg/m<sup>2</sup>)<sup>19</sup> <ul style="list-style-type: none"> <li>○ OR = 2.073, 95%CI = 1.056-4.068)</li> </ul> </li> <li>• Underweight (BMI &lt;18.5) prior to pregnancy<sup>21</sup> <ul style="list-style-type: none"> <li>○ RR:2.05, 95% CI: 1.3-3.23)<sup>30</sup></li> </ul> </li> <li>• Vitamin B12 deficiency<sup>35</sup></li> <li>• Low folate levels (<math>\leq 2.19</math> ng/mL (4.9 nmol/L)<sup>36</sup> <ul style="list-style-type: none"> <li>○ OR: 1.47, 95% CI: 1.01-2.14)</li> </ul> </li> <li>• Concentrations of 25(OH)D &lt;50 nmol/L<sup>37</sup></li> </ul>
<b>Comorbidities</b>	<ul style="list-style-type: none"> <li>• Thyroid abnormalities (hypothyroidism, hyperthyroidism, subclinical hypothyroidism)<sup>20,38</sup></li> <li>• Poorly controlled type 1 or type 2 diabetes<sup>18</sup> <ul style="list-style-type: none"> <li>• Type II diabetes<sup>18, 20,39</sup></li> <li>○ OR: 1.38, 95 % CI: 1.26-1.51</li> </ul> </li> <li>• Uterine abnormalities: congenital anomalies, adhesions, leiomyoma<sup>18,20,40</sup></li> <li>• Uterine fibroids<sup>20</sup></li> <li>• Uterine polyps (especially if <math>\geq 2</math> cm)<sup>20</sup></li> </ul>

- Endometriosis<sup>41, 42</sup>
  - OR: 1.22; 95 % CI: 1.15 - 1.29
  - OR: 1.81, 95% CI: 1.44-2.28<sup>39</sup>
- Adenomyosis<sup>42, 43</sup>
- Fever during pregnancy<sup>24</sup>
- Atherosclerosis<sup>30</sup>
  - OR- 2.22, 95% CI: 1.42-3.49
- Hypertensive disorders<sup>30</sup>
  - OR: 1.19, 95 % CI: 1.13 - 1.26
- Hypoparathyroidism<sup>30</sup>
  - OR: 2.58, 95% CI: 1.35 - 4.92
- Cushing syndrome<sup>30</sup>
  - OR: 1.97; 95 % CI: 1.06 - 3.65
- Crohn's disease<sup>30</sup>
  - OR: 1.31, 95% CI: 1.18 -1.45
- Celiac disease<sup>18,30</sup>
- Psychological problems at the time of conception<sup>23</sup>, including
  - Anxiety due to a previous adverse outcome of pregnancy or prior infertility<sup>23</sup>
    - OR: 3.08; 95% CI: 0.92-10.25
  - Anxiety or depression due to employment situation or marital/partnership disturbances<sup>23</sup>
    - OR: 3.35; 95% CI: 1.41-8.00
- Hyperemesis gravidarum in women with eating disorders or anxiety disorders<sup>44</sup>
- Bleeding in the 1<sup>st</sup> trimester<sup>17</sup>
  - OR: 7.35, 95% CI:5.74-9.41
- pH value of leucorrhea  $\geq 4.5$  prior to pregnancy<sup>30</sup>
  - RR: 2.13, 95% CI: 1.48-3.07
- Red blood cell count  $< 5$  /L prior to pregnancy<sup>30</sup>
  - RR: 1.52, 95% CI: 1.02-2.26

	<ul style="list-style-type: none"> <li>• Antithrombin deficiency<sup>45</sup></li> <li>• Hyperhomocysteinemia<sup>35,45,46,47</sup></li> <li>• Factor V Leiden<sup>45</sup></li> <li>• Prothrombin G20210A variation<sup>45</sup></li> <li>• Protein S-deficiency<sup>45</sup></li> <li>• Factor-XII deficiency<sup>48</sup></li> <li>• Autoimmune diseases (particularly antiphospholipid syndrome <sup>18,20</sup></li> <li>• Inherited thrombophilia<sup>20</sup></li> <li>• Systemic lupus erythematosus (SLE)<sup>49</sup></li> <li>• Behcet's disease<sup>50</sup></li> <li>• Oligomenorrhea<sup>51</sup></li> </ul>
<b>Surgical procedure or Trauma</b>	<ul style="list-style-type: none"> <li>• Abdominal trauma<sup>24</sup></li> </ul>
<b>Infection</b>	<ul style="list-style-type: none"> <li>• Positive IgG antibodies to human cytomegalovirus prior to pregnancy <sup>30</sup> <ul style="list-style-type: none"> <li>○ RR: 1.45, 95% CI: 1.02-3.14)</li> </ul> </li> <li>• Maternal infections including<sup>18,52, 53, 54</sup> <ul style="list-style-type: none"> <li>○ Bacterial vaginosis OR: 6.32, 95% CI: 3.65-10.94, OR: 9.91; 95% CI: 1.99-49.34)<sup>55, 56</sup></li> </ul> </li> <li>• Mycoplasmosis <ul style="list-style-type: none"> <li>○ Herpes simplex (OR- 3.81, 95% CI: 1.96-7.41)<sup>58</sup></li> </ul> </li> <li>• Toxoplasmosis</li> <li>• Listeriosis</li> <li>• Chlamydia</li> <li>• Human immunodeficiency virus</li> <li>• Syphilis</li> <li>• Parvovirus B19 (OR: 2.42, 95% CI: 1.76-3.33)</li> <li>• Malaria</li> <li>• Dengue<sup>57</sup></li> <li>• Gonorrhoea</li> <li>• Rubella</li> <li>• Cytomegalovirus (OR-1.61, 95% CI: 1.14-2.27)<sup>58</sup></li> <li>• Ureaplasma urealyticum</li> <li>• Brucellosis infection <sup>59</sup></li> </ul>

<b>Medication / Toxin</b>	<ul style="list-style-type: none"> <li>• Medications<sup>18</sup> including <ul style="list-style-type: none"> <li>• Misoprostol (Cytotec)</li> <li>• Retinoids</li> <li>• Methotrexate</li> <li>• Nonsteroidal anti-inflammatory drugs</li> </ul> </li> <li>• Exposure to toxins<sup>18, 20</sup> including <ul style="list-style-type: none"> <li>• Heavy metals</li> <li>• Arsenic</li> <li>• Cadmium<sup>60</sup></li> <li>• Lead<sup>60</sup></li> <li>• Mercury</li> <li>• Ethylene glycol</li> <li>• Carbon disulfide</li> <li>• Polyurethane</li> <li>• Organic solvents</li> <li>• Ionizing radiation</li> <li>• Phthalate<sup>61</sup></li> </ul> </li> </ul>
<b>Paternal factors</b>	<ul style="list-style-type: none"> <li>• Paternal age (<math>\geq 35</math> years<sup>20</sup>, <math>&gt; 50</math> years)<sup>24</sup></li> <li>• Husband is blood-related<sup>24</sup></li> </ul>
<b>Vaccine</b>	<ul style="list-style-type: none"> <li>• No association with maternal immunization (tetanus, influenza, pertussis) or vaccines often inadvertently administered to women of reproductive age leading to unintentional exposure during pregnancy (e.g. HPV, meningococcal (quadrivalent meningococcal conjugate vaccines or monovalent meningococcal A conjugate vaccine), measles, mumps, and rubella, varicella or OPV) found</li> </ul>

TABLE 3.2 Ectopic Pregnancy risk factors

<b>Age</b>	<ul style="list-style-type: none"> <li>• Age <math>&gt; 40</math> years<sup>62</sup> <ul style="list-style-type: none"> <li>○ Compared with women aged <math>\leq 26</math> years, the risk of EP for women aged 27-32, 33-38 and <math>\geq 39</math> years were 3.9, 4.3- and 9-fold higher risk (OR =1.11, CI- 1.06–1.16)<sup>63</sup></li> </ul> </li> </ul>
<b>Maternal history</b>	<ul style="list-style-type: none"> <li>• Women who conceived with an intrauterine device (IUD) in situ<sup>63, 64, 65, 66, 67</sup></li> <li>• Copper containing IUD in situ- EP rate of 39 per 1000 pregnancies<sup>68</sup></li> <li>• Progestin-only IUDs in situ<sup>62</sup>- EP rate of 171 per 1000 pregnancies<sup>68</sup></li> </ul>

	<ul style="list-style-type: none"> <li>• Levonorgesterel (LNG)-IUD in situ- Pregnancy with the LNG IUS in situ is rare, 53% EP rate<sup>69</sup></li> <li>• Oral contraceptive pills use (AOR = 3.02, 95% CI: 1.16-7.86)<sup>70</sup></li> <li>• Levonorgestrel emergency contraception (AOR = 4.75, 95% CI: 3.79-5.96)<sup>70</sup></li> <li>• History of utilization of progestin-only oral contraceptives<sup>67</sup></li> <li>• Prior history of EP <sup>66,71</sup></li> <li>• One prior EP (OR: 2.98, 95% CI:1.88-4.73)</li> <li>• 2 or more prior EP (OR: 16.04, 95% CI: 5.39-47.72 <sup>66,71</sup>; OR: 17.16, CI:1.89–155.67)<sup>63, 72</sup></li> <li>• Prior EP -recurrence rates depending on the modality used to treat the previous EP<sup>73</sup> <ul style="list-style-type: none"> <li>• 15.4% following laparotomy</li> <li>• 15.5% following laparoscopic procedure</li> <li>• 9.8% following partial or total salpingectomy</li> <li>• 8% following single-dose methotrexate</li> </ul> </li> <li>• History of diethylstilbestrol exposure in utero<sup>65, 71</sup>- rates 4-5 times higher than baseline<sup>74</sup></li> <li>• History of infertility or difficulty in conception<sup>75</sup> (OR: 6.13, CI-2.70–13.93)<sup>63</sup></li> <li>• Assisted reproductive technology- increase in EP risk of 2.2- 4.5%<sup>76,77,78</sup></li> <li>• In vitro fertilization and embryo transfer (IVF-ET) (AOR: 8.99, 95% CI: 1.98-40.84)<sup>70</sup></li> <li>• Induced ovulation, in vitro fertilization, delayed ovulation<sup>79</sup> and migration of the ovum to the contralateral tube<sup>65</sup></li> <li>• History of abortion<sup>80</sup> <ul style="list-style-type: none"> <li>• 2 or more induced abortions, or illegal abortions<sup>65, 66</sup></li> <li>• Prior medical induced abortion (AOR: 2.8, 95% CI: 1.1-7.2)<sup>81</sup></li> <li>• Prior spontaneous abortions<sup>79,81</sup> (OR: 1.93, CI: 1.11–3.36)<sup>63</sup></li> </ul> </li> <li>• Lifetime number of sexual partners<sup>71</sup> -risk increases with the number of sexual partners<sup>75</sup></li> <li>• Vaginal douching, especially with commercial products<sup>65</sup></li> <li>• Gravidity (OR: 1.50, CI 1.25–1.80)<sup>63</sup></li> <li>• Longer interval between marriage and first pregnancy (OR: = 1.01, CI: 1.00–1.02)<sup>63</sup></li> </ul>
<p><b>Behavior</b></p>	<ul style="list-style-type: none"> <li>• Maternal smoking<sup>64, 71</sup> (OR: 1.77)<sup>82</sup></li> </ul>

	<ul style="list-style-type: none"> <li>○ AOR: 3.9, 95% CI: 2.6- 5.9 for &gt;20 cigarettes/day vs. women who had never smoked)<sup>81</sup></li> </ul>
<b>Comorbidities</b>	<ul style="list-style-type: none"> <li>● Documented tubal pathology<sup>71</sup></li> <li>● Tubal blockage (OR: 10.85, CI-2.02–58.08)<sup>63</sup></li> <li>● Thickening of the tube seen in salpingitis isthmica nodosa<sup>6</sup></li> <li>● Post-traumatic stress disorder (OR:1.7, 95% CI:1.1- 2.8)<sup>27</sup></li> <li>● Endometriosis<sup>64</sup> (OR: 2.66)<sup>82</sup></li> </ul>
<b>Surgical procedure</b>	<ul style="list-style-type: none"> <li>● Prior tubal ligation,<sup>67, 70, 71, 82, 83</sup> including laparoscopic,<sup>65</sup> if it creates fistulas</li> <li>● Probability of EP per 1000 procedures according to the method of tubal occlusion<sup>83</sup> <ul style="list-style-type: none"> <li>○ Bipolar coagulation - 17.1 (9.8–24.4)</li> <li>○ Spring-clip application- 8.5 (1.0–16.0)</li> <li>○ Interval partial salpingectomy- 7.5 (0.0–15.9)</li> <li>○ Silicone rubber-band application- 7.3 (1.6–12.9)</li> <li>○ Postpartum partial salpingectomy - 1.5 (0.0–3.6)</li> <li>○ Unipolar coagulation - 1.8 (0.0–5.2)</li> <li>○ All methods- 7.3 (5.0–9.6)</li> </ul> </li> <li>● Microsurgical reconstruction and conservative surgery for prior EP<sup>65</sup></li> <li>● Women sterilized by bipolar tubal coagulation before the age of 30 years had an EP probability 27 times as high as that among women of similar age who underwent postpartum partial salpingectomy (31.9 vs. 1.2 ectopic pregnancies per 1000 procedures, P &lt; 0.001)<sup>83</sup></li> <li>● The proportion of ectopic pregnancies for all methods combined was three times as high in the 4<sup>th</sup>- 10<sup>th</sup> years after sterilization (0.61) as in the first 3 years (0.20); (P &lt;0.001)<sup>83</sup></li> <li>● History of abdominal surgery<sup>66, 80</sup>, including for appendectomy, cesarean delivery, and other abdominal surgery<sup>75</sup></li> </ul>
<b>Infection</b>	<ul style="list-style-type: none"> <li>● Previous genital infections 71 (pelvic inflammatory disease (OR: 1.5, 95% CI- 1.11-2.05;72 AOR ratio- 3.4, 95% CI- 2.4-5.0) 81, chlamydia trachomatis,<sup>84</sup> gonorrhoea)</li> <li>● Pelvic infection, including chlamydia<sup>82</sup> or gonorrhoea 65, 75, 80, 85, 86</li> </ul>

	<ul style="list-style-type: none"> <li>○ Rate of EP in a woman with a history of two chlamydial infections- OR: 2.1, 95% CI: 1.3-3.487</li> <li>○ Three or more infections – OR: 4.5, 95% CI 1.8- 5.3</li> <li>○ Infection with both chlamydia and gonorrhoea- OR:5.3, 95% CI 1.9-15</li> </ul>
<b>Paternal factors</b>	<ul style="list-style-type: none"> <li>● Spouse's cigarette smoking (OR:1.73, CI:1.05–2.85)<sup>63</sup></li> </ul>
<b>Vaccine</b>	<ul style="list-style-type: none"> <li>● No correlation seen with maternal immunization or vaccines often inadvertently administered to women of reproductive age leading to unintentional exposure during pregnancy</li> </ul>

\*OR- Adjusted odds ratio

\*\*AOR- Adjusted odds ratio

\*\*\* RR- Relative risk

## APPENDIX 4

### Spontaneous Abortion and Ectopic Pregnancy Key Caveats for Real Time Investigation and Case Definition Working Group Guidance for Data Analysis and Presentation



## 4. Spontaneous Abortion and ectopic pregnancy Case Definition<sup>1</sup> Key Caveats for Diagnosis, Data Analysis and Presentation

### 4.1 Key elements of Case Definition (CD) <sup>1</sup>

- Spontaneous Abortion is a pregnancy loss that occurs up to 21 weeks 6 days. Outcomes after that pertain to the stillbirth or preterm birth categories
  - 1<sup>st</sup> trimester spontaneous abortion is till <14 weeks 0 days of gestation
  - 2<sup>nd</sup> trimester spontaneous abortion is between 14 weeks 0 days of gestation and 21 weeks 6 days of gestation
- Ectopic pregnancy is when the fertilized egg implants in a location other than the uterine endometrium. Most ectopic pregnancies occur in the fallopian tube (up to 97%)
  - Ectopic pregnancies are not viable and virtually all ectopic pregnancies rupture at about 6-16 weeks
- Accurate assessment of Gestational Age (GA) is a key feature of the three case definitions for the identification and classification of spontaneous abortion in the 1<sup>st</sup> and 2<sup>nd</sup> trimester and ectopic pregnancy
- Assessment of GA for the case definitions can be done utilizing the information in the preterm birth case definition<sup>87</sup> and the “Preterm birth and Assessment of Gestational Age Companion Guide. Sonali Kochhar, 27 October 2022”, accessed on <https://zenodo.org/record/7273900#.Y3StSHZBzIV>, page 39-43
- GA is typically discussed in terms of completed weeks. The ability to accurately determine the completed weeks of gestation varies widely between pregnancies, with the most precise assessment methods not uniformly available across different settings
- For **1<sup>st</sup> trimester Spontaneous Abortion**, there are 3 levels of certainty: 1 (Definite case), 2 (Probable case) and 3 (Possible case)
  - The levels of certainty can be determined based on examinations including ultrasound (transvaginal or transabdominal), gestational age, pregnancy test, histopathological evaluation and cervix examination
  - Level 1 of diagnostic certainty aims to demonstrate a non-viable, intrauterine pregnancy with an empty gestational sac with no visible embryo or yolk sac or a gestational sac containing an embryo or fetus without a visible heartbeat and a positive urine or blood pregnancy test that becomes negative or histopathological evaluation of pregnancy tissue showing products of conception or cervical examination showing vaginal bleeding and visible expulsion of pregnancy tissue
  - GA has to be within the 1st trimester for all 3 levels of certainty

- Of critical importance to meet level 2 of diagnostic certainty is a transvaginal ultrasound documenting an embryo or fetus without fetal heart activity or a gestational sac without a visible embryo seen on a transabdominal ultrasound
- For both Levels 1 and 2 of diagnostic certainty, the GA assessment must be at a level 1 or 2 of certainty.
- ⊖ For level 3 of diagnostic certainty, ~~GA is within the 1<sup>st</sup> trimester and~~ the GA assessment is at level 3 of certainty. ~~These cases do not qualify for a Level 1 and 2 of diagnostic certainty for the 1<sup>st</sup> trimester spontaneous abortion case definition~~
- For **2<sup>nd</sup> trimester Spontaneous Abortion**, there are 2 levels of certainty: 1 (Definite case), 2 (Probable case)
  - Level 1 and 2 require documentation of an ultrasound showing no visible heartbeat, cervical examination showing visible expulsion of pregnancy tissue/products of contraception and histopathological evaluation of uterine contents shows products of conception
  - GA has to be within the 2<sup>nd</sup> trimester for both levels of certainty
  - ⊖ Level 1 and 2 of certainty are distinguished by the level of certainty for GA assessment:
    - ⊖ Level 1 or 2 of GA assessment is required for Level 1 2<sup>nd</sup> trimester Spontaneous Abortion
    - ⊖ Level 3 of GA assessment is accepted for Level 2 2<sup>nd</sup> trimester Spontaneous Abortion.
- For **Ectopic pregnancy**, there are 3 levels of certainty: 1 (Definite case), 2 (Probable case) and 3 (Possible case)
  - Level 1 of certainty of ectopic pregnancy can be determined by evaluation of a woman with a pregnancy of uncertain location by an transvaginal ultrasound examination showing no intrauterine pregnancy and a pregnancy test showing a serum beta human chorionic gonadotropin ( $\beta$ -HCG) > 2000 mIU/ml or a transvaginal ultrasound showing an extrauterine pregnancy and a histopathological evaluation showing no products of conception on endometrial curettage after a D&C procedure
  - GA can be in the 1<sup>st</sup> or 2<sup>nd</sup> trimester and is at a high level of 1-2 in the Level 1 and 2 case definitions
  - Level 2 of certainty of ectopic pregnancy can be determined by a transvaginal ultrasound showing no intrauterine pregnancy or a histopathological evaluation showing no products of conception found on endometrial curettage after a D&C procedure
  - For level 3 of certainty of ectopic pregnancy, there is a positive urine pregnancy test and no products of conception found on endometrial curettage after a D&C procedure seen on a histopathological evaluation
  - GA can be in the 1<sup>st</sup> or 2<sup>nd</sup> trimester and at a level 2-3 for Level 3 of certainty of the case definition

#### Factors that are not part of either case definition

- Brighton case definitions are designed for use in epidemiologic settings and are not intended to guide management or assign causality. Accordingly, neither response to treatment nor defined risk intervals from vaccination to event onset are included as criteria in the case definitions. The Brighton case definitions are a key first step in causality assessment but are not designed to assign causality. They also support determination of background incidence as well as case incidence among non-exposed controls.

#### 4.2 Duration of Surveillance<sup>1</sup>:

This should be till the spontaneous abortion outcome has been determined, but specific surveillance may be further predefined based on biologic characteristics of the:

- Vaccine and vaccine platform
- Vaccine targeted disease
- Spontaneous Abortion and ectopic pregnancy (e.g. patterns identified in previous trials)
- Vaccinee (e.g. age, nutrition, underlying disease, immunosuppression).

Similarly, the duration of follow-up for individual cases should be predefined, and at a minimum should continue until the resolution of the event.

#### 4.3 Data Collection Guidelines: the following should be documented:

1. Clinical description of signs & symptoms and whether there was medical health professional confirmation
2. Date and time of onset, first observation, definitive diagnosis, end of episode
3. Final outcome or outcome at last observation (including spontaneous resolution or response to therapeutic intervention; return to baseline health prior to illness onset or event persistence, sequelae or fatality)
4. Concurrent signs, symptoms, and diseases in immunized woman
5. Test measurement(s):
  - 5.1 Values and units of routinely measured parameters (e.g. temperature, blood pressure), especially those indicating the severity of the event
  - 5.2 Methods of measurements
  - 5.3 Results of laboratory/imaging investigations, surgical and/or pathological findings and diagnoses, if present
  - 5.4 If multiple ultrasound scans and/or maternal clinical examinations are done, record all dates and results
  - 5.5 If multiple measurements of a particular criterion are done record all dates and results. The value corresponding to the greatest magnitude of the criterion should be taken as the basis of the analysis
6. Treatment given for:
  - 6.1 Spontaneous Abortion and ectopic pregnancy to mother, especially medicine and dosing, or specific intervention
  - 6.2 Outcome at last observation
7. Objective clinical evidence supporting classification of the event as 'serious'
8. Exposures, other than the immunization, 24 hours before and after immunization considered potentially relevant to the reported event (e.g. food, infections, environmental)

Most of the above go beyond the criteria needed to meet the case definition of Spontaneous Abortion and ectopic pregnancy, which are the focus of the data abstraction forms in Appendix 5. Accordingly, separate forms will be required to capture the data outlined in the bullets.

#### 4.4 Data Analysis Guidelines<sup>1</sup>

All reported Spontaneous Abortion and ectopic pregnancy should be classified in one of five categories (see algorithms in appendix 5):

- Levels 1, 2 or 3 of the case definitions for Spontaneous Abortion and ectopic pregnancy
- Level 4: reported Spontaneous Abortion and ectopic pregnancy with insufficient evidence to meet the case definition
- Level 5: not a case of Spontaneous Abortion and ectopic pregnancy

The interval between immunization and reported Spontaneous Abortion and ectopic pregnancy can be defined as date/time of immunization to the date/time of onset of the event. If only a few cases are reported, the actual time course should be presented for each. If a large number of cases are reported or found as part of a study, data can be analyzed as the number (%) of cases occurring in the following time intervals after immunization:

- <24 hrs
- 2- <7 days
- 8-<42 days
- >42 days and weekly increments following that.

The duration of possible spontaneous abortion and ectopic pregnancy can be analyzed as the interval from the date/time of onset of the first symptoms and/or signs consistent with the definition to the end of the episode (defined as the time when the event no longer meets the lowest level of the case definition (level 3) or the final outcome. Whichever is used should be used consistently within and across study groups.

If more than one measurement of a particular criterion is taken and recorded, the highest measured value could be the basis for analysis.

## APPENDIX 5

### Spontaneous Abortion and Ectopic Pregnancy Data Abstraction and Interpretation Forms With Algorithms for Assessing Level of Certainty



## 5.1 Spontaneous Abortion and Ectopic Pregnancy Data Abstraction and Interpretation Form for Medical Chart Review

This appendix provides tools that can be used to gather data pertinent to Spontaneous Abortion and ectopic pregnancy and to use the data to assess the level of certainty based on the published Brighton case definition.<sup>1</sup> These tools can be used in a variety of settings including: medical chart review to validate Spontaneous Abortion and ectopic pregnancy cases; summarize known case information from an AEFI report and guide what supplemental information would be needed to assign a level of certainty; guide data collection and case investigation during a clinical vaccine trial or as part of active surveillance; and to guide data collection for epidemiologic studies of background incidence or to assess causality.

Seven tables and 3 figures are included in this appendix:

- **Table 5.1** lists all Brighton case definition<sup>1</sup> criteria for Spontaneous Abortion and ectopic pregnancy and identifies likely sources of information for each.
- **Table 5.2** is the main data abstraction form that can be used to record data pertinent to Spontaneous Abortion and ectopic pregnancy
- **Table 5.3** provides a guide for assigning a 'Yes', 'No' or 'Unknown' status to each case definition criterion based on data entered into table 5.2
- **Table 5.4** is a brief summary of the final value for each criterion, as per table 5.3
- **Table 5.5, 5.6 and 5.7** is used to determine Spontaneous Abortion and ectopic pregnancy LOC from Table 5.4
- **Table 5.8** Glossary of Terms
- **Figures 5.1, 5.2 and 5.3** shows a pictorial algorithm for determining level of certainty for Spontaneous Abortion and ectopic pregnancy.

Brief instructions are provided with each table.

**TABLE 5.1. SPONTANEOUS ABORTION AND ECTOPIC PREGNANCY KEY CASE DEFINITION CRITERIA, LIKELY AND ACTUAL SOURCES OF INFORMATION**

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Ultrasound examination results	For pregnant woman <ul style="list-style-type: none"> <li>• Antenatal care</li> <li>• Antenatal care visit progress notes</li> <li>• Consultation reports</li> <li>• Imaging report</li> <li>• Admitting history/exam</li> <li>• Emergency report</li> <li>• Discharge summary</li> <li>• Billing codes</li> <li>• Diagnostic and procedure codes</li> </ul>	
B	Gestational age		
C	Pregnancy testing		
D	Histopathological evaluation		
E	Cervix examination		

**TABLE 5.2. Spontaneous Abortion and ectopic pregnancy DATA ABSTRACTION FORM:** Record specific information, to the extent possible, for all rows in the table below. The numbered rows with red font identify specific criteria related to the Spontaneous Abortion and ectopic pregnancy case definition. Check all the boxes that are applicable.

i. Date of event onset	
ii. Hospital admission?	
iii. Admitting diagnosis:	
iv. Discharge diagnosis:	
<p>1. Criterion A: Ultrasound examination results</p> <p>NOTE: pay careful attention to whether the type of ultrasound is specified to be transvaginal or transabdominal. If not specified than either would be acceptable.</p>	<p>Check all that apply for 1-12 or check only 13 or 14</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> 1. Ultrasound shows no visible heartbeat</li> <li><input type="checkbox"/> 2. Transvaginal ultrasound shows crown-rump length &gt;7 mm and no visible heartbeat</li> <li><input type="checkbox"/> 3. Transvaginal ultrasound shows crown-rump length &gt;15 mm and no visible heartbeat</li> <li><input type="checkbox"/> 4. Ultrasound exam shows mean gestational sac diameter &gt;25mm and no visible embryo or yolk sac</li> <li><input type="checkbox"/> 5. Ultrasound exam shows mean gestational sac diameter <math>\geq</math> 25 mm and no visible embryo</li> <li><input type="checkbox"/> 6. 2<sup>nd</sup> transvaginal ultrasound done &gt; 7 days after a 1<sup>st</sup> ultrasound confirms diagnosis of non-viable pregnancy</li> <li><input type="checkbox"/> 7. 2<sup>nd</sup> transabdominal ultrasound done &gt; 14 days after a 1<sup>st</sup> ultrasound confirms diagnosis of a non-viable pregnancy</li> <li><input type="checkbox"/> 8. Absence of embryo with heartbeat &gt;2 weeks after a transabdominal ultrasound that showed a gestational sac without a yolk sac</li> <li><input type="checkbox"/> 9. Absence of embryo with heartbeat &gt;11 days after a transvaginal scan that showed a gestational sac with a yolk sac</li> <li><input type="checkbox"/> 10. Ultrasound exam demonstrated an empty uterine cavity in a woman who had clear evidence of intrauterine pregnancy on previous ultrasound exam.</li> </ul>



	<input type="checkbox"/> 11. Transvaginal ultrasound shows no intrauterine pregnancy <input type="checkbox"/> 12. Transvaginal ultrasound shows extrauterine pregnancy <input type="checkbox"/> 13. None of the above <input type="checkbox"/> 14. Unknown if 1-12 are present
<p>2. Criterion B: Gestational Age (from preterm birth and assessment of gestational age case definition, accessed on <a href="https://zenodo.org/record/7273900#.Y3StSHZBzIV">https://zenodo.org/record/7273900#.Y3StSHZBzIV</a>, page 39-43)</p>	<p>Check all that apply for 1-5 OR check only 6 OR 7</p> <input type="checkbox"/> 1. Gestational age in 1 <sup>st</sup> trimester (<14 weeks 0 days gestation) <input type="checkbox"/> 2. Gestational age in 2 <sup>nd</sup> trimester (between 14 weeks 0 days and 21 weeks 6 days) <input type="checkbox"/> 3. Level 1 of certainty <input type="checkbox"/> 4. Level 2 of certainty <input type="checkbox"/> 5. Level 3 of certainty <input type="checkbox"/> 6. None of the above <input type="checkbox"/> 7. Unknown if 1-5 are present
<p>3. Criterion C: Pregnancy testing</p>	<p>Check all that apply for 1-3 or check only 4 OR 5</p> <input type="checkbox"/> 1. Positive blood or urine pregnancy test that becomes negative after 7 days <input type="checkbox"/> 2. B- HCG serum blood test >2000 mIU/ml <input type="checkbox"/> 3. Positive urine pregnancy test <input type="checkbox"/> 4. None of the above <input type="checkbox"/> 5. Unknown is 1-3 are present
<p>4. Criterion D: Histopathological evaluation</p>	<p>Check all that apply for 1-3 or check only 4 OR 5</p> <input type="checkbox"/> 1. Histopathological evaluation of pregnancy tissue shows products of conception <input type="checkbox"/> 2. Histopathological evaluation of uterine contents shows products of conception <input type="checkbox"/> 3. No products of conception found on endometrial curettage after D&C procedure <input type="checkbox"/> 4. None of the above <input type="checkbox"/> 5. Unknown if 1-3 are present

<b>5. Criterion E: Cervix examination</b>	Check all that apply for 1 and 2 or check only 3 OR 4 <input type="checkbox"/> 1. Vaginal bleeding <input type="checkbox"/> 2. Visible expulsion of pregnancy tissue/products of conception <input type="checkbox"/> 3. Neither 1 nor 2 is present <input type="checkbox"/> 4. Unknown if either 1 or 2 is present
<b>6. Criterion X: Viable pregnancy</b>	Choose the one best answer <input type="checkbox"/> 1. A viable pregnancy was found <input type="checkbox"/> 2. A viable pregnancy was not found

**TABLE 5.3. INTERPRETATION FORM FOR SPONTANEOUS ABORTION AND EXTOPIC PREGNANCY CRITERION VALUES**

Based on clinical data entered into Table 2, assign a value to each criterion using the rules in the Criterion Options columns.

CRITERIA		CRITERION OPTIONS: Criterion =			Criterion Value
		YES (Y) IF:	NO (N) IF:	UNKNOWN (U) IF:	
A. Ultrasound examination results	A-I	__ A = (2 or 3 or 4)	__ A = 13 or A not equal to 2, 3, 4 or 14	__ A = 14	A-I = Y N U
	A-II	__ A = (6 or 7 or 8 or 9)	__ A = 13 or A not equal to 6, 7, 8, 9 or 14		A-II = Y N U
	A-III	__ A = 10	__ A = 13 or A not equal 10 or 14		A-III = Y N U
	A-IV	__ A = 2 or 3 or 5	A = 13 or A not equal to 2, 3, 5 or 14		A-IV = Y N U
	A-V	__ A = 1	A = 13 or A not equal to 1 or 14		A-V = Y N U
	A-VI	__ A = 11	A = 13 or A not equal to 11 or 14		A-VI = Y N U
	A-VII	__ A = 12	A = 13 or A not equal to 12 or 14		A-VII = Y N U
B. Gestational Age	B-1	__ B = 1	__ B = 6 or B not equal to 1, 2,3,4, 5 or 7	__ B = 7	B-1 = Y N U
	B-2	__ B = 2			B-2 = Y N U
	B-3	__ B = 3			B-3 = Y N U
	B-4	__ B = 4			B-4 = Y N U
	B-5	__ B = 5			B-5 = Y N U
C. Pregnancy test	C-1	__ C = 1	__ C = 4 or C not equal to 1 or 5	__ C = 5	C-1 = Y N U
	C-2	__ C = 2	__ C = 4 or C not equal to 2 or 5		C-2 = Y N U
	C-3	__ C = 3	C = 4 or C not equal to 3 or 5		C-3 = Y N U
D. Histopathological evaluation	D-1	__ D = 1	__ D = 4 or D not equal to 1 or 5	__ D = 5	D-1 = Y N U
	D-2	__ D = 2	__ D = 4 or D not equal to 2 or 5		D-2 = Y N U
	D-3	__ D = 3	__ D = 4 or D not equal to 3 or 5		D-3 = Y N U
E. Cervix examination	E-1	__ E = 1 and 2	__ E = 3 or E not equal to 1, 2 or 4	__ E = 4	E-1 = Y N U
	E-2	__ E = 2	__ E = 3 or E not equal to 2 or 4		E-2 = Y N U

X. Viable pregnancy	X-1	__X = 1	__X = 2	Not applicable	X 1= Y N
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**TABLE 5.4. SUMMARY OF SPONTANEOUS ABORTION AND ECTOPIC PREGNANCY CRITERION VALUES**

Record final values for each Criterion from Table 5.3.

Criterion	A-I	A-II	A-III	A-IV	A-V	A-VI	A-VII	B-1	B-2	B-3	B-4	B-5	C-1	C-2	C-3	D-1	D-2	D-3	E-1	E-2	X-1	
Final Value																						

Use the final values of all criteria recorded in Table 5.4 to determine LOC based on the formulae below. The highest row in the table where **all criteria are met** will be the LOC.

**TABLE 5.5 TABULAR ALGORITHMS TO DETERMINE SPONTANEOUS ABORTION 1<sup>ST</sup> TRIMESTER LEVEL OF CERTAINTY (LOC) BASED ON CRITERION VALUES**

Level of Certainty of Spontaneous abortion 1st Trimester	
Level 1	(A-I AND A-II = YES) OR [(B-1 AND (B-3 or B-4) = YES) AND (A-III OR C-1 OR D-1 OR E-1 = YES)]
Level 2	Doesn't meet level 1 AND (B-1 AND (B-3 or B-4) = YES) AND (A-IV= YES)
Level 3	Doesn't meet level 1 or 2 AND (B-1 AND B-5) = YES
Level 4	Reported spontaneous abortion 1st Trimester with insufficient evidence to meet the case definition
Level 5	Not a case of spontaneous abortion 1 <sup>st</sup> trimester (X-1 =YES)

**TABLE 5.6 TABLE TO DETERMINE SPONTANEOUS ABORTION 2<sup>ND</sup> TRIMESTER LEVEL OF CERTAINTY (LOC)**

Level of Certainty of Spontaneous Abortion 2 <sup>nd</sup> trimester	
Level 1	(B-2 AND (B-3 or B4 = YES) AND (A-V or D-2 OR E-2 = YES)
Level 2	Doesn't meet level 1 AND (B-2 AND B-5 = YES) AND (A-V or D-2 OR E-2 = YES)
Level 3	No level 3

Level 4	Reported spontaneous abortion 2 <sup>nd</sup> trimester with insufficient evidence to meet the case definition
Level 5	Not a case of spontaneous abortion 2 <sup>nd</sup> trimester (X-1=YES)

**TABLE 5.7 TABLE TO DETERMINE ECTOPIC PREGNANCY LEVEL OF CERTAINTY (LOC)**

Level of Certainty of ectopic pregnancy	
Level 1	(B-1 or B-2) AND (B-3 or B-4) = YES) AND [(A-VI AND C-2 = YES) OR (A-VII AND D-3= YES)]
Level 2	Doesn't meet level 1 AND [(B-1 or B-2) AND (B-3 or B-4) = YES)] AND (A-VI or D-3 = YES)
Level 3:	Doesn't meet level 1 or 2 AND [(B-1 or B-2) AND (B-4 or B-5) = YES)] AND (C-3 AND D-3 = YES)
Level 4	Reported ectopic pregnancy with insufficient evidence to meet the case definition
Level 5	Not a case of ectopic pregnancy (A-VI OR A-VII= NO) AND (B1 or B-2) = YES)

**Table 5.8 GLOSSARY OF TERMS USED IN THE CASE DEFINITION**

<b>Abdominal ultrasound</b>	A quick, painless diagnostic imaging test that uses high-frequency sound waves to bounce off internal organs and produce detailed images of the organs. A handheld probe (a transducer) is placed on the skin of the pregnant woman’s abdomen to captures pictures of the developing fetus. Abdominal ultrasounds are used after about 12 weeks of pregnancy
<b>Cervical os</b>	The cervix is located in the pelvic region within the female reproductive system. It is typically just over 1.5 inches in length and bridges the distance between the vagina and the uterus. The external os of the cervix is the opening on the outer, vaginal side of the canal and the internal os is the opening on the inner side of the canal near the uterus
<b>Dilation and curettage (D&amp;C) procedure</b>	A minor surgical procedure in which the cervix (lower, narrow part of the uterus) is dilated (expanded) so that the uterine lining (endometrium) can be scraped with a curette (spoon-shaped instrument) to remove abnormal tissues. It is done to diagnose and treat certain uterine conditions - such as abnormal uterine bleeding e.g. heavy bleeding, bleeding between periods or bleeding after menopause, to clear the uterine lining after a spontaneous abortion, for a surgical abortion (pregnancy termination), incomplete medical abortion or investigations of female infertility
<b>Ectopic pregnancy</b>	When a fertilised egg gets implanted outside of the uterus, usually in one of the fallopian tubes (tubes which connect the ovaries to the uterus), or the ovary, abdominal cavity or the lower part of the uterus (cervix). About 90% of ectopic pregnancies happen in the fallopian tubes. An ectopic pregnancy cannot proceed normally as the fertilized egg cannot survive and the growing tissue may cause life-threatening bleeding, infection and sometimes, death in the pregnant woman if left untreated
<b>Endometrial curettage</b>	Scraping or removal of the tissue lining the uterine cavity (endometrium) with a surgical instrument called a curette
<b>Gestational sac</b>	A fluid-filled structure inside the uterus which surrounds a developing embryo during the very early stages of pregnancy. It is the first structure seen in pregnancy by ultrasound at 4.5- 5 weeks of gestational age when it is approximately a 2-3 mm rounded collection of fluid. It is 97.6% specific for the diagnosis of an intrauterine pregnancy. Mean sac diameter (MSD) is a sonographic measurement of the gestational sac and is calculated by the sum of the length, height and width of the gestational sac divided by 3. A MSD of >25 mm without an visible embryo or yolk sac is indicative of pregnancy failure.

<b>Products of conception</b>	Any tissues that develop from a fertilized egg in a pregnancy, including the fetus, placenta and any other tissues
<b>Spontaneous abortion (spontaneous miscarriage)</b>	Involuntary, spontaneous loss of a pregnancy before 22 completed weeks of gestation
<b>Transvaginal ultrasound</b>	A small ultrasound probe (a transducer) is placed in the vaginal canal to create an image. Images from a transvaginal ultrasound are clearer in early pregnancy as compared to an abdominal ultrasound. In early pregnancy, this ultrasound helps to detect a fetal heartbeat, determine the gestational age, assess the condition of the placenta, check for an ectopic pregnancy, for problems with the cervix e.g. a short cervix, which increase the risk of early labour, or monitor pregnancies with a higher risk of pregnancy loss. A transvaginal ultrasound is more common in the first 11-12 weeks of pregnancy
<b>Viable pregnancy</b>	A pregnancy is termed viable if it has the potential to result in a live-born neonate. The two major criteria that must be met for a pregnancy to be viable are a normal location within the uterus and a potentially viable fetus which can survive outside the uterus. Medical viability is generally considered to be between 23 and 24 weeks.
<b>Yolk sac</b>	The round or pear-shaped pouch made up of membranes, 3-5 mm in diameter, that provides nutrients to the developing embryo until the placenta takes over. The yolk sac attaches to the outside of the developing embryo and is an important indicator of pregnancy health. It is usually visible on a transvaginal ultrasound between 5.5- 6 weeks gestation and disappears on ultrasound examination by weeks 14-20

FIGURE 5. 1 PICTORIAL ALGORITHM FOR 1<sup>ST</sup> TRIMESTER SPONTANEOUS ABORTION

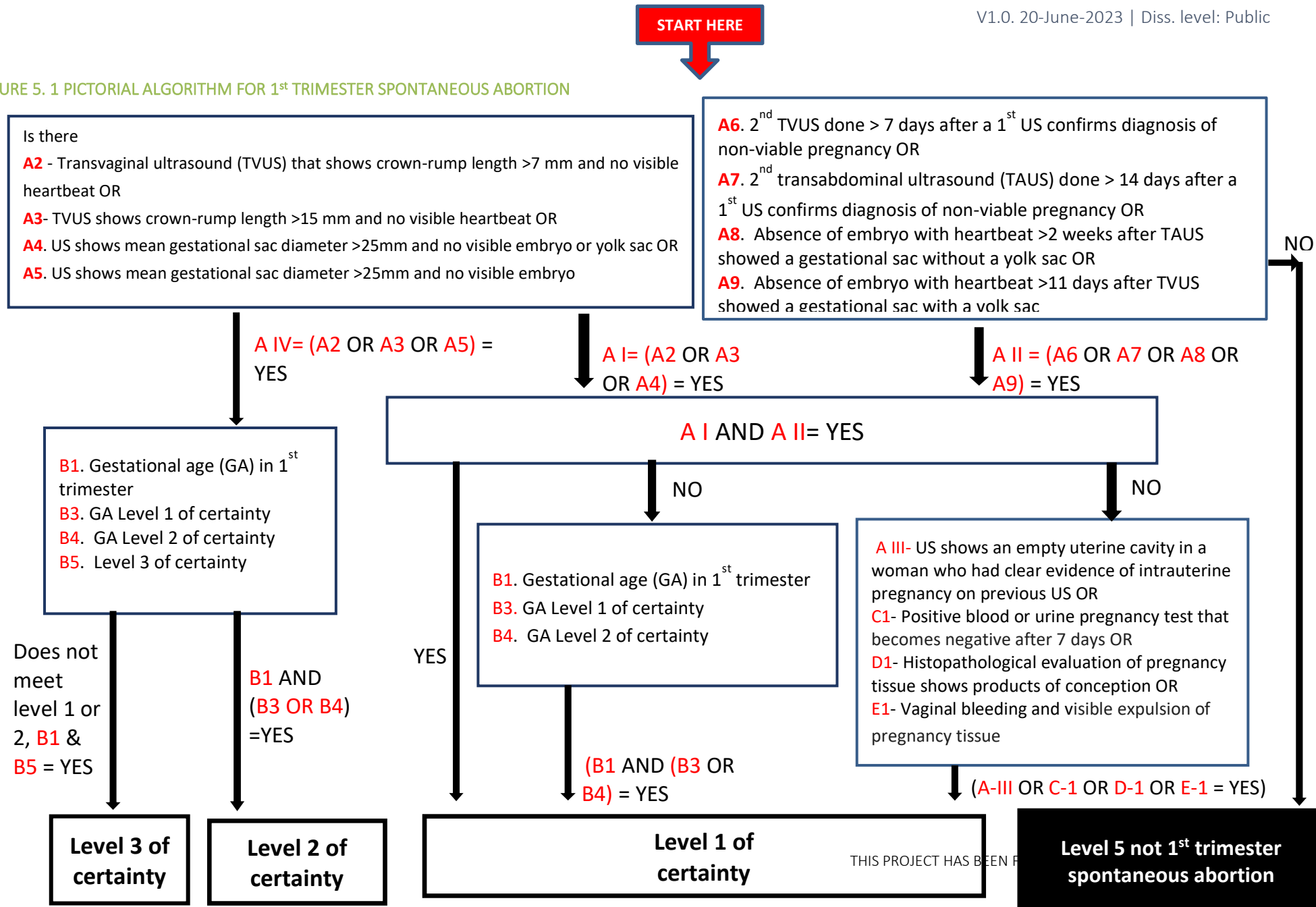




FIGURE 5. 2 PICTORIAL ALGORITHM FOR 2<sup>nd</sup> TRIMESTER SPONTANEOUS ABORTION

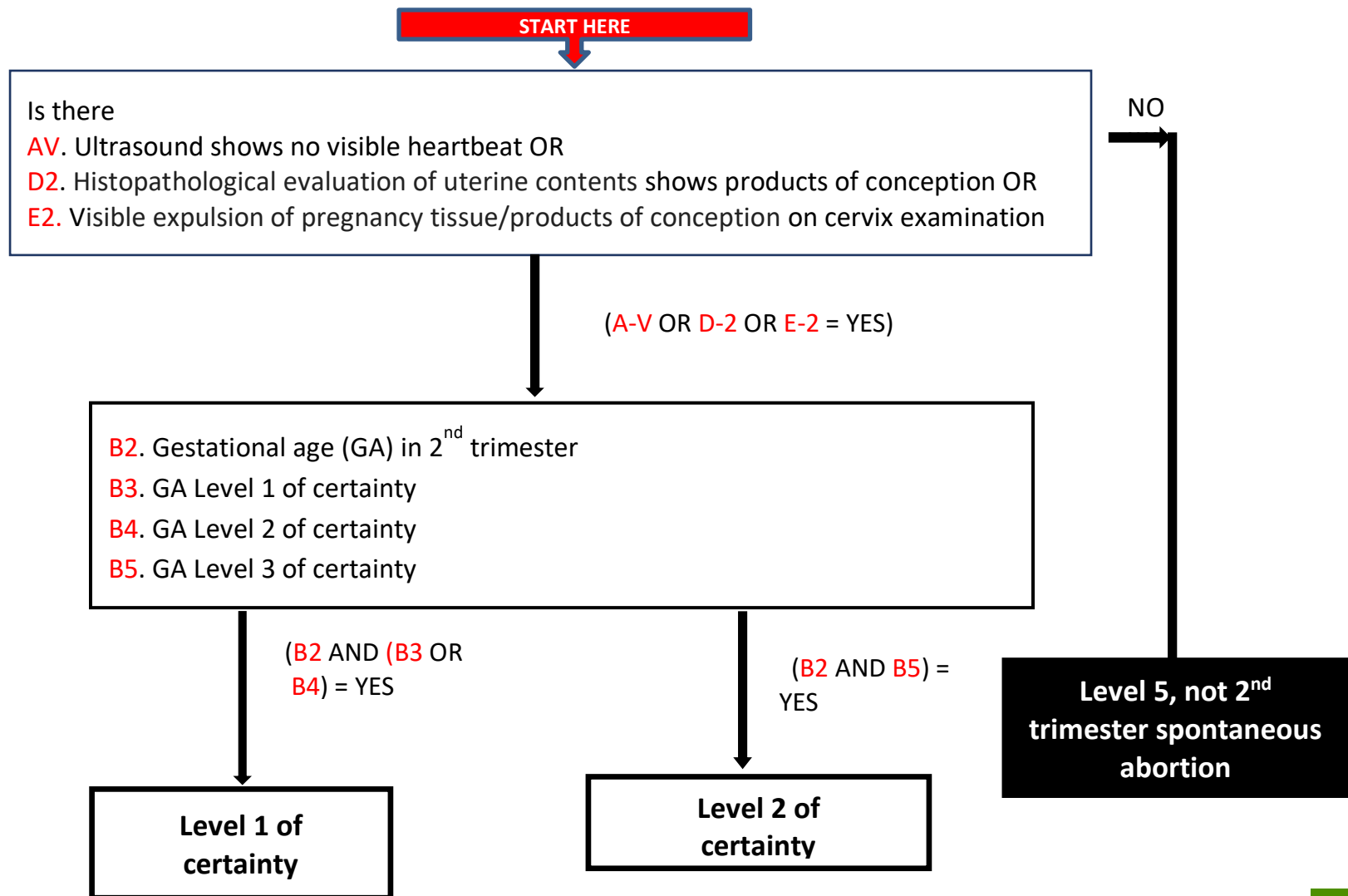
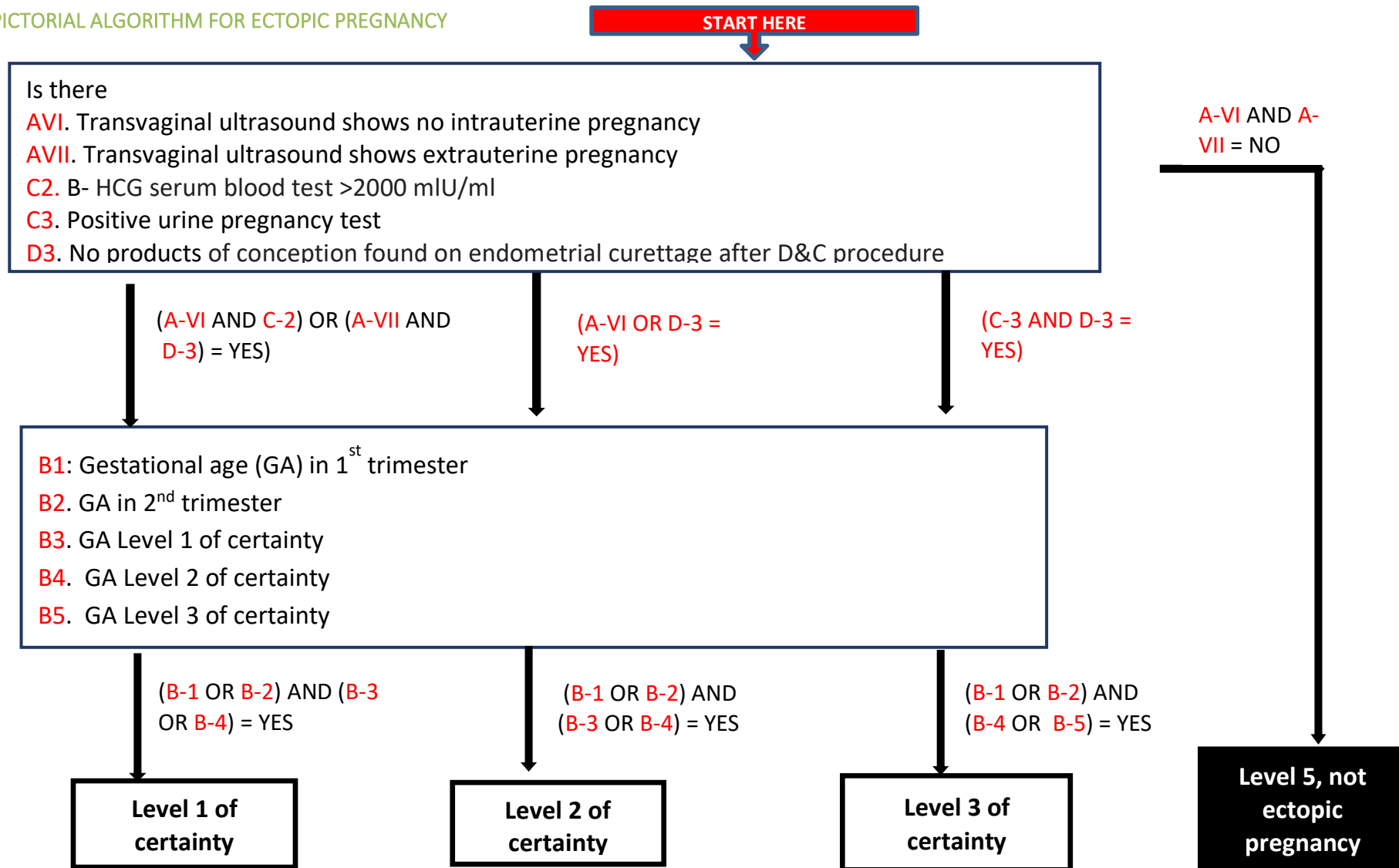


FIGURE 5. 3 PICTORIAL ALGORITHM FOR ECTOPIC PREGNANCY



## APPENDIX 6

### Methodology: Brief Summary

#### 6.1. Spontaneous Abortion and ectopic pregnancy ICD-9/10-CM and MedDRA Codes <sup>2-6</sup>

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<sup>2</sup> 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.<sup>3</sup> 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.<sup>4,5</sup> A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.<sup>6</sup> 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 (SK) familiar with the Spontaneous Abortion and ectopic pregnancy Brighton case definitions for all Tier 1 AESI. The concepts identified for Spontaneous Abortion and ectopic pregnancy were considered relevant for background incidence rate

determination as well as to study hypotheses related to Spontaneous Abortion and ectopic pregnancy 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. Spontaneous Abortion and ectopic pregnancy Background Incidence

A systematic literature search to estimate the incidence of Spontaneous Abortion and ectopic pregnancy in the population was conducted using the following search strategy:

“Spontaneous Abortion and ectopic pregnancy ” OR “premature birth” OR “premature delivery”

AND ("Incidence"[Mesh:noexp] OR "incidence"[tiab])

AND English[lang]

AND ("2000/01/01"[PDAT]: "3000/12/31"[PDAT])

AND ("Observational Study"[Publication Type] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "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 Spontaneous Abortion and ectopic pregnancy were extracted. Spontaneous Abortion and ectopic pregnancy 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. Screened in articles were reviewed and relevant data abstracted for inclusion in the background rate table (MRV) when novel articles were found from systematic reviews, these were included.

The spreadsheet with all extracted background incidence data is available in the CEPI Developers' Toolbox and on the Brighton Collaboration website.

### 6.3. Spontaneous Abortion and ectopic pregnancy Risk Factors

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

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

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

The published Brighton Case definition<sup>1</sup> for Spontaneous Abortion and ectopic pregnancy was reviewed for evidence related to associated risk factors. In addition, a systematic search was conducted to identify evidence for risk factors using the same search strategy shown for background incidence in section 6.2 above. The expert (SK) screened all retrieved articles and set aside and reviewed all that pertained to the epidemiology of Spontaneous Abortion and ectopic pregnancy. Additional relevant articles were found by a hand search of the included article reference list and articles identified after expert consultation. The included articles were used not only to inform the Risk factor table(s) in Appendix 3, but also guidance on real time investigation in Appendix 5.

A PubMed search for articles focused on Spontaneous Abortion and ectopic pregnancy following vaccination was conducted by SK on April 17, 2023.

A single reviewer (SK) screened the articles first on title and abstract to identify case reports, case series, reviews, descriptive and research studies focused on humans. Editorials, letters to the editor, other commentaries, erratum, guidelines and articles focused only on management or therapy were excluded. A full text review was conducted for all screened in articles. Articles were judged to be contributory or non-contributory for the purpose of the Companion guide which was to identify vaccine as a risk factor for Spontaneous Abortion and ectopic pregnancy and to describe up to date information related to the Spontaneous Abortion and ectopic pregnancy safety signal associated with maternal immunization. Hypothesis-testing studies as well as descriptive datalink or other epidemiologic studies that provided risk analyses (Incidence Rate, Incidence Reporting Ratio, Incidence Rate Difference) or disproportionality analyses (Reporting Odds Ratio, Information Component)

or that systematically reviewed published case reports and case series or that provided endomyocardial histopathology were considered contributory.

#### **6.4. Spontaneous Abortion and ectopic pregnancy Case Definition key caveats for diagnosis, data analysis and presentation <sup>1</sup>**

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

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

#### **6.5. Tabular Checklist and Algorithms for Level of Certainty Determination <sup>1</sup>**

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

The Spontaneous Abortion and ectopic pregnancy criteria were displayed in a tabular format to enable recording of all relevant clinical data (based on history, physical examination, laboratory investigation and temporal criteria as relevant to each case definition) needed to meet each criterion.

Algorithms were developed for each level of diagnostic certainty based on the values of each criterion as described in the published case definition.<sup>1</sup> Two types of algorithm were developed for each case definition. For one, formulae based on the logic in the case definition were put into tables with each row representing a level of certainty. For the second a more visual decision tree algorithm was developed.

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