Safety Platform for Emergency vACcines

SO2- D2.5.2.2 - AESI Case Definition Companion Guide

Acute Respiratory Distress Syndrome (ARDS)

V1.0 – [17 October 2022]

Authors: Barbara Law, Marta Rojo Villaescusa

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In case you have used this or any other Brighton Collaboration case definition companion guide, please take 3 minutes to respond to this survey, it will help us to improve our tools.

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DOCUMENT INFORMATION

Main Author(s)	Barbara Law Marta Rojo Villaescusa (sub-contracted)	E-mail: Barbara.law@cepi.net E-mail: martusred@gmail.com
WP Leader	Barbara Law	E-mail: barbara.law@cepi.net

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

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

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ALERT

This Companion Guide for the Brighton Case Definition of ARDS, follows the format of all such guides with appendixes presenting:

1. Diagnostic codes (MedDRA, ICD-9, ICD-10, SNOMEDCT-US);
2. Global background incidence data based on systematic review of the literature;
3. Risk Factors also based on systematic literature review;
4. Key caveats regarding the case definition and guidelines for real time investigation;
5. A data abstraction form with instructions for defining the criteria needed to meet the case definition and to assign a specific level of certainty.

The Brighton Collaboration ARDS case definition was published in January 2021[1] whereas the Guide was not developed until September 2022. In the process of carefully reviewing the case definition publication, in order to create the tools for the Guide (data abstraction form, guide to assigning 'yes', 'no' or 'unknown' to each criterion, algorithms to go from criterion values to level of certainty), some key issues were identified that needed clarification from the ARDS case definition Working Group. A meeting was held on Sept 15, 2022 with 5 Working Group ARDS subject matter experts (Nathan Serazin, Sarah Williams, Justin Ortiz, Patricia Bastero and Flor Munoz) to discuss and resolve the issues. In brief, the issues and their resolution were as follows:

1. The published case definition very clearly states that Level 1 is met if previously published consensus criteria for ARDS are met: i.e., Berlin criteria[38] for adults; PALICC criteria[40] for children. The published case definition table 5 is consistent with this but the algorithm in Figure 1 has an inconsistency for children which could be confusing and result in an erroneous classification as Level 2 for children where the indicator of hypoxemia is based on pulse oximetry instead of arterial pAO2. For clarification in applying the criteria, this guide provides separate algorithms for adults and children (see Appendix 5, Figures 5.1 and 5.2 for adults and children, respectively).
2. Level 2 is reserved for cases where there are specified deviations from the Berlin (not on positive pressure ventilation or use of pulse oximetry instead of pAO2 for hypoxemia or infiltrates shown by chest ultrasound instead of chest x-ray) or PALICC (not on positive pressure ventilation or infiltrates shown by chest ultrasound instead of chest x-ray) criteria. The case definition defines A and B subgroups for Level 2, but there are actually more than 2 variations of acceptable deviation(s). Accordingly, in this guide the A and B distinctions are not used, but all combinations of criteria to reach Level 2 are specified.
3. Figure 1 in the case definition starts with a box that states, "Does patient have findings consistent with ARDS?". An answer of 'No' to this question leads to a Level 5 – 'Not a case of ARDS'. In a pharmacovigilance setting, where some clinical information may be missing, this could create some uncertainty in terms of applying the case definition. For example, a physician may report a case indicating that the 'Berlin' or 'PALICC' criteria were all met – but not spell out the individual components. Clearly anyone meeting the 'Berlin' or 'PALICC' criteria would have findings consistent with ARDS, but this may not be obvious to non-experts trying to apply the case definition. The Companion Guide algorithm pathways start with what is needed for Level 1 and then Level 2, both

of which are based on the Berlin (for adults) and PALICC (for children) criteria. The clinical findings consistent with ARDS are then specified as a requirement for Level 3, which is a 'suspect' case of ARDS (see point 4 below).

4. Level 3 is based on clinical criteria alone which include 3 history and 5 physical examination criteria and absence of 2 alternate explanations for the clinical findings (Table 3 in the published case definition, which is reproduced in Appendix 4, Table 4.1 in this guide). However, there are no WG recommendations as to how many of these criteria are required to meet Level 3. It was agreed by the subject matter experts on the call, that there is no way to be more specific and that at the very best, Level 3 can only be considered a 'suspect' case of ARDS and additional expert consultation would be strongly advised. Accordingly, this Guide requires all 10 clinical criteria to meet Level 3 (see Appendix 5, Criteria D and X) and repeats the advice for expert consultation.
5. In order to meet either Level 1 or Level 2 of ARDS, based on the Berlin and PALICC criteria, the timeframe from the insult that precedes ARDS must be 7 days or less. In the published Brighton case definition, a deviation from this is enabled since it is unclear what the timeframe might be following immunization. The guidelines accompanying the case definition recommend analysing cases using pre-specified intervals from immunization to onset of ARDS of: ≤7 days, 8-14 days; 15 - ≤42 days; and >42 days. This guidance is maintained in the Companion Guide, but an added suggestion, agreed to by the WG members, is to classify cases that have onset in the ≤7 days timeframe as A (i.e., Level 1A, 2A or 3A) whereas those that onset >7 days after immunization as B (i.e., Level 1B, 2B or 3B). For analysis purposes the added breakdown should still be included for B cases (8-14, 15-≤42 and >42). This A or B distinction will likely be of greatest relevance to pharmacovigilance settings.

DEFINITIONS & ACRONYMS

AECC	American European Consensus Conference (to define ARDS)
AEFI	Adverse Event Following Immunization
AESI	Adverse Events of Special Interest
ALI	Acute lung injury
APACHE	Acute physiology and chronic health evaluation (scoring system used in intensive care settings. Usually applied once within 24 hours of admission.
ARDS	Acute Respiratory Distress Syndrome
BC	Brighton Collaboration
CD	Case Definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CI	Confidence Interval
CMV	Cytomegalovirus
COVID-19	Coronavirus infectious disease – 2019 (caused by SARS-CoV-2)
CPAP	Continuous positive airway pressure (measured in cm H_2O)
CPRD	Clinical practice research database (UK resource)
CT	Computed Tomography
CUI	Concept Unique Identifier
EBV	Epstein Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ER	Emergency Room
EVALI	E-cigarette or vaping associated lung injury
FiO_2	Inspired fraction of Oxygen (expressed as a decimal – e.g., 21% O_2 = 0.21)
H_2O	Water; relates to measurement units (in cm H_2O for PEEP or CPAP)
HBV	Hepatitis B Virus
HF	Heart Failure
Hg	Mercury
HHV	Human Herpes Virus
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
GPRD	General Practice Research Database (UK resource)
GP	General Practice
ICD-9-CM	International Classification of Diseases-9th Revision-Clinical Modification
ICD-10-CM	International Classification of Diseases-10th Revision-Clinical Modification
ICU	Intensive Care Unit
LMIC	Lower or Middle Income Country
LOC	Level of Certainty

MAP	Mean alveolar pressure
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle Eastern respiratory syndrome
mm	millimeters
MMR	Measles Mumps Rubella vaccine
MRI	Magnetic Resonance Imaging
ne	Not equal to
nmol	nanomole
NOS	Not otherwise stated (relevant to medical codes)
OI	Oxygenation index (calculated as [MAP x FiO_2 x 100] / PaO_2)
OSI	Oxygen saturation index (calculated as [MAP x FiO_2 x 100] / SpO_2)
OPV	Oral Polio Vaccine
PALICC	Pediatric acute lung injury consensus conference (to define ARDS)
PaO_2	Partial pressure of arterial oxygen (measured in mm Hg)
PCR	Polymerase Chain Reaction
PEEP	Positive end expiratory pressure (measured in cm H_2O)
P/F	Ratio of PaO_2 to FiO_2
RSV	Respiratory Syncytial Virus
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1 (cause of SARS)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 (cause of COVID-19)
SD	Standard Deviation
S/F	Ratio of SpO_2 to FiO_2
SNOMEDCT	SNOMED Clinical Terminology
SPEAC	Safety Platform for Emergency Vaccines
SpO_2	Hemoglobin oxygen saturation (expressed as a percentage - %)
TB	Tuberculosis
Tdap	Tetanus diphtheria acellular pertussis vaccine (formulated for ≥7-year-olds)
TRALI	Transfusion related acute lung injury
UMLS	Unified Medical Language System
VAERS	Vaccine Adverse Event Reporting System
VZV	Varicella Zoster Virus

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 each AESI including:

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

All tools and resources noted above, with possible exception of a glossary of terms, are compiled together into a companion guide for selected Brighton AESI case definitions. That is the purpose of this deliverable, which focuses on ARDS.

2. Objective of this deliverable

To collate SPEAC & BC tools and resources that have been developed for ARDS for ease of deployment in the field.

3. Methods

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

- Diagnostic Codes: SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes
- Background rates and risk factors: SO1-D2.4 Tier 1 AESI: Risk Factors and Background Rates
- Case definition key caveats for diagnosis, data analysis and presentation: SO1-D2.7 Guidance for CEPI Developers
- 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 ARDS

A total of 229 articles were retrieved of which 185 were screened out for the following reason: 2 duplicates, 82 focused on treatment, diagnosis or prevention and 101 non-contributory to risk factors or general population background incidence. Of 44 articles screened in for full text review there were 13 with potential to provide data on background incidence of ARDS. Of these, only 4 provided original source population-based data and are included in Appendix 2.[7,9,12,17] The remainder were review articles and hand search of the included citations yielded an additional 20 articles with original source data that are included in Appendix 2. [8,10,11,13-16,18-26] Finally, incidence data from the European ACCESS study[27], published after the searches were done, are included as well. Studies reporting ARDS incidence as a percentage of hospital or ICU admissions were excluded from the incidence data in Appendix 2.

The remaining 31 screened in articles were reviewed in full for data relevant to ARDS risk factors or real time investigation. The primary source for ARDS risk factors was the recently published case definition.[1] In addition, 7 articles found in the literature search added additional evidence on risk factors[28-31,34,36,37] and 3 provided information on real-time investigation presented in Appendix 4.[40-42] The remaining 21 articles were not used because they did not contribute anything new to the data on risk factors. Finally, 5 additional articles were found while reviewing the screened in publications and contributed to the risk factor data in Appendix 3 [32,33,35] or to considerations for real time investigation in Appendix 4. [38,39]

4.2 All outputs are provided in separate Appendices as shown below:

1. ARDS Diagnostic Codes: ICD-9-CM, ICD-10-CM, MedDRA and SNOMEDCT
2. ARDS background rates
3. ARDS risk factors
4. ARDS case definition key caveats for diagnosis, data analysis and presentation plus recommendations for real time investigation.
5. ARDS data abstraction and interpretation forms with algorithms for assessing level of certainty.
6. 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 ARDS including ICD-9/10-CM, SNOMED and MedDRA codes for data entry or database searching; population-based background rates for calculating 'expected' cases; risk factors to aid in investigation and possibly causality assessment; guidance for real time investigation; and tools for collecting and interpreting clinical data to apply the Brighton Collaboration ARDS case definition and determine the level of diagnostic certainty. Some important caveats were noted regarding application of the published case definition[1,] and interpretation applied to the tools and resources in Appendices 4 and 5 of this Guide. These are summarized in the Executive Summary above and are not repeated here.

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

ARDS. 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

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

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

TABLE 1. NARROW TERMS FOR ARDS

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0035222	Respiratory Distress Syndrome, Adult	Acute respiratory distress syndrome	10001052		J80	67782005
		Adult respiratory distress syndrome	10001409	518.52	J80	155627006
		Adult respiratory distress syndrome	10001410			196150004
		Adult respiratory distress syndrome				196154008
		Adult respiratory distress syndrome				266411000
		Adult respiratory distress syndr	10001408			
		Adult RDS	10001407			
		ARDS	10003083			
		A.R.D.S	10000036			
		Distress respiratory syndrome adults	10013493			
		Respiratory distress syndrome adult	10038691			
		Syndrome respiratory distress adult	10042839			
		Syndrome adult respiratory distress	10042787			
		Syndrome adult respiratory	10042786			
		Adult respiratory stress syndrome	10001410			
		Shock lung	10040579			
		Respiratory distress syndrome	10038689			206281003
C5397144	Acute respiratory distress syndrome due to COVID-19					674814021000119106

TABLE 2. BROAD TERMS FOR ARDS

UMLS Concept		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0155919	Acute pulmonary edema	Acute pulmonary edema	10001024		J81.0	40541001
		Acute pulmonary oedema	10001029			
		Acute pulmonary edema NOS		518.4		196149004
		Pulmonary edema – acute				195113008
		Acute edema of lung, unspecified	10000728	518.4		196148007
		Acute oedema of lung, unspecified	10000948			
		Acute edema of lung, NOS				123262009
C0034063	Pulmonary Edema	Pulmonary edema	10037375			19242006
		Pulmonary edema NOS	10037426	514		196119001
		Edema – pulmonary NOS				266408001
		Pulmonary oedema	10037423		J81	
		Pulmonary oedemas	10037424			
		Pulmonary edema NOS	10037426		J81.1	
		Lung edema	10025084			19242006
		Lung oedema	10025112			
		Edema lung	10014233			
		Oedema lung	10055929			
		Edema pulmonary	10014253			
		Oedema pulmonary	10030126			
C0264490	Acute respiratory failure	Acute respiratory failure	10001053	518.81	J96.0	65710008
		ARF	10003088			
C1145670	Respiratory Failure	Respiratory failure	10038695			409622000
		Respiratory failure				196165003
		[D] Respiratory failure				158731006
		[D] Respiratory failure				207552005
		Respiration failure	10038651			
		Failure respiratory	10016162			

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		Respiratory failure NOS [D] Respiratory failure NOS [D] Respiratory failure NOS Respiratory failure, unspecified		518.81	J96.9	207555007 158734003
C4039867	Acute hypoxemic respiratory failure					709111008
C0340194	Hypoxemic respiratory failure	Hypoxemic respiratory failure Respiratory failure type 1 Respiratory failure without hypercapnia	 10082414			106768410 0119101 233765002
C0865850	Acute respiratory insufficiency		10069144	518.82		111282000
C0035229	Respiratory insufficiency	Respiratory insufficiency Respiratory insufficiency [D]Respiratory insufficiency Respiratory insufficiency [D] Respiratory insufficiency [D]	10038701	786.09		409623005 51395007 207056002 158378009 297107002
C1368021	Pulmonary insufficiency following shock					196151000
C0302379	Other pulmonary insufficiency, not elsewhere classified			518.82		
C0877746	Other pulmonary insufficiency NEC		10032440			
C2349744	Continuous invasive mechanical ventilation for less than 96 consecutive hours			96.71		
C2349745	Continuous invasive mechanical ventilation for 96 consecutive hours or more			96.72		
C0748355	Acute respiratory distress Acute respiratory distress				R06.03	111281007 373895009
C0476273	Respiratory distress	Respiratory distress [D] Respiratory distress [D] Respiratory distress Distress respiratory	10038687 10013492			271825005 158377004 207055003
C0162297	Respiratory arrest	Respiratory arrest Respiratory arrest [D] Respiratory arrest [D] [D] Respiratory arrest Pulmonary arrest	10038669 10037323	799.1	R09.2	87317003 158733009 274270007 207554006

		Arrest pulmonary Arrest respiratory Breathing arrested	10003114 10003115 10006337			
C0001127	Acidosis, Respiratory	Acidosis respiratory Respiratory acidoses Respiratory acidosis	10000485 10038660 10038661	276.2	E87.2	12326000
C0600228	Cardiopulmonary arrest	Cardiopulmonary arrest Cardiopulmonary arrest Cardiorespiratory arrest Cardiorespiratory arrest Cardio-respiratory arrest	10007644 10007617	 427.5 		30298009 397912004 233926006 410430005 195085006
C1444565	Cardiorespiratory failure	Cardiorespiratory failure Cardio-respiratory failure [D] Cardiorespiratory failure [D] Cardiorespiratory failure Cardiopulmonary failure	 10049125 10051093	799.1		410431009 158732004 207553000
C1260909	Cardiorespiratory failure as a complication of care					213215000
C0034076	Pulmonary insufficiency following trauma and surgery		10037414	518.5		
C1368020	Pulmonary insufficiency following trauma					196153002
C1368022	Pulmonary insufficiency following surgery			518.52		196152007 67782005
C0340255	Trauma and postoperative pulmonary insufficiency Trauma and postoperative pulmonary insufficiency NOS					196150004 266370006 196155009
C0587247	Postprocedural respiratory failure Postprocedural respiratory failure NOS			J95.82 J95.821		196192009 309775007

APPENDIX 2.
ARDS Background Rates

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2.1 ARDS Background Rates

TABLE 1. ACUTE RESPIRATORY DISTRESS SYNDROME BACKGROUND RATES. All included studies were population-based (as opposed to proportion of ICU or hospital admissions). All rates are for ARDS alone, excluding Acute Lung Injury. The definition used for ARDS was: * AECC; ** Berlin; *** medical code - code system(s) used provided in 1st cell of row. ICD10CM and SNOMED have specific ARDS codes, but ICD9CM does not (see Appendix 1, ARDS Diagnostic codes).

Country reference (case ascertainment method)	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
AMERICAs					
Ohio, USA[7] *	April 1996–March 1997	> 18	11.4 (16)		
	April 1997–March 1998	> 18	19.8 (29)		
	April 1998–March 1999	> 18	14.4 (21)		
	Overall	> 18	15.3 (66)		
Minnesota, USA[8] * Article notes trend in ARDS incidence decreasing over the 8 years of the study, but only gives data for 2001 and 2008	2001 2008	≥ 18 ARDS	81 38.3		
Washington, USA[9] *	1999-2000	≥ 15	64.0 (828)		
Washington, USA[10] *	1999-2000	<15	9.5 (29)		
Brazil[11] **	2006-2007	18-75	6.3[5.1–8.0] (81)		
ASIA					
Taiwan[12] *** ICD-9 codes 518.5, 518.82	1997-2011	≥18	15.19	21.97 (crude)	10.20 (crude)
Singapore[13] **	2015	≥21	5.8 (15)		
AUSTRALIA/OCEANIA					
Australia[14] *	1999	> 15	22 (108)		
Australia[15] *	1990–1994	28-81	7.3 (32)		
Australia and New Zealand[16] *	2004-2005	< 16	2.59 (103)		
EUROPE					
France[17] **	2012	≥18	32 (240)		
Germany[18] *	1997, 2001, 2004	1 month - 18 years	3.4 [1.7-7.0] (12)		
Scotland[19] *	1999	> 15	16 (367)		
Netherlands[20] *	2004-2006	0-16	2.2 (41)		
Finland[21] *	2007	≥16	5.0		
Spain[22] *	2010-2011	1 month to 15 years	3.9 (146)		
Spain[23] *	2008-2009	≥18	7.2 (255)		

Spain[24] *	2001	15-29 30-44 45-59 60-74 ≥75 Total	4.6 (4) 13.6 (8) 21.6 (11) 51 (26) 73.9 (12) 23 (61)		
Iceland[25] *	1988–2010	1-90 ≥ 18	7.21[6.54–7.93] 9.49[8.59–10.46]		
Sweden, Denmark, and Iceland[26] *	1997	≥15	13.5 (221)		
Netherlands[27] *** PHARMO Database Network ICD10-CM (inpatient); ICPC (GP)	2017	All ages inpatient: GP and inpatient:	 23.55 [22.55-24.58] 38.36 [32.87-44.50]		
Denmark[27] *** Danish Registries (DCE-AU) ICD10CM (in & outpatient)	2010	All ages	96.38 [93.84-98.99]		
Spain[27] *** BIFAP; ICD10CM (inpatient); ICD9CM & SNOMED (GP)	2017	All ages GP based: GP and inpatient:	 48.24 [46.85-49.66] 74.17 [71.60-76.81]		
Spain[27] *** SIDIAP ICD10CM (GP & inpatient)	2017	All ages GP based: GP and inpatient:	 7.74 [7.04- 8.50] 13.13 [11.37-15.08]		
Spain[27] *** FISABIO ICD9CM & ICD10CM (in & outpatient)	2017	All ages	141.15 [137.97- 144.38]		
Italy[27] *** PEDIANET database ICD9CM (GP based)	2018	0-14	2.72[0.74-6.97]		
Italy[27] *** ARS database; ICD9CM (Inpatient & Emergency room)	2017	All ages	30.69 [28.33-33.19]		
United Kingdom[27] *** CPRD & HES; SNOMED & RCD2	2017	All ages	22.87 [21.34-24.48]		
Germany[27] GePaRD (claims data)	2017	All ages	5.48 [3.58-8.03]		
MIDDLE EAST NONE FOUND					

APPENDIX 3.
ARDS Risk Factors

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3.1. ARDS Risk Factors

TABLE 1. ARDS RISK FACTORS

The recently published Brighton Case Definition[1] is the main source for risk factors in the table below. Additional evidence from the systematic review is cited in the table. Primary pulmonary infection and extrapulmonary sepsis cause the majority of ARDS in both adult and pediatric populations.

Age	• In hospital settings, among patients with at least 1 predisposing factor for ARDS, after adjusting for disease severity and risk factors for ARDS, patients aged ≥80 had a lower risk of developing ARDS than those aged <80.[28]
Ethnicity	• COVID-19 associated ARDS higher in Hispanic and African-American adolescents and adults

Behavior	• Chronic alcohol abuse[29]
	• Current or past history of smoking [30,31]
	  ○ May 'prime the lung' (via one or more mechanisms including endothelial and epithelial injury, neutrophilic infiltration, oxidative stress, macrophage activation, altered pulmonary microbiome and impaired coagulation) for a 'second insult' (sepsis, respiratory infection, transfusions, trauma) resulting in ARDS[30]
	  ○ independent risk factor for development of ARDS among patients admitted to Surgical ICUs (including elective surgery)[31]
	• E-cigarette use or vaping associated lung injury (EVALI): recognized syndrome, especially among younger adults (<35 years). Relevant because the presenting features (bilateral ground glass opacities, need for mechanical ventilation) may fulfill Berlin criteria and be diagnosed as ARDS[30]

Nutrition	• Vitamin D deficiency[32] 25(OH) Vitamin D_3 measured in 52 patients with acute ARDS (for most triggered by pneumonia or extra-pulmonary sepsis); 66 undergoing oesophagectomy (high risk for developing ARDS), of whom 8 were on Vitamin D supplements prior to surgery; and 18 healthy controls; Vitamin D deficiency confirmed in all 52 non-operative ARDS patients; Vitamin D deficiency documented in 96% of the oesophagectomy group; 37.5% with severe deficiency (serum level <20nmol/liter) developed post-op ARDS versus 15% with mild deficiency (serum level <50nmol/liter) and none of the 8 patients on Vitamin D supplements pre-operatively.
Surgical procedure or Trauma	• Severe trauma with shock and multiple transfusions • Near drowning, burn injury • Reperfusion pulmonary edema after a procedure; cardiopulmonary bypass • Fat emboli in association with acute trauma, especially bony injury • Burns – A systematic review and meta-analysis of 35 studies with adult patients showed a pooled estimate of 24% developing ARDS (95% CI 20-28). Higher incidence was associated with inhalation injury.[33]
Infection	• Pneumonia – multiple potential etiologies for direct lung injury ○ Bacterial: Streptococcus pneumoniae, S aureus, H influenzae, Chlamydia pneumoniae, Neisseria species, Enterococcus species, Leptospira species[34] Mycobacterium tuberculosis, Mycobacterium avium

	○ Viral: Influenza A or B; Parainfluenza 1, 2 or 3; RSV, Coronavirus (including SARS-CoV-1, SARS-CoV-2, MERS and others); Adenovirus; Human Metapneumovirus, Rhinovirus[35] Measles, Varicella Zoster ○ Fungal: Aspergillus species, Blastomyces species, Cryptococcus species, Pneumocystis jiroveci ○ Parasites: Malaria, Scrub typhus[34] • Tropical settings ○ India[34] : 75 patients prospectively enrolled: 18.7% leptospirosis, 17.3% bronchopneumonia (no specific etiology), 12% scrub typhus, 12% dengue, 5.3% swine flu, 4% cellulitis, 1 case each of: Malaria, pancreatitis, urosepsis, snake bite • Sepsis (causing indirect lung injury)
Medication / Toxin	• Inhalational injury ○ 2021 extensive but non-systematic review[30] cited growing evidence for link between air pollution, (especially ozone, and particulate matter <2.5 um diameter) and risk of ARDS if exposed to an additional predisposing factor including trauma, transfusion or among older patients, presence of comorbid condition(s). Similar to smoking, pollution may prime the lung for a second insult resulting in ARDS ○ A prospective observational cohort study enrolled 1558 critically ill patients admitted to a tertiary care medical study, all of whom lived <50 kilometers from an air quality monitor (US states – Missouri, Arkansas, Tennessee, Kentucky, Indiana, Ohio, West Virginia, North Carolina, South Carolina, Georgia and Alabama).[36] Logistic regression analysis controlled for age, race, sex, smoking, alcohol, rural vs urban residence and severity of illness [APACHE2 score]). Long term ozone exposure increased the risk of ARDS developing in critically ill patients with at least one risk factor for developing ARDS. The association was particularly strong where the risk factor was trauma or if the patient currently smoked. • Drug overdose • Blood product transfusion(s). Primarily seen in the setting of critical illness including known predisposing factors for ARDS like sepsis, mechanical ventilation. Transfusion-related acute lung injury (TRALI) may be part of the ALI/ARDS spectrum of disease. Details are beyond the scope of the Companion Guide but for further discussion see review by Juffermans[37]
Vaccine	• The ARDS case definition working group did a systematic search to Aug 20, 2020 to identify reports of ARDS after any vaccination and found nothing but occasional temporally related associations but no evidence for causality.

APPENDIX 4

ARDS Key Caveats for Real Time Investigation and Case Definition Working Group Guidance for Data Analysis and Presentation

4.1. ARDS Case Definition[1] Key Caveats for Diagnosis, Data Analysis and Presentation

4.1.1 Key elements of Case Definition (CD)

- There are no reliable biomarkers for ARDS (unlike myocarditis where Troponin is included in the case definition criteria). For all ages the key criteria for diagnosing ARDS include oxygenation status (measured in arterial or capillary blood), requirement for respiratory support using a minimum applied airway pressure (PEEP or CPAP), demonstration of new pulmonary infiltrates in the absence of alternate causes of pulmonary edema (i.e., fluid overload, heart failure) and the presence of a known stimulus that can cause lung injury and that precedes ARDS onset by ≤1 week.
- For use in the context of immunization it is impossible to specify an interval between vaccine administration and ARDS onset. Accordingly, the working group recommended that strict adherence to the 1-week timeline not be part of the definition. They further advised that cases be analyzed according to time of onset as outlined in section 3.1.5.2 below. In order to enable ready classification of reported cases based on whether or not the ≤7 days timeline from insult to ARDS onset is met or not, this guide suggests a sub-classification scheme for Levels 1, 2 and 3 into category A (onset timeline ≤7 days) and B (onset timeline >7 days). This was agreed to by subject matter experts on the WG (see Executive summary, page 4-5).
- The ARDS case definition has 3 levels of certainty and 2 separate case definitions – one for adults and one for children. Levels 1 and 2 follow previously established expert consensus guidelines as noted below.
    - Berlin criteria for adults[38]
        - Level 1 meets the Berlin criteria as specified;
        - Level 2 meets the criteria except there is no requirement for positive pressure ventilation and alternate methodology is outlined in the sub-bullets. Of note these modifications to the Berlin criteria follow those proposed in the Kigali modification[39] of the Berlin criteria to enable meeting the case definition in low- and middle-income country settings. Specifically:
            - Indicator of hypoxemia: Instead of P/F (ratio of arterial oxygen pressure to inspired fraction of oxygen ratio), S/F can be used: ratio of hemoglobin oxygen saturation, measurable by pulse oximeter, to inspired concentration of oxygen
            - Chest imaging: chest US acceptable substitute for CXR or CT demonstration of bilateral pulmonary infiltrates
    - PALICC criteria for children[40]
        - Level 1 meets the PALICC criteria
        - Level 2 also meets the PALICC criteria but accepts chest US as a substitute for CXR or chest CT for demonstration of new infiltrates (bilateral or unilateral) indicative of parenchymal disease.

- For both adults and children, Level 3, is considered a 'suspect case' at best, and depends on clinical findings only, as shown in Table 1. In such cases the WG strongly recommends additional expert consultation be sought.

TABLE 1. CLINICAL FEATURES OF ARDS (as presented in the published ARDS case definition, Table 3)

History	Physical examination	Other considerations
• Cough, shortness of breath or difficulty breathing • May be a several days period of feeling ill followed by worsening of respiratory symptoms • May be clinical evidence of preceding infection (e.g., fever, chills, abdominal pain, nausea, vomiting)	• Tachypnea • Increased work of breathing • Hypoxemia • Abnormal lung sounds, bilaterally (e.g., coarse or decreased breath sounds) • Absent signs associated with primary cardiogenic process: ○ No gallop rhythm	• Symptoms not due to new or worsening heart failure • Symptoms not due to pre-existing conditions (such as chronic lung disease)

	○ No jugular venous distention	

- ARDS will be diagnosed primarily if not exclusively in hospital-based settings, and usually in ICUs. The case definition, for Levels 1 and 2, is very technical and requires some knowledge of respiratory physiologic indicators. Data abstractors may need training to ensure they can gather the needed data from the medical charts.

4.1.2. Recommendations for real time assessment

- **Investigate possible triggers of ARDS (pneumonia, sepsis most common)**
  - Microbiology for pulmonary pathogens such as nasopharyngeal aspirate for viral culture / PCR; lung fluid (aspirated from endotracheal tube) for bacterial, fungal, mycobacterial pathogens as well as viruses.
  - Serum lipase re possible pancreatitis
- **Investigate alternate causes for ARDS signs/symptoms**
  - Transthoracic echocardiogram for cardiogenic causes of pulmonary edema

4.1.3 Recommendations for Duration of Surveillance

- If immunization leads to direct lung injury (via stimulation of innate or adaptive immune mechanisms), ARDS would be expected to occur within 1 to 6 weeks after vaccine administration.
- A longer duration of surveillance might be considered if there was potential for vaccine exposure to be a priming stimulus for increased risk of ARDS following a second hit by known risk factors. Such a mechanism is postulated for some risk factors such as smoking or air pollution. This might be more relevant for inhaled vaccines especially if they are adjuvanted. Another possible situation where longer surveillance should be considered would be if there is a possibility of vaccine associated enhanced disease.

4.1.4 Data Collection Guidelines

- Severity is not part of the Brighton ARDS case definition but is included in the Berlin and PALICC case definitions, and would be useful for case classification, if multiple cases are studied. The parameters for classifying cases as mild, moderate or severe are shown in Table 2A and 2 B below.

TABLE 2A. ARDS severity based on P/F (adult patients) or OI / OSI (pediatric patients) parameters.

ARDS Severity	Adult		Pediatric	
	Respiratory Support	P/F	Respiratory Support	OI or OSI
Severe	PEEP ≥ 5cm H_2O	≤ 100 mm Hg	Intubated, PEEP ≥5cm H_2O	OI ≥ 16 OSI ≥ 12.3
Moderate	PEEP ≥ 5cm H_2O	From > 100 to ≤ 200 mm Hg	Intubated, PEEP ≥5cm H_2O	8 ≤ OI < 16 7.5 ≤ OSI < 12.3
Mild	PEEP or CPAP ≥ 5 cm H_2O	From > 200 to ≤ 300 mm Hg	Intubated, PEEP ≥5cm H_2O	4 ≤ OI < 8 5 ≤ OSI < 7.5

TABLE 2B. ARDS severity based on S/F parameter

ARDS Severity	Adult		Pediatric	
	Respiratory Support	S/F	Respiratory Support	S/F
Severe	CPAP ≥ 5cm H_2O	≤ 144	CPAP ≥5cm H_2O	≤ 155
Moderate	CPAP ≥ 5cm H_2O	From > 144 to ≤ 235	CPAP ≥5cm H_2O	From >150 to ≤ 221

Mild	CPAP ≥ 5 cm H_2O	From > 235 to ≤ 315	CPAP ≥5cm H_2O	From >221 to ≤ 264

4.1.5 Data Analysis and Presentation Guidelines

4.1.5.1 All cases should be classified as

- Meets case definition:
  1. Level 1A or 1B
  2. Level 2A or 2B
  3. Level 3A or 3B
- Does not meet case definition:
  4. Level 4: insufficient information to meet any level of the case definition (this classification should serve as a trigger for further follow-up since more data might be found to enable meeting the CD
  5. Level 5: Not a case of ARDS. This would be true for cases where an alternate explanation for the respiratory illness is found such as fluid overload or acute cardiac failure.

4.1.5.2 The following categories for onset interval should be used:

- ≤ 7 days
- 8 – 14 days
- 15 to ≤ 42 days
- > 42 days

APPENDIX 5

ARDS Data Abstraction and Interpretation Forms With Algorithms for Assessing Level of Certainty

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

This appendix provides tools that can be used to gather data pertinent to ARDS and to use the data to assess the level of certainty based on the published Brighton case definition.[1] These tools can be used in a variety of settings including: medical chart review to validate ARDS 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. NOTE: ARDS will be diagnosed primarily if not exclusively in hospital-based settings, and usually in ICUs. The case definition, for Levels 1 and 2, is very technical and requires some knowledge of respiratory physiologic indicators. Data abstractors may need training to ensure they can gather the needed data from the medical charts.

Five tables and 1 figure are included in this appendix:

- **Table 1** lists all Brighton case definition[1] criteria for ARDS and identifies likely sources of information for each.
- **Table 2** is the main data abstraction form that can be used to record data pertinent to ARDS
- **Table 3** provides a guide for assigning a '**Y**es', '**N**o' or '**U**nknown' status to each case definition criterion based on data entered into table 5.2.
- **Table 4** is a brief summary of the final value for each criterion. As per table 5.3
- **Table 5** provides the formulae used to assign level of certainty for ARDS based on criterion values summarized in Table 5.4.
- **Figures 1 and 2** show pictorial algorithms for determining level of certainty for adult and pediatric ARDS respectively.

TABLE 1. ARDS KEY CASE DEFINITION CRITERIA, LIKELY AND ACTUAL SOURCES OF INFORMATION

Criterion	Criterion category	Likely sources of information	Actual sources of information
A	Berlin criteria for ARDS are met	ICU admission and progress notes; Specialist consultation and progress notes (e.g., Respirology, Anaesthesiology, Intensivist, Emergency Room physician); Radiology reports: CXR, chest CT, chest US	
B	PALICC criteria for ARDS are met		
C	Deviation(s) from Berlin or PALICC criteria	Pulse oximetry measurements (for SpO_2) Chest ultrasound reports	
D	Clinical signs & symptoms consistent with ARDS	Medical history, symptoms and signs as recorded in: Emergency room notes; Admitting history for hospital and ICU; Progress notes; Consultation reports;	`
E	ARDS onset timing	Medical history regarding possible prior events that could initiate lung injury, including but not limited to: pneumonia, sepsis, major trauma, specific chest trauma, cardiopulmonary surgery, burn with or without inhalation injury, near drowning, fat embolism, air pollution, E-cigarettes or vaping, aspiration, pancreatitis, immunization.	
Not a CD criterion	Insults prior to ARDS onset that may have caused lung injury		
X	Other pathology to explain clinical illness	Medical history especially pre-existing lung or cardiac disease; medical management that could lead to fluid overload	

TABLE 2. ARDS DATA ABSTRACTION FORM: Complete all rows in the table to the extent possible. Red font identifies specific ARDS criteria.

1.Date of illness onset			
2.Hospital admission?			
3.Admitting diagnosis			
4.Discharge diagnosis			
5. Criterion A Meets Berlin Criteria (not including timing – see Criterion E)	Check all that apply for options 1-5 below:		
	☐ 1. P/F ≤ 300 ☐ 2. Intubated; PEEP ≥5 cm H2O ☐ 3. Not intubated; CPAP ≥5 cm H2O	☐ 4. Bilateral chest opacities on CXR or Chest CT not explained by other process. ☐ 5. Pulmonary edema not explained by fluid overload or cardiogenic edema	
6. Criterion B Meets Pediatric PALICC* criteria (not including timing – see Criterion E)	Check all that apply for options 1-8 below:		
	☐ 1. P/F ≤300 ☐ 2. S/F ≤264 ☐ 3. OI ≥4 ☐ 4. OSI ≥5	☐ 5. Intubated; PEEP ≥5 cm H2O ☐ 6. Not intubated; CPAP ≥5 cm H2O ☐ 7. CXR or chest CT shows new infiltrate(s) consistent with acute pulmonary parenchymal disease. ☐ 8. The new infiltrate(s) cannot be explained by fluid overload or cardiogenic edema	
7. Criterion C Deviations from Berlin or PALICC criteria • P/F ratio not measured OR • CXR or CT not done	C-1 Adults Choose the one best answer (1, 2, 3 or 4)	☐ 1. P/F not done **AND** S/F ≤315 **AND** bilateral infiltrates seen on CXR or chest CT ☐ 2. P/F not done **AND** S/F ≤ 315 **AND** bilateral infiltrates seen on chest US ☐ 3. P/F ≤300 **AND** CXR/Chest CT not done **AND** bilateral infiltrates seen on chest US ☐ 4. No information available for either S/F ratio or chest US	
	C-2 Pediatrics Choose the one best answer (1 or 2)	☐ 1. CT/CXR not done **AND** Chest US shows new infiltrate(s) consistent with acute pulmonary parenchymal disease, not fully explained by fluid overload or cardiogenic edema ☐ 2. CT/CXR not done **AND** Chest US not done, or unknown if done or done but results unknown	
8. Criterion D Clinical signs and symptoms consistent with ARDS diagnosis	Check all that apply for options 1-7 below or only option 8:		
	☐ 1. Cough ☐ 2. Shortness of breath ☐ 3. Difficulty breathing	☐ 4. Tachypnea (observed rapid breathing) ☐ 5. Increased work of breathing (indrawing; use of accessory muscles) ☐ 6. Abnormal lung sounds	☐ 7. Cyanosis ☐ 8. Unknown if any of 1-7 present or absent

9. Criterion X. Alternate explanation for clinical symptoms and signs *Choose the most appropriate option(s): multiple options should only be checked if 2, 3 or 4 apply.*	☐ 1. There was no alternate explanation for the observed clinical symptoms and signs ☐ 2. These was pre-existing chronic lung disease which could have explained the clinical symptoms and signs. ☐ 3. There was new or worsening heart failure that could have explained the clinical symptoms and signs. ☐ 4. One or more of the following was present and could indicate a primary cardiogenic process: gallop rhythm, jugular venous distension, other signs suggesting a primary cardiogenic process ☐ 5. It is unknown if there was an alternate explanation for the observed clinical symptoms and signs				
10. Criterion E **ARDS onset timing**	Choose the one best answer from the options below to describe the interval following a known clinical insult or presence of new or worsening respiratory symptoms to ARDS onset:				
	☐ 1. ≤ 7 days	☐ 2. 8-14 days	☐ 3. 15-≤42 days	☐ **4. >42 days**	☐ **5. Unknown**
12.Possible insults (not a CD criterion) **Event(s) that preceded onset of clinical signs and symptoms and may have caused lung injury directly or indirectly** *Choose all that apply among options 1 – 15, or only option 16 or option 17.*	☐ 1. Pneumonia (bacterial, viral, fungal or parasitic) ☐ 2. Sepsis (severe infection involving bloodstream) ☐ 3. Severe trauma with shock & multiple transfusions ☐ 4. Pulmonary contusion ☐ 5. Near-drowning ☐ 6. Aspiration of stomach contents ☐ 7. Burn injury ☐ 8. Inhalational injury ☐ 9. Recent cardiopulmonary bypass procedure		☐ 10. Acute pancreatitis ☐ 11. Blood product transfusion(s) ☐ 12. Drug overdose ☐ 13. Fat emboli ☐ 14. Reperfusion pulmonary edema after procedure ☐ 15. Other (describe:) ☐ 16. No event preceded onset of signs & symptoms ☐ 17. Unknown if any of 1-15 above occurred		

*Most ARDS patients are likely to be managed in intensive care settings. In such cases, there may be notation in the medical chart that the Berlin (for adult patients) or PALICCI (for pediatric patients) criteria have been met. The specific criteria for each scoring system may be recorded in the progress notes as should status regarding CPAP (non-intubated patients) or PEEP (intubated patients). If P/F or S/F ratios are not provided it is possible to calculate as follows: P/F ratio = PaO2/FiO2 S/F ratio = SpO2/FiO2 OI = (MAP x FiO2 x 100) / PaO2. OSI = (MAP x FiO2 x 100) / SpO2. It is likely that multiple measurements of either PaO2 or SpO2 as well as MAP were made. Seek expert help to determine which measurements to use – ideally would use the ones that deviate the most from normal on the day of admission to hospital or ICU or within the first week in hospital.

TABLE 3. INTERPRETATION FORM FOR ARDS CRITERION VALUES: Based on clinical data entered into Table 2, assign a value to each criterion using the rules in the Criterion Options columns. *(≠ stands for not equal to)*

CRITERIA		OPTIONS FOR CRITERION VALUE			Criterion Value
		YES (Y) IF:	NO (N) IF:	UNKNOWN(U) IF:	
Criterion A Meets Berlin criteria		__A = [1 + (2 or 3) + 4 + 5]	__A ≠ [1 + (2 OR 3) + 4 + 5]	Not applicable	A = Y N
Criterion B Meets PALICC criteria		__B = [(1, 2, 3 or 4) + (5 or 6) + 7 + 8]	__B ≠ [(1, 2, 3 or 4) + (5 or 6) + 7 + 8]	Not applicable	B = Y N
Criterion C Deviation from Berlin or PALICC criteria	C-1	__(A = 5) + (C-1 = 1 or 2 or 3)	Not applicable	__C-1 = 4	C-1 = Y U
	C-2	__B = [(1, 2, 3 or 4) + (5 or 6) + 8] + [C-2 = 1]	Not applicable	__C-2 = 2	C-2 = Y U
Criterion D ARDS Signs & Symptoms		__D = 1 + 2 + 3 + 4 + 5 + 6 + 7	__D = ≤6 of (1, 2, 3, 4, 5, 6 or 7)	__D = 8	D = Y U
Criterion E Onset timing	E-1	__E = 1	__E = 2, 3 or 4	__E = 5	E = Y N U
	E-2	__E = 2, 3 or 4	Not applicable		E = Y U
Criterion X Alternate explanation for clinical symptoms and signs		__X = 2 or 3 or 4	__X = 1	__X = 5	X = Y N U

TABLE 4. SUMMARY OF ARDS CRITERION VALUES Record the final value for each Criterion from Table 5.3.

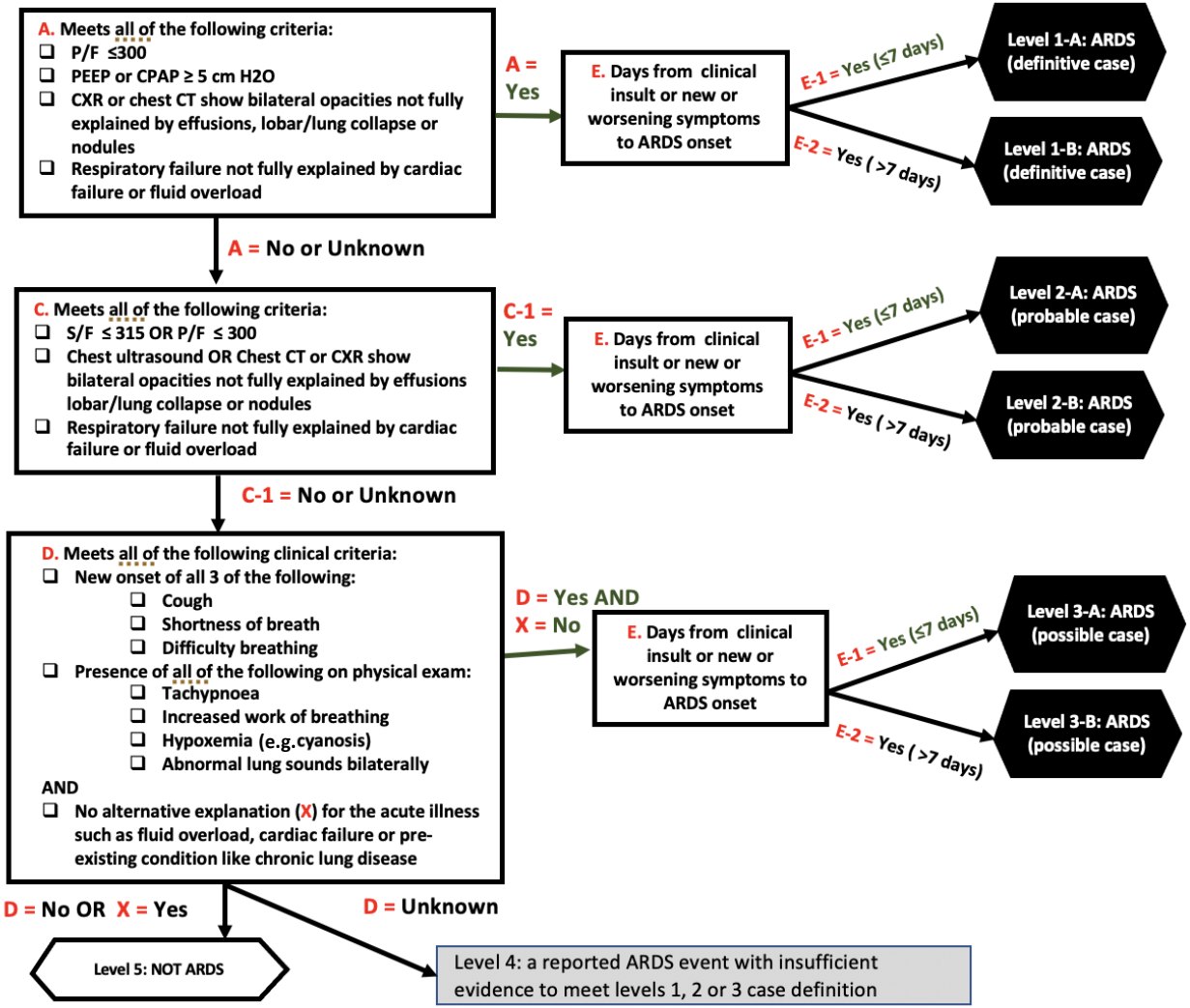
Criterion	A	B	C-1	C-2	D	E-1	E-2	X
Final Value								

TABLE 5. TABULAR ALGORITHM TO DETERMINE ARDS LEVEL OF CERTAINTY (LOC) BASED ON CRITERION VALUES Use 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.

Level of Certainty		ADULT ARDS	PEDIATRIC ARDS
Level1	1-A	A = Yes + E-1 = Yes	B = Yes + E-1 = Yes
	1-B	A = Yes + E-2 = Yes	B = Yes + E-2 = Yes
Level 2	2-A	A = No + C-1 = Yes + E-1 = Yes	B = No + C-2 = Yes + E-1 = Yes
	2-B	A = No + C-1 = Yes + E-2 = Yes	B = No + C-2 = Yes + E-2 = Yes
Level 3	3-A	(A + C-1 = No or Unknown) + D = Yes + X = No + E-1 = Yes	(B + C-2 = No or Unknown) + D = Yes + X = No + E-1 = Yes
	3-B	(A + C-1 = No or Unknown) + D = Yes + X = No + E-2 = Yes	(B + C-2 = No or Unknown) + D = Yes + X = No + E-2 = Yes

Level 4	(A + C-1 = No or Unknown) + D = Unknown	(B + C-2 = No or Unknown) + D = Unknown
Level 5	[(A + C-1 = No or Unknown) + (D = No)] OR X = Yes	[(B + C-2 = No or Unknown) + (D = No)] OR X = Yes

FIGURE 1. PICTORIAL ALGORITHM FOR DETERMINING ARDS LEVEL OF CERTAINTY IN ADULTS



Acronyms and Abbreviations

P/F = PaO2 / FiO2.

Note: where altitude is >1000 meters, apply a correction factor as follows: P/F = [PaO2/FiO2 x (barometric pressure/760)]

PaO2 = partial pressure of oxygen in arterial blood (mmHg)

FiO2 = inspired fraction of oxygen

S/F = SpO2 / FiO2

SpO2 = peripheral capillary oxygen saturation (%)

PEEP = Positive End Expiratory Pressure

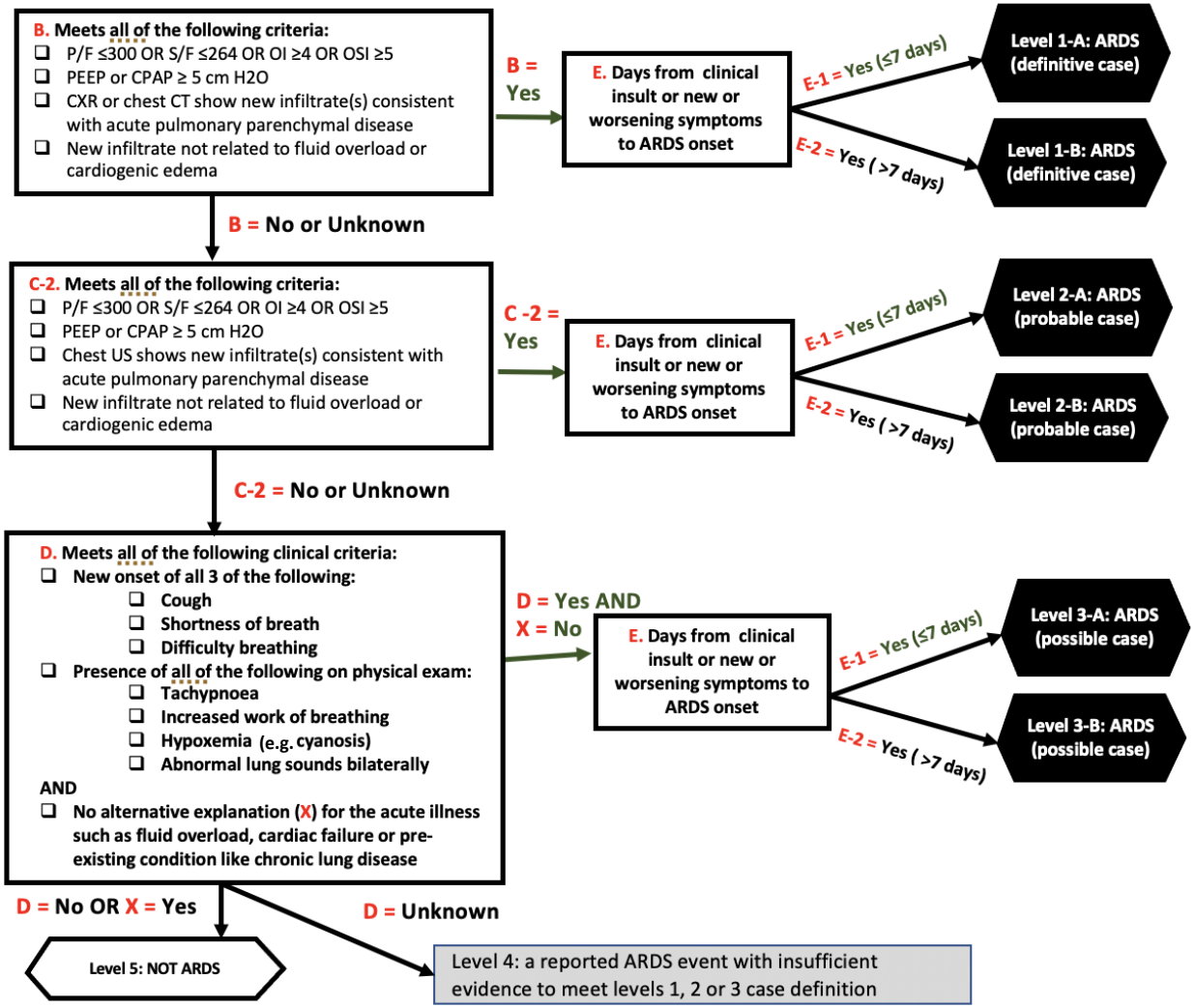
CPAP = Continuous Positive Airway Pressure

CXR = Chest X-Ray

CT = Computed Tomography

US = Ultrasound

FIGURE 2. PICTORIAL ALGORITHM FOR DETERMINING ARDS LEVEL OF CERTAINTY IN CHILDREN



Acronyms and Abbreviations

P/F = PaO2 / FiO2.

Note: where altitude is >1000 meters, apply a correction factor as follows: P/F = [PaO2/FiO2 x (barometric pressure/760)]

PaO2 = arterial partial pressure of oxygen (mmHg)

FiO2 = inspired fraction of oxygen

S/F = SpO2 / FiO2

SpO2 = peripheral capillary oxygen saturation (%)

PEEP = Positive End Expiratory Pressure

CPAP = Continuous Positive Airway Pressure

MAP = Mean Airway Pressure

OI = Oxygenation Index = (MAP x FiO2 x 100) / PaO2

OSI = Oxygen Saturation Index = (MAP x FiO2 x 100) / SpO2

CXR = Chest X-Ray

CT = Computed Tomography

US = Ultrasound

APPENDIX 6.

Methodology: Brief Summary

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

6.1. ARDS ICD-9/10-CM and MedDRA Codes 2-6

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, and updated to the most recent versions SNOMED-2022_03_01 MedDRA 24.1

CodeMapper[2] 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.[3] 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.[4,5] A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.[6] 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 Anaphylaxis Brighton case definitions for all Tier 1 AESI. The concepts identified for Anaphylaxis were considered relevant for background incidence rate determination as well as to study hypotheses related to Anaphylaxis 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. ARDS Background Incidence

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

"Acute respiratory distress syndrome" OR "ARDS"

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 Anaphylaxis were extracted. Anaphylaxis 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 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. ARDS 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. Attributes include genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published Brighton Case definition[1] for ARDS 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 same expert (BL) screened all retrieved articles and set aside and reviewed all that pertained to the epidemiology of ARDS. Additional articles were retrieved by a hand search of the article citations. 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 4 as appropriate.

6.4. ARDS Case Definition key caveats for diagnosis, data analysis and presentation [1]

The published Brighton case definition for Anaphylaxis was reviewed and key aspects identified with particular relevance to real time assessment of Anaphylaxis in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published Anaphylaxis 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 [1]

The Brighton Collaboration case definition for ARDS[1] 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.

The ARDS 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.[1] Two types of algorithms 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 (Appendix 6). For the second a more visual decision tree algorithm (Appendix 7). 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.