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Acute respiratory distress syndrome (ARDS) as an adverse event following immunization: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data

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1. Preamble

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Abstract
This is a Brighton Collaboration Case Definition of the term “Acute Respiratory Distress Syndrome – ARDS” to be utilized in the evaluation of adverse events following immunization. The Case Definition was developed by a group of experts convened by the Coalition for Epidemic Preparedness Innovations (CEPI) in the context of active development of vaccines for SARS-CoV-2 vaccines and other emerging pathogens. The case definition format of the Brighton Collaboration was followed to develop a consensus definition and defined levels of certainty, after an exhaustive review of the literature and expert consultation. The document underwent peer review by the Brighton Collaboration Network and by selected Expert Reviewers prior to submission. The comments of the reviewers were taken into consideration and edits incorporated in this final manuscript.

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Acute respiratory distress syndrome (ARDS) is a life-threatening condition resulting from acute inflammatory lung injury. It is characterized by diffuse alveolar damage with hypoxemia and poor lung compliance. While multiple insults can result in ARDS, the final common pathway ends in direct epithelial pulmonary injury with or without injury to the endothelium. This process increases permeability of the lung epithelial barrier, filling of the alveolar spaces with inflammatory fibrinous exudates, and collagen deposition with minimal interstitial edema.

Although the condition was first reported in 1821 [1], the term ARDS was first used in the biomedical literature in 1967 [2]. Since then, it has been described using multiple other terminologies including acute lung injury, adult respiratory distress syndrome, non-cardiogenic pulmonary edema, and increased-permeability pulmonary edema. In efforts to standardize terminology and diagnosis, clinical definitions have been proposed and revised to reflect improved understanding of ARDS pathogenesis. The first clinical definition was proposed in 1988 [3], revised in 1994 [4], and revised again in 2012. The 2012 “Berlin Definition,” named for the site of the expert convening, defines the most current and widely used diagnostic criteria for ARDS in adults [5,6].

While the Berlin Definition is the most widely used, several other definitions have been developed to improve recognition

### Table 1
Comparison of the ARDS definitions- Berlin Definition Kigali Definition, and PALICC Definition.

| Parameters | Berlin Definition (2012) [5] | Kigali modification of Berlin Definition (2017) [8] | PALICC Definition (2015) [7] |
|------------|-----------------------------|---------------------------------|-----------------------------|
| Onset timing | Within one week of a known clinical insult or new or worsening respiratory symptoms | Within one week of a known clinical insult or new or worsening respiratory symptoms | Within one week of a known clinical insult or new or worsening respiratory symptoms |
| Oxygenation status (defines disease severity) | PaO2/FIO2 ≤ 300 | SpO2/FIO2 ≤ 315 | Non-intubated patients: PaO2/FIO2 ratio ≤ 300 or SpO2/FIO2 ≤ 264 |
| Mild severity | 200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H2O b | Not mentioned | For intubated patients only |
| Moderate severity | 100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥ 5 cm H2O | Not mentioned | 4 ≤ OI < 8 |
| Severe severity | PaO2/FIO2 ≤ 100 mm Hg with PEEP ≥ 5 cm H2O | Not mentioned | 5 ≤ OSI < 7.5 |
| PEEP requirement | Minimum 5 cm H2O CPAP for non-intubated patients or PEEP ≥ 5 for intubated patients | No PEEP requirement | Minimum 5 cm H2O CPAP for non-intubated patients or PEEP ≥ 5 for intubated patients. |
| Chest imaging | Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules | Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules | Chest imaging of new infiltrates consistent with parenchymal disease (does not have to be bilateral) |
| Imaging Modality sufficient for diagnosis | | | |
| Chest Radiograph (CXR) | Yes | Yes | Yes |
| Chest Ultrasound | Not included d | May be used to make diagnosis but not required | Not included |
| CT scan | Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present. | Respiratory failure not fully explained by cardiac failure or fluid overload. | Respiratory failure not fully explained by cardiac failure or fluid overload. |
| Origin of edema | Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present. | Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present. | Echocardiography only recommended if suspected cardiac disease / dysfunction. |

Abbreviations: CT, computerized tomography; CXR, chest x-ray; CPAP, continuous positive airway pressure; FiO2, fraction of inspired oxygen; OI, Oxygen Saturation Index; PaO2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

a If altitude is higher than 1000 m, the correction factor should be calculated as: [PaO2/FIO2 X (barometric pressure/760)].

b This may be delivered noninvasively in the mild ARDS severity group.

c Though mentioned as an example to rule out hydrostatic edema in the initial definition, echocardiography is not necessary longer required to make the diagnosis of ARDS, and clinical evaluation/judgment is sufficient.
and diagnosis for other specific patient populations. Important examples include the Pediatric Acute Lung Injury Consensus Conference (PALICC) Definition [7], and the Kigali Modification to the Berlin Definition for use in resource-limited settings [8] (Table 1).

1.2. Epidemiology

ARDS is responsible for substantial morbidity and mortality worldwide. However, quantifying this burden can be challenging and depends on the morbidity measure used, such as intensive care unit (ICU) prevalence or incidence, ICU/hospital prevalence, or population incidence (Table 2). Regardless, a population-based incidence estimate of ARDS is not available, and the available disease burden estimates are likely underestimates.

1.3. Pathology

The pathological features of ARDS are typically described as passing through three overlapping and progressive phases – an inflammatory or exudative phase, a proliferative phase, and a fibrotic phase. The inflammatory or exudative phase occurs within the first 7 days from initial insult and is characterized by interstitial edema, acute inflammation, type II alveolar pneumocyte hyperplasia, and hyaline membrane formation. The proliferative stage begins around 10 days after the initial trigger (2–4 weeks), is characterized by resolution of pulmonary edema, proliferation of type II alveolar cells, squamous metaplasia, interstitial infiltration by myofibroblasts, and early deposition of collagen. It lasts about two to three weeks. Lastly, the fibrotic stage, starting approximately 2–4 weeks into the insult, is characterized by obliteration of normal lung architecture, fibrosis, and cyst formation. The degree of fibrosis can range from minimal to severe in patients who reach this third phase [36].

1.4. Pathophysiology

ARDS is caused by a complex interplay between the immune and inflammatory systems. The inflammatory or exudative phase begins shortly after an inciting insult activates and amplifies the response of the innate immune system. Complement activation, release of proinflammatory mediators (e.g., TNF, IL6, IL17), and chemokines (e.g., IL8, CCL2, CCL7) drive activation of innate lymphoid cells, adaptive immune cells, and recruitment of neutrophils. This leads to damage of the epithelial-alveolar barrier and increased permeability [37], resulting in interstitial and intra-alveolar edema with concurrent deactivation of surfactant. The process manifests clinically as heterogeneous areas of pulmonary edema and atelectasis that cause mismatch of lung ventilation and blood perfusion (V/Q mismatch) and hypoxemia. In the proliferative phase, there is proliferation of fibroblasts, myofibroblasts, and locally generated pluripotent mesenchymal progenitor cells that begin the repair process. This response marks the proliferative phase. Endothelial and progenitor cell proliferation restore endothelial barrier function [38]. In the fibrotic phase, expression of multiple pro-fibrotic mediators (e.g., PDGF, TGF-β, IGF-1 etc.) results in dramatic expansion and differentiation of resident fibroblasts into highly synthetic myofibroblasts [39]. This final phase of ARDS may not occur in all patients.

1.5. Diagnosis of ARDS

While the understanding of ARDS has improved over time, accurate diagnosis remains a challenge. The gold standard diagnostic test is histopathology, which is infeasible in most clinical settings. Furthermore, reliable biomarkers of ARDS remain elusive [40,41]. As a result, diagnosis remains largely based on clinical criteria that focus on recognizing an acute primary pulmonary illness with diffuse parenchymal involvement and hypoxemia. The Berlin Definition of ARDS has achieved widespread use globally, and it

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**Table 2**

Epidemiology of the ARDS in adults and children.

| Population | Location [references] | Morbidity measure used | Burden | Mortality (%) | Severity level included |
|------------|------------------------|------------------------|--------|---------------|-------------------------|
| Adults     | North America [9–11]   | Population incidence   | 38.3–82.4⁴ | 38.5–45 | Adults                  |
|            | South America [12]     | ICU incidence          | 6.9⁴   |               |                         |
|            | Europe [11,13–19]      | Population incidence   | 10.1⁴  | 49.2          | All                     |
|            |                       | ICU incidence          | 1.8⁰   | 49.2          | All                     |
|            | Australia [20]         | Population incidence   | 7.2–48.4⁴ | 42.7–47 | All                     |
|            |                       | ICU incidence          | 3.6–23⁰ | 12–78   | All                     |
|            |                       |                        | 7.1–19⁰ | 32.1–54.7 |                         |
|            | Asia [21–23]           | Population incidence   | 28⁵    | 32           | All                     |
|            |                       | ICU incidence          | 7.3–9.3⁰ | 59       | Mod-Sev                 |
|            |                       |                        |        |               | All                     |
|            | Africa [24]            | ICU incidence          | 4⁰     | 50           | All                     |
|            | Multi-country [11,25]  | ICU incidence          | 4.5–15.7⁴ | 40–57.8 | All                     |
|            | North America [26,27]  | Population incidence   | 12.8⁵  | 18           | All                     |
|            |                       | ICU incidence          | 5.8⁰   | 22.7         | All                     |
|            | Europe [28–30]         | Population incidence   | 2.2–9.6⁴ | 20.4–27.4 | Children               |
|            | Australia [31]         | Population incidence   | 7.7⁰   | 35           | All                     |
|            |                       | ICU incidence          | 1.9⁰   |              | All                     |
|            | Asia [32,33]           | ICU incidence          | 2.7–9.9⁰ | 44.8–57.3 | –                      |
|            | Multi-country [34]     | ICU incidence          | 3.5⁴   | 33.7         | All                     |
|            | Pooled [35]            | Population incidence   | 3.2⁰   | 17.1         | All                     |
|            |                       | ICU incidence          | 2.3⁰   |              | All                     |

* Studies reported “All severity” which included mild, moderate or severe illness, or “Moderate to Severe” illness as indicated.

† population-based incidence: cases per 100,000 person-years; † ICU-based incidence per 1000 admissions
has been recommended for use by the World Health Organization (WHO) and many professional societies [5]. The Berlin Definition criteria consist of 1) new or worsening respiratory symptoms within one week of an inciting clinical insult; 2) chest radiograph or computed tomography (CT) scan showing bilateral infiltrates not fully explained by effusions, pulmonary or lobar collapse, or pulmonary nodule; 3) cardiogenic edema ruled out as an etiology of pulmonary edema; and 4) ratio of arterial partial pressure of oxygen (PaO2) to fraction of inspired oxygen (FiO2), called the P/F ratio, of at least 300 mmHg and positive end-expiratory pressure (PEEP) of at least 5 cm H2O [5].

While ARDS has a similar constellation of clinical findings in children, there is growing recognition that there are important clinical and pathologic differences between the two groups [42]. This is evidenced by the fact that direct application of the Berlin Definition to a pediatric population may miss up to 50% of cases as it requires a PaO2 for case definition[43]. To address this limitation, a separate pediatric definition for ARDS, the Pediatric Acute Lung Injury Consensus Conference (PALICC) Definition was developed. It uses similar criteria including onset after an inciting factor, radiographic abnormalities not caused by cardiogenic edema, and hypoxemia. However, bilateral infiltrates are not required to make a diagnosis; instead, any parenchymal abnormality on chest radiograph is sufficient. Lastly, preference is given to the use of oxygenation index (OI) or oxygenation saturation index (OSI) to quantify the degree of hypoxemia rather than the P/F ratio for intubated pediatric patients. Diagnosis requires an OI ≥ 4 or OSI of ≥5. Alternatively, for non-intubated patients requiring ≥5 cm H2O of continuous positive airway pressure (CPAP), hemoglobin oxygen saturation (SpO2) to fraction of inspired oxygen (FiO2), called the S/F ratio, may be used. In this case, an S/F of ≤264 is required to make the diagnosis.

A modification of the Berlin Definition has been advocated for diagnosis of ARDS in resource-limited settings. In this “Kigali modification of the Berlin Definition” of ARDS [24,44], named for the city in Rwanda where it was first used, the criteria for timing and origin of edema are kept the same, but a diagnosis can be made in the absence of mechanical or non-invasive positive-pressure ventilation (NIPPV), PaO2 measurement, or chest CT scan. The Kigali Definition criteria regarding timing, imaging, etiology, and oxygenation are the following: 1) new or worsening respiratory symptoms within one week of an inciting clinical insult; 2) chest radiograph or pulmonary ultrasound showing bilateral infiltrates not fully explained by effusions, pulmonary or lumbar collapse, or pulmonary nodule; 3) cardiogenic edema ruled out as an etiology of pulmonary edema; and 4) S/F ratio of at most 315 in adults. The S/F ratio has been validated as a surrogate for P/F ratio, and is commonly used in research studies of ARDS in high and low resource settings [45].

### 1.6. Evaluation of ARDS

In addition to the application of diagnostic criteria, clinicians often make several other considerations in the evaluation of ARDS (Table 3). A physical exam is generally non-specific, but the expected findings include evidence of respiratory distress, hypoxemia, and presence of coarse or diminished breath sounds bilaterally. Notably, a physical exam should also be used to help exclude alternative diagnoses to ARDS. For example, peripheral edema, presence of a third heart sound (S3), and jugular venous reflux would provide evidence in support of a cardiogenic cause of the patient’s respiratory process. ARDS can result from a number of different clinical insults. These are typically categorized as either resulting from direct lung

| History | Exam | Other Considerations |
|---------|------|----------------------|
| Cough, shortness of breath, and/or difficulty breathing | Tachypnea, increased work of breathing, hypoxemia | Symptoms are not due to new or worsening heart failure, symptoms are not due to pre-existing conditions (such as chronic lung disease) |
| Respiratory symptoms tend to worsen after several days history of feeling ill | Abnormal lung sounds bilaterally (such as coarse or decreased breath sounds) | |
| May be preceded by symptoms of infection (such as fever or chills), or less commonly by abdominal pain, nausea, and/or vomiting | Absence of gallop rhythm, jugular venous distention, or other signs suggestive of primary cardiogenic process | |

### Table 3

History and exam findings consistent with ARDS.

### Table 4

Examples of Clinical Insults Associated with ARDS.

| Direct lung injury | Indirect lung injury | Less Common |
|--------------------|----------------------|-------------|
| More Pneumonia [45,46] | Sepsis | Cardiopulmonary bypass |
| Bacterial: Streptococcus pneumoniae (A and b), S. aureus, H. influenzae, Chlamydia pneumoniae, Mycobacteria (M. tuberculosis, M. avium), Neisseria sp., Enterococcus sp. | Severe trauma with shock and multiple transfusions | Drug overdose |
| Viral: Influenza A and B, parainfluenza 1–3, RSV, Coronavirus, SARS-CoV-1, SARS-CoV-2 and MERS, adenovirus, hMPV, measles, varicella | | Acute Pancreatitis |
| Fungal: Aspergillus, blastomyces, cryptococcus, Pneumocystis jiroveci | | Transfusion of blood products |
| Parasites: Malaria | | |

Less Common

- Pulmonary contusion
- Pneumonia
- Viral: SARS-CoV-1,MERS, Measles
- Fungal: Aspergillus
- Mycobacteria: M. avium
- Near-drowning
- Fat emboli
- Aspiration of gastric contents
- Inhalational injury
- Burn injury
- Reperfusion pulmonary edema after procedure
injury (such as pneumonia) or indirect lung injury (such as sepsis). Table 4 shows a variety of more common and less common clinical insults of each type. Further, while a patient may meet imaging and oxygenation criteria for ARDS as a result of a pre-existing condition (e.g., cyanotic heart disease) at baseline, this does not exclude the patient from being diagnosed with ARDS. However, the clinical status must represent an acute change from baseline, such as new imaging findings and worsening hypoxemia.

While the PaO₂ measurement is the only laboratory value included by the Berlin and PALICC Definitions, clinicians may find several other laboratory tests useful during the evaluation of ARDS to investigate alternative and additional diagnoses, underlying etiologies, and sequelae. For example, studies to evaluate cardiac disease or pulmonary embolism may be useful depending on the clinical context. Laboratory tests may help identify an etiology for ARDS, such as a white blood cell count and microbiologic studies to assess for infection, and lipase to evaluate for pancreatitis.

As noted in the imaging component of ARDS consensus definitions, the presence of bilateral infiltrates on chest radiograph or CT scan are required for the diagnosis of ARDS in adults, whereas any infiltrate on chest radiograph is sufficient for the diagnosis in pediatric patients. In the absence of these imaging modalities, lung ultrasound can be considered, and per the Kigali modification of the Berlin Definition, imaging criteria would be met in the presence of B-lines without evidence of effusion in at least one field on each side of the chest in adults [24]. Ultrasound has been an increasingly used imaging modality in the evaluation of patients with respiratory disease and has been found to be sensitive and specific in ARDS [47]. An additional imaging modality that may be employed in the evaluation of acute respiratory illness is the transthoracic echocardiogram (TTE) to evaluate cardiogenic causes of edema and left ventricular function.

1.7. Severity evaluation of ARDS

Severity of ARDS is defined by the patient’s oxygenation status. In the Berlin Definition, patients with PEEP or CPAP of >5 cm H₂O or greater can be categorized into three different severity groups based on arterial oxygenation. P/F ratio defines mild disease (>200 to <300 mmHg), moderate disease (>100 to <200 mmHg), and severe disease (≤100 mmHg). Severity category in adults is associated with differential 90-day mortality: 27% for mild disease, 32% for moderate disease, and 45% for severe disease [5].

In contrast to adults, in children the severity of ARDS is first distinguished between those requiring mechanical ventilation and those receiving NIPPV. For patients who are intubated, severity is then classified by calculation of a patient’s oxygen index (OI) or oxygen saturation index (OSI). This measurement is the mean airway pressure (MAP) multiplied by FiO₂, which is then divided by PaO₂ (OI) or SpO₂ (OSI). Comparable to adults, severity is defined as mild, moderate, or severe according to increasing OI or OSI. While these categories do not reliably stratify risk of mortality in between mild and moderate groups, the severe category has a significantly higher risk of in-hospital mortality (10–15% vs. 33%) [34,45,48].

Both P/F and OI/OSI have important limitations to consider. First, P/F and OI rely on measurement of PaO₂. This can be both resource-intensive and technically challenging, making it infeasible in some clinical settings. While OSI is an accepted substitution for OI in pediatrics, the Berlin Definition does not include considerations for use of S/F ratios to diagnose ARDS. However, other studies have addressed this challenge. Reported criteria for severity based on S/F ratios include mild disease >235 but ≤315, moderate disease as >144 but ≤235, and severe disease as ≤144 [45,49]. In addition, the Kigali modification of Berlin Definition defines describes any ARDS as having S/F ratio below 315 (with no PEEP or CPAP requirement), and authors have proposed a S/F ratio below 250 (also with no PEEP or CPAP requirement) to define moderate/severe ARDS [50].

1.8. ARDS after SARS-CoV-2 illness

Severe respiratory distress syndrome associated with SARS-CoV-2 infection deserves special consideration given the current pandemic. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) illness was first described in December 2019 in Wuhan, China, and has caused over 1,000,000 deaths worldwide as of October 2020. Clinical illness caused by SARS-CoV-2 infection is designated COVID-19 and can manifest in a range of respiratory illness, including ARDS.

An estimated 10–20% of patients with COVID-19 require admission to ICU [52,53]. ARDS is the most common complication of COVID-19 [54], and its incidence has ranged between 14 and 52% [53,55]. COVID-19 ARDS is a risk factor for mortality [56]. Obesity, chronic lung, cardiac and/or renal failure, immune deficiencies and active neoplasms, are risk factors for COVID-19 ARDS [25]. Similar to other causes of ARDS, patients with older age, diabetes, hypertension, obesity, cardiovascular disease and malignancies have a higher risk of developing severe COVID-19 and mortality [55–57].

In most cases, COVID-19 is milder in children than in adults. However, children with underlying complex medical conditions are at higher risk of ICU admission and developing severe COVID-19, than healthy children, with approximately 38% requiring mechanical ventilation [58] and a 30% incidence of ARDS [59]. Up to 71–74% of the pediatric patients developing COVID-19 ARDS had at least one co-morbidity, and up to almost 30% had two [58,59]. Obesity, pre-existing respiratory illness, hematologic, oncologic and/or immune disease and existing neurologic diseases were associated with the development of COVID-19 ARDS. Hispanic and African-American adolescents and adults of are at higher risk of COVID-19 ARDS [59].

ARDS can be caused by a variety of different insults, some with direct impact to the lungs and others via a secondary mechanism. Early reports of ARDS in COVID-19 described an inconsistency between the severity of hypoxia and the findings in lung imaging [60]. When compared to ARDS by other viruses they found certain differences, such as lung compliance and laboratory markers, timing of onset of illness, and preliminary histopathology data, questioning the similarities with classic ARDS, its definition, and therefore, the approach to medical treatment. Recent studies, however, suggest that the physiological differences between COVID-19 patients and ARDS from other etiologies are clinically negligible, and some report up to 85% of the ICU patients meeting Berlin Definition criteria, and responding to standardized therapies such as: low tidal volumes ventilation; conservative fluid management, and in some instances, prone ventilation [61,62].

The presence of ARDS is associated with high mortality risk in adults, and lower probability of hospital discharge in children [59].

1.9. ARDS after vaccination

We conducted a PubMed search on August 20, 2020, to identify reports of ARDS after any vaccination. The terms used in the search were: (“Vaccines”[Mesh] OR “vaccine” [tiab] OR “vaccines”[tiab] OR “vaccination”[Mesh] OR “vaccination”[tiab] OR “vaccinations”[tiab] OR “vaccinate”[tiab] OR “vaccinated”[tiab] OR “immunization”[mesh] OR “immunization”[tiab] OR “immunizations”[tiab] OR “immunisation”[tiab]
influenza, and other respiratory virus vaccines [65].

tration of formalin-inactivated vaccines against respiratory syncy-

which is distinct in its pathogenesis, was described after adminis-

(VAED), a phenomenon that may present clinically like ARDS but

2020).

ARDS [64]. In the US VAERS reporting system, 124 events of ARDS

ules, vessel wall inflammation and other signs consistent with

led to ARDS. According to the report, the lung had fibroblastic nod-

Case definition of ARDS as an Adverse Event Following Immunization.

The occurrence of possible vaccine associated enhanced disease
(VAED), a phenomenon that may present clinically like ARDS but

which is distinct in its pathogenesis, was described after adminis-

tration of formalin-inactivated vaccines against respiratory syncy-

tial virus (RSV) in the 1960s, and some measles, pandemic

influenza, and other respiratory virus vaccines [65].

In a recent summary of key findings in non-human primates and

phase I/II studies of the most advanced SARS-CoV-2 vaccine

candidates [66], there was no evidence for COVID-19 enhanced dis-

dease either based on antibody dependent enhancement or on

enhanced infiltration of eosinophils into the lung upon infection

post-immunization. Clinical data have shown acceptable safety

and reactogenicity profiles across different vaccine candidate plat-

forms, production of varying neutralizing antibody titers, and some

vaccine candidates also elicited T-cell responses. However, addi-

tional long-term monitoring of persons exposed to SARS-CoV-2

vaccines is required in pre- and post-licensure stages to determine

the risk of vaccine associated disease enhancement, particularly

once neutralizing antibody titers start to wane [67].

2. Case definition of ARDS

The Working Group evaluated existing definitions of ARDS and
developed a case definition for the assessment of ARDS as a poten-
tial adverse event following any immunization. Within this defini-
tion, a level of diagnostic certainty is ascribed based on the quality
of evidence to support the criteria used to make the diagnosis. The
Level 1 definition is highly specific for ARDS. As maximum speci-
cicity normally implies a loss of sensitivity, we included two addi-
tional diagnostic levels in the definition, offering a stepwise
increase in sensitivity from Level 1 down to Level 3, while retaining
an acceptable specificity at all levels. In addition, the case defini-
tion also allows for characterization of severity as mild, moderate,
or severe based on the degree of hypoxemia. This was included to

Table 5
Case definition of ARDS as an Adverse Event Following Immunization.

| Category      | Adult                                                                 | Pediatric               |
|---------------|-----------------------------------------------------------------------|-------------------------|
| Level 1       | Berlin Definition                                                     | PALICC Definition       |
| Confirmed     | To make diagnosis, must meet ALL of the following criteria:            | To make diagnosis, must meet ALL of the following criteria:         |
|               | 1) Hypoxemia                                                          | 1) Hypoxemia            |
| ARDS          | - P/F Ratio < 300                                                     | - P/F ≤ 300 or S/F ≤ 264 for non-intubated patients                |
|               | 2) Positive Pressure Requirement:                                     | 2) Positive Pressure Requirement:                                   |
|               | 3) - PEEP/CPAP ≥ 5 cmH2                                               | 3) - PEEP/CPAP ≥ 5 cmH2                                           |
|               | 4) Imaging: Chest imaging with bilateral chest opacities not          | 4) Imaging: Chest imaging findings of new infiltrate(s) consistent  |
|               | explained by other process                                            | with acute pulmonary parenchymal disease                            |
|               | 5) Origin of edema: not related to fluid overload or cardiogenic      | 5) Origin of edema: new infiltrate not related to fluid overload or  |
|               | edema                                                                | cardiogenic edema                                                  |
|               | 6) Timing: within 1 week of known clinical insult^                    | 6) Timing: within 1 week of known clinical insult^                  |
| Level 2       | Meet Berlin Definition excluding PPV requirement (#2)                 | Meet PALICC Definition excluding PPV requirement (#2)               |
| Probable      | -AND-                                                                | -AND-                                                               |
| ARDS          | If PaO2 unavailable, then can classify as Level 2a using S/F criteria | If PaO2 unavailable, then can classify as Level 2a using S/F criteria |
|               | -OR-                                                                 | -OR-                                                                |
|               | If CXR/CT unavailable, then can classify as Level 2b using chest US.  | If CXR/CT unavailable, then can classify as Level 2b using chest US. |
| Level 3       | Strong clinical concern1 but CXR, CT, or US not available to meet     | Strong clinical suspicion1 but CXR, CT, or US not available to meet  |
| Suspected     | Berlin Definition                                                     | Berlin Definition                                                  |
|               | - Diagnosis based on clinical exam and assessment                      | - Diagnosis based on clinical exam and assessment                    |
| ARDS          | Clinical suspicion but insufficient data to classify as Level 1–3      | Clinical suspicion but insufficient data to classify as Level 1–3    |
| Level 4       | Clinical suspicion for ARDS                                           | Patients that do not meet above criteria for ARDS but may have      |
| Clinical suspicion for ARDS | Patients that do not meet above criteria for ARDS but may have           | hypoxemia and/or chest imaging findings due to other pathologic     |
| Level 5       | Not a case of ARDS                                                    | process                                                             |

Abbreviations:

P/F ratio = PaO2 to FiO2 ratio (arterial oxygen pressure to inspired fraction of oxygen ratio); S/F ratio = Saturation by pulse oximeter to FiO2 ratio; PEEP = positive end expiratory pressure; CPAP = continuous positive airway pressure; CXR = chest x-ray; CT = chest tomography; US = ultrasound; OI = oxygenation index; OSI = oxygen saturation index.

1 Complexity criteria for ARDS, may vary after vaccination.

2 Severity as defined by S/F: For adults, mild ≤ 315 but > 235, moderate ≤ 235 but > 144, severe S/F ≤ 144. For pediatrics, mild ≤ 264 but > 221, moderate ≤ 221 but > 150, severe S/F ≤ 150.

3 Strong clinical concern as defined in Table 3.
align the case definition with existing definitions for ARDS. However, the three levels of certainty must not be misunderstood as reflecting different groups grades of clinical severity.

While standard definitions of ARDS include consideration for timing between insult and the onset of respiratory findings, our definition does not prescribe a specified time between vaccination and the onset of ARDS, as long as all other criteria for diagnosis are fulfilled. However, a temporal association consistent with the expected clinical course of ARDS would be suggested by a typical interval of one to two weeks between the insult and ARDS. Therefore, when considering the possibility of ARDS as an adverse event following immunization it is unlikely that ARDS would occur months after the exposure. Therefore, in application of this definition, special consideration must be given to how details of this interval are collected and reported.

Similarly, the Working Group decided against using “treatment” or “treatment response” towards fulfillment of the ARDS case definition. A treatment response or its failure is not in itself diagnostic and may depend on variables like clinical status, time to treatment, and other clinical parameters. The case definition is not meant to determine causality, and, therefore, known causes of ARDS should be evaluated (see Table 4).

The case definition is accompanied by guidelines which are structured according to the steps of conducting a clinical trial, i.e., data collection, analysis and presentation (Appendix A). Neither case definition nor guidelines are intended to be used for management of ill infants, children, or adults. Review of the definition with its guidelines is planned on a regular basis and as needed.

3. Rationale for selected decisions about the case definition of ARDS as an adverse event following immunization

3.1. Levels of certainty in the diagnosis of ARDS

Because ARDS is a heterogeneous disease process, diagnostic accuracy under typical circumstances is imperfect [68]. Furthermore, case definitions that require positive pressure or mechanical ventilation, chest imaging, and blood gas analyses pose barriers to diagnosis in resource-limited settings [69]. To address these concerns, the working group developed diagnostic criteria that are stratified according to level of certainty as summarized in Table 5 and Fig. 1. These levels reflect the accuracy of the evidence to support the diagnosis. Levels of certainty include confirmed ARDS (Level 1), probable ARDS (Level 2), and suspected ARDS (Level 3). In addition, Level 4 defines cases with insufficient data to make the diagnosis, and Level 5, cases for which there is sufficient data to attribute ARDS to another cause (i.e., not a case of ARDS).

3.2. Specific levels of certainty

Confirmed cases of ARDS (Level 1) are reserved for patients that meet the criteria set forth by the Berlin Definition for adults and PALICC Definition for pediatrics. These criteria represent the most widely accepted clinical criteria used to diagnose ARDS in adults and children, respectively. While the working group gave consideration to a single set of criteria, evidence supports that this would lead to missed cases [33], and therefore, we developed separate adult and pediatric criteria. Consistent with the standard ARDS definitions which were derived from heterogeneous data sets that used variable age cutoffs, we do not provide guidance on age cutoffs for each.

While the Berlin and PALICC Definitions are the most widely used criteria, there are limitations to each that result in potential missed cases of ARDS [49]. To address this, alternative criteria were reviewed and included to define probable (Level 2) and suspected (Level 3) cases of ARDS. The relevant clinical scenarios are those without access to blood gas analysis, settings without radiographs or computed tomography scans, or patients not supported with positive pressure ventilation (PPV).

For Level 2, or probable ARDS, the relevant considerations are access to arterial blood gas analysis and chest imaging, which are used to subdivide the group into levels 2a and 2b. Level 2a is applicable in settings without access to arterial blood gases and uses an S/F rather than P/F ratio. While the discriminatory power of S/F to predict mortality with mild/moderate cases is inferior to P/F, it is comparable in severe cases [49,70]. Furthermore, it accurately predicts increasing mortality with worsening hypoxemia.

![Fig. 1. Algorithm for the assessment of ARDS using the Brighton Collaboration Case Definition.](3034)
In comparison, Level 2b definition is applicable to clinical settings where chest radiograph or CT scans are unavailable. While typically thought of as an adjunct to routine imaging, chest ultrasound is becoming increasingly common, and has been shown to accurately identify ARDS in both adult and pediatric populations [8,71]. Although data are inconclusive regarding chest ultrasound equivalence to routine imaging, there are sufficient data to merit its inclusion as an alternative imaging modality [72].

Note that for Level 2 cases and below, PPV is not a requirement to meet the case definition for ARDS. Given that high-flow nasal cannula support is becoming increasingly common, especially as an alternative form of non-invasive support for patients with ARDS [73], the working group determined that inclusion of PPV would lead to too many missed cases. This would be especially true in resource-limited settings where access to PPV may be limited.

Lastly, because ARDS is a clinical diagnosis, special designation was given to include suspected ARDS (Level 3). In this category, a clinician would make the diagnosis based on a thorough history, physical examination, and characterization of hypoxemia, and then the clinician would make the assessment on a clinical basis alone (Table 3). This is most relevant in the setting where chest radiograph, CT scan, and ultrasound are unavailable. While it is difficult to estimate the performance of diagnosis based on clinical criteria alone, the working group believes that it is important to include this category while acknowledging the decreased diagnostic certainty, so clinical expertise in limited resource settings is also considered.

3.3. Special clinical scenarios

The diagnosis of ARDS is challenging, especially in patients with pre-existing conditions. For example, patients with cyanotic heart disease or chronic lung disease may meet several criteria for ARDS at baseline. To account for this, the case definition specifies that a patient's clinical presentation must represent an acute change from baseline, which aligns with other criteria for ARDS.

Disclaimer

The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporation).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.01.053.

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