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REVIEW

Ventilator associated pneumonia (VAP) in children: a diagnostic challenge

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Abstract

Respiratory support in critically ill children is crucial and often mechanical ventilation (MV) is needed for lifesaving intervention. MV can lead to complications with, ventilator associated pneumonia (VAP) being one of the most serious and has been associated with prolonged length of mechanical ventilation (LOV) and length of stay in hospital (LOS), morbidity and mortality. Despite the importance of VAP, the definition (both clinically and epidemiologically) is limited. Some of the criteria used for the definition of VAP are subjective. In addition, the use of different diagnostic parameters in VAP definition has resulted in major limitations in terms of surveillance and prevention. Pediatric VAP as well as other pediatric medical conditions are based on a number of different criteria in adult studies. The various challenges and different approaches to defining VAP, especially in children, are obvious in the most recent literature. During the last decade, there has been an attempt to overcome some of these previous challenges and limitations. With this historical context in mind, a new surveillance definition of VAP was proposed for adults in 2013, ventilator-associated events (VAEs). In 2020, the pediatric definition of VAE (pedVAE) was introduced by centers for disease control and prevention (CDC) with adjusted criteria for the pediatric population. One of the clinical definitions, clinical pulmonary infection score (CPIS), has been modified (mCPIS) and adjusted to pediatric VAP. This narrative review describes the different definitions that are currently available for epidemiological as well as clinical purposes. We target to summarize the differences and similarities in all proposed definitions in order to help clinicians and investigators better evaluate this complicated medical condition that presents in their patients.

Keywords

Pediatric ventilator-associated pneumonia (VAP); Pediatric ventilator-associated event (VAE); PedVAE; Ventilator-associated condition (VAC); Diagnostic criteria; PICU

1. Introduction

VAP is identified as one of the most serious complications of MV in critically ill patients who need intensive care. VAP has been associated with increased morbidity, mortality and healthcare costs [1–10]. In the literature, most of the VAP definitions are based on research in adult intensive care unit (ICU) patients in contrast, as pediatric patients are not miniature adults, children as well as neonates often require further classification, because of the differences in terms of underlying physiology and pathology. In neonatal intesnive care unit (NICU), newborns up the age of 1month old are hospitalized and in pediatric intensive care unit (PICU), patients are aged from 1 month to 16 years, and sometimes up to 18 years old or even to 21 years old, according to local policies. There are limited studies addressing pediatric VAP including epidemiological definitions as a method for deriving a common basis for reference, comparison and research in this field, with a view to ultimately improving and implementing appropriate prevention bundles. VAP definition in children is still controversial and new diagnostic algorithms are currently being investigated by different expert centers. Most of the studies conducted in critically ill children and neonates (in PICU and NICU), investigated incidence and prevalence of VAP as part of the epidemiology of healthcare infections. Few studies have focused on risk factors for pediatric VAP [11–13]. The major limitation of these studies is the different VAP definitions used that make their results incomparable [2, 8, 14–19].

Traditional diagnostic algorithms of VAP in adults and children are based on clinical, radiological and microbiological criteria. In 2013, the CDC/NHSN (national healthcare safety network) introduced a new surveillance definition, Ventilator-

associated Event (VAE), which was based on objective criteria focusing on adult patients. In 2016 the term pediatric VAE was introduced in order to include potential diagnostic criteria for this condition in critically ill children and later CDC/NHSN surveillance introduced the term pedVAE for surveillance in pediatric population [20]. However, beyond the CDC, other sites have used different criteria for pedVAEs. In this article we review all currently available definitions of VAP and VAE in children.

2. Pathogenesis and risk factors

The exact mechanism of pathogenesis is not fully clear, especially in infants and children. The role of microbiome and host immune responses have been studied. Micro-aspiration and biofilm formation within the endotracheal tube, the presence of bacteria in inhaled aerosols, translocation of bacteria via the gastrointestinal tract and the rarer bloodstream infections in mechanically ventilated patients all contribute to the pathogenesis of VAP [21, 22]. Risk factors for developing VAP are associated with the duration of mechanical ventilation and medical interventions associated with the respiratory system, *e.g.*, reintubation, endotracheal suctioning, bronchoscopy, thoracocentesis or the presence of different catheters like central line catheters. In addition, some medications have been implicated such as opiates and neuro-muscular blockade and acid suppression medicines. Also, genetic or acquired disorders in the respiratory system as well as transport out of ICU are included in risk factors. Incidence of VAP is understood to be infectious episodes per 1000 ventilator days [3, 6, 7, 20, 23–35].

3. Definitions of VAP and VAEs

Pneumonia is stratified by the CDC utilizing specific criteria that must be met for definitions of PNU1, clinically defined pneumonia, PNU2, pneumonia with specific laboratory findings and PNU3, for immunocompromised patients [20]. VAP is a pneumonia which occurs in a patient who is on MV for >2 consecutive calendar days on the date of event and the ventilator was in place on the date of the event or the day before. The ventilator day count begins with the admission date to the first inpatient location if the ventilator was in place prior to inpatient admission and if MV break occurs for at least one full calendar day, a new count or ventilator association starts upon re-initiation of mechanical ventilation [20].

A Ventilator is a device used to support, assist, or control respiration (weaning period included) delivering positive pressure to the airway through an artificial airway (endotracheal or tracheostomy tube) [20].

There are specific radiological, clinical and microbiological criteria based on CDC guidelines for VAP diagnosis depicted in Tables 1 and 2 [20].

The Great Ormond Street Hospital (GOSH) diagnostic criteria for VAP have been described in 2012 by Brierley *et al.* [14] and defined VAP as pneumonia occurring >48 hours after intubation and using specific CXR findings and at least 3 clinical or laboratory findings (Table 3).

Another term that has been used in the literature is "ventilator associated respiratory infections (VARIs)" which include VAP but also ventilator associated tracheobronchitis (VAT). VAT is another infectious complication of the lower respiratory system in patients on invasive MV when there are no radiologic criteria for pneumonia, whereas there is strong clinical likelihood of infection of the lower respiratory system with clinical signs and symptoms and purulent sputum and positive endotracheal aspirate culture [36–39]. The terms "*early- and late- onset VAP*" have been used in literature as opposed to intubation associated pneumonia (IAP) [40, 41]. IAP occurs in children who fulfill VAP criteria but within 48 hours of intubation and is due to peri-intubation aspiration of contaminated fluids. The time of appearance of VAP defines early-onset VAP which occurs within the first 4 days of intubation and late-onset VAP which occurs after 5 days of intubation. The bacteria that are associated with early-onset VAP are usually antimicrobial susceptible bacteria while late-onset VAP is caused by multi-resistant microorganisms [42].

In 1991, Pugin *et al.* [43] developed the clinical pulmonary infection score (CPIS) as a diagnostic tool for clinical purposes. This score contains six variables (temperature, WBC, tracheal aspiration, oxygenation, pulmonary radiography, semi-quantitative tracheal aspirate culture) and each of them gives 0–2 points, with a maximum summary score of 12. Originally the authors suggest a CPIS ≥6 to have 93% sensitivity and 100% specificity for the diagnosis of VAP. Modified CPIS (mCPIS) without the tracheal aspirate culture, were used because of the unavailability of culture results at the time of initial assessment of patients. The mCPIS has a maximum score of 10 points and sensitivity and specificity for VAP diagnosis were found to be as low as 60% and 43%, respectively [43–48]. This score was initially used with adults in ICU but there are studies that have used CPIS adjusted for children in PICU. An example of a mCPIS in children is showed in Table 4 [46, 49].

Additionally, modified CPIS are suggested for the pediatric population with differences between infants <12 months and children 1–12 years old [46, 50]. Fine tuning of the clinical criteria have resulted in differences for oxygenation [4, 51, 52]. Automatic calculators may facilitate the physician in entering data as the parameters and CPIS score is automatically produced [53]. In 2019 the PICU from the University Hospital of Leicester (UHL), in collaboration with the National Health Service (NHS) Trust published the diagnostic VAP algorithm with customized criteria for infants and children. These are described in Table 5 [23].

The subjectivity of clinical, laboratory and radiological criteria for the diagnosis of VAP results in limited diagnostic value, including specificity and sensitivity [54–57]. Additionally, differences in surveillance methods introduce variability in reporting incidence of VAP. In 2013 a CDC/NHSN working group introduced the VAE surveillance definition algorithm initially only for adults based on objective, automatable criteria which were repeatable with different physicians. Since 2013 some modifications, with the last update in 2022, have been made and have driven to 3 different medical conditions included in the VAE algorithm for adults and described in Table 6 [58]:

TABLE 1. Radiological and clinical criteria for VAP diagnosis by CDC (adapted from reference 20).

PNU 1 (radiological + clinical + laboratory)			
Age	<1 year	1–12 years	Any age
Condition	>2 days on invasive MV	>2 days on invasive MV	>2 days on invasive MV
	≥2 serial (or 1 if no cardiac or pulmonary disease)	≥2 serial (or 1 if no cardiac or pulmonary disease)	≥2 serial (or 1 if no cardiac or pulmonary disease)
	CXRs:	CXRs:	CXRs:
Radiological criteria			
	● Infiltrate	● Infiltrate	● Infiltrate
	● Consolidation	● Consolidation	● Consolidation
	● Cavitation	● Cavitation	● Cavitation
	● Pneumatocele		
Clinical criteria			
	Deterioration of gas exchange[a] AND ≥3 of 7	Presence of ≥3 of 6:	T °C > 38 °C OR WBC disorders AND 3 of 4
	(1) Unstable temperature (T °C)	(1) Deterioration of gas exchange[a]	(1) Deterioration of gas exchange[a]
	(2) WBC ≤4000 or ≥15,000 WBC/mm^3 or left shift ≥10%	(2) T °C > 38 °C or <36 °C	(2) Character of sputum or secretions[b]
	(3) Character of sputum or secretions[b]	(3) WBC ≤4000/mm^3 or ≥15,000/mm^3	(3) New onset or worsening cough, or dyspnea, or tachypnea[c]
	(4) Apnea, tachypnea[c], nasal flaring with retraction of chest wall or nasal flaring with grunting	(4) Character of sputum or secretions[b]	(4) Rales/crackles or bronchial breath sounds
	(5) Wheezing, rales/crackles or rhonchi	(5) New onset or worsening cough or dyspnea or apnea or tachypnea[c]	For immunocompromised patients[c] at least one of the above or Hemoptysis or Pleuritic pain
	(6) Cough	(6) Rales/crackles or bronchial sounds	
	(7) Bradycardia (<100 beats/min) or tachycardia (>170 beats/min)		

VAP: Ventilator Associated Pneumonia; CDC: Centers for Disease Control and Prevention; PNU: Pneumonia; MV: mechanical ventilation; CXRs: chest X-rays; FiO_2: Fraction inspired Oxygen. [a]Deterioration of gas exchange: either O_2 desaturations or increased requirements of FiO_2 or other respiratory support requirements on ventilator; [b]Outset of purulent respiratory secretions or deterioration in quantity or quality of respiratory secretions or increased suctioning requirements with purulent respiratory secretions containing ≥25 neutrophils and ≤10 squamous epithelial cells per low power field (×100); [c]Tachypnea: based on age (for prematures born <37 gestation weeks and until 40th week is >75 breaths per minute, for <2 months old is >60 breaths per minute, for 2–12 months old is >50 breaths per minute, for >1 year old is >30 breaths per minute); [c]immunocompromised patients defined by (1) neutropenia (absolute neutrophil count or WBC <500/mm^3); (2) leukemia, lymphoma, or HIV (+) with CD4 <200; (3) splenectomy; (4) history of solid organ or hematopoietic stem cell transplant; (5) on chemotherapy with cytotoxic agents; (6) on medication with enteral or parenteral steroids (not inhaled and topical) daily for >14 days on the date of event; WBC: White Blood Cells; T °C: Body Temperature.

TABLE 2. Microbiological evidence of VAP by CDC (adapted from reference 20).

CDC	Common bacterial or filamentous fungi	Virus, Legionella and others
Laboratory findings (any ages)		
PNU2 (PNU1 + 1 lab criterion)		
	≥1 of	≥1 of
	(1) Found in blood	
	(2) Found in pleural fluid	
	(3) Positivation of quantitative or semi-quantitative culture from minimally-contaminated LRT specimen	(1) Presence of Virus, Bordetella, Legionellla, Chlamydia, or Mycoplasma in culture or non-culture exams of respiratory secretions or tissue, performed for diagnosis or treatment purposes (for example, not ASC/AST)
	(4) Direct microscopic exam (like Gram's strain) identifies ≥5% BAL cells with intracellular bacteria	(2) Serological fourfold increase in paired sera (IgG) for pathogen (like influenza viruses, Chlamydia)
	(5) Positive quantitative culture or corresponding semi-quantitative culture result of lung tissue	(3) Indirect IFA identify fourfold increase in Legionella pneumophila serogroup 1 antibody titer to ≥1:128 between acute and convalescent phase
	(6) Pneumonia evidence in histopathologic examination like: -Presence of abscess or foci of consolidation with intense PMN accumulation in bronchioles and alveoli -Fungal infection evidence in lung parenchyma (hyphae or pseudohyphae)	(4) Legionella pneumophila serogroup 1 antigen found in urine by RIA or EIA
Alternative laboratory criteria for immunocompromised patients (*PNU3*):		
	≥1 of	
-neutropenia (absolute neutrophil count or WBC <500/mm^3	(1) Candida spp. In blood PLUS 1: sputum, endotracheal aspirate, BAL or protected specimen brushing	
-leukemia, lymphoma,	(2) Fungi presence (excluding any Candida and yeast not otherwise specified) from minimally-contaminated LRT specimen (specifically BAL, protected specimen brushing or endotracheal aspirate) from one of the following:	
OR	● Direct microscopic exam ● Positive culture of fungi	
-HIV (+) with CD4 <200		
-splenectomy		
-history of solid organ or		
-hematopoietic stem cell transplant		
-on chemotherapy	Non-culture diagnostic laboratory test	
-on enteral or parenteral steroids (not inhaled and topical) daily for >14 days on the date of event		

VAP: Ventilator Associated Pneumonia; CDC: Centers for Disease Control and Prevention; PNU: Pneumonia; WBC: White Blood Cells; HIV: Human Immunodeficiency Virus; CD4: Cluster of differentiation 4. Diagnosis of VAP cannot be based on following detected bacteria: a. "Normal respiratory flora," "normal oral flora," "mixed respiratory flora," "mixed oral flora," "altered oral flora" or other commensal bacteria of URT and b. Following organisms, can be used to define VAP only if identified in lung tissue specimen or pleural fluid specimen (that was collected during thoracentesis or within 24 hours of chest tube placement, otherwise pleural fluid is not eligible): i. Any Candida species as well as a report of "yeast" that is not otherwise specified ii. Any coagulase-negative Staphylococcus species iii. Any Enterococcus species. As for SBSI to pneumonia due to the above pathogens, can met the definition if a matching organism is detected in the above specimen collected as described and in blood collected within the SBSI Attribution Period. Especially for Candida species or yeast not otherwise specified detected in blood SBSI to VAP can be attributed if VAP is identified using the blood and a sputum, endotracheal aspirate, bronchoalveolar lavage (BAL), or protected specimen brushing with matching Candida species and both specimens have a collection date in the Interval Window Period. Blastomyces, Histoplasma, Coccidioides, Paracoccidioides, Cryptococcus, and Pneumocystis are also excluded. Culture specimens threshold to diagnose pneumonia are as follows: (a) Lung tissue ≥10^4 CFU/g tissue (colony forming units/grams of tissue), (b) Bronchoalveolar lavage (BAL) ≥10^4 CFU/mL, for both bronchoscopically and nonbronchoscopically obtained specimens , (c) PSB ≥10^3 CFU/mL , both bronchoscopically and nonbronchoscopically obtained specimens, (d) ETA ≥10^5 CFU/mL, LRT: Lower Respiratory Tract, PMN: Polymorphonuclear Leukocyte, ASC/AST: Active Surveillance Culture/Testing , IgG: Immunoglobulin G, IFA: Immunofluorescence, BAL: Bronchoalveolar Lavage, URT: Upper Respiratory Tract, SBSI: Secondary blood stream infection, PSP: Protected specimen brushing, ETA: Endotracheal aspirate.

TABLE 3. GOSH diagnostic criteria for VAP (adapted from reference 14).

GOSH diagnostic criteria (all ages) for VAP (Radiological + clinical or laboratory)		
Condition	≥ 48 hours after intubation and initiation of MV	
Radiological		
	In ≥2 serial chest X-rays with:	
	New or progressive pulmonary	
	• infiltrates	
	• consolidation or	
	• cavitation	
	• pneumatoceles for infants ≤1 year old	
	with gradual resolution (rapid resolution suggests non-infective causes)	
Patient related factors	Non-immunocompromised children	Immunocompromised children
Clinical /laboratory		
	3 of 5	2 of 5 (as leucopenia/leukocytosis is unreliable in these patients)
	(1) New/worsening purulent bronchial secretions	
	(2) Core temperature ≥38.5 °C or <36 °C (no other recognized cause)	
	(3) Leucopenia or leukocytosis (by age)	
	• 0 day–1 week	>34 $\times 10^9$/L
	• 1 week–1 month	>19.5 or <5 $\times 10^9$/L
	• 1month–1 year	>17.5 or <5 $\times 10^9$/L
	• 2–5 years	>15.5 or <6 $\times 10^9$/L
	• 6–12 years	>13.5 or <4.5 $\times 10^9$/L
	• 13 to 18 years	>11 or <4.5$\times 10^9$/L
	(4) Significant positive culture from respiratory secretions (endotracheal secretions or BAL with semi- quantitative cultures). (5) Relevant culture from alternative site of infection (positive blood cultures of likely respiratory tract pathogens, unrelated to other source of infection, significant cultures of pleural fluid, lung parenchyma biopsy, or pathogens detected by validated immunofluorescence)	

GOSH: Great Ormond Street Hospital; VAP: Ventilator Associated Pneumonia; MV: Mechanical Ventilation; BAL: Bronchoalveolar Lavage. Immunocompromised children were the patients with any of: Neutropenia (count <1.0 × 10^9/L), HIV, chemotherapy, leukemia/lymphoma/post marrow transplant, post splenectomy, immunosuppressive drugs (long term steroids, any dose >7 days), azathioprine, ciclosporin, mycophenolate mofetil, tacrolimus, methotrexate, anti-TNF.

TABLE 4. Modified Clinical Pulmonary Infection Score (mCPIS) for children (adapted from reference 49).

Variable	CPIS
Temperature (°C)	
36.5–38.4	0
38.5–39	1
<36 or >39	2
Leukocyte count ($\times 10^9$/L)	
4.0–11	0
≤3.9 or ≥11.1 and absence of band forms or ≥11.1 to 17.0 if no differentiation done	1
≥11.1 with band forms on differentiation or ≥17.1 if no differentiation done	2
Chest radiography	
No chest radiography taken or no infiltrate	0
Diffuse or patchy infiltrate	1
Localized infiltrate	2
Pulmonary secretions	
Absent or minimal	0
Present and nonpurulent	1
Present and purulent	2
PaO_2/FiO_2 (mm Hg)	
240 or ARDS	0
≤240 and no evidence of ARDS	2
Culture of nonbronchoscopic BAL	
Negative or not done	0
Positive	2

PaO_2: arterial partial pressure of oxygen; FiO_2: Fraction of inspired Oxygen; ARDS: Acute respiratory distress syndrome; BAL: bronchoalveolar lavage.

In mechanically ventilated patients various complications may occur (VAP included). The VAE Surveillance Algorithm is expected to contribute to better management of these complications [59, 60]. This VAE definition is not clinical in nature or used for clinical management of patients. In addition to Pneumonia, atelectasis, ARDS, hemorrhage and pulmonary oedema are frequent causes of VACs [58, 61, 62]. The objective criteria used for VAE diagnosis are deterioration of respiratory status after a period of stability or improvement on the ventilator, evidence of infection or inflammation and laboratory evidence of respiratory infection. Based on the definition of VAE, the earliest day of VAE is day 3 on MV [58]. Infection related VAC (IVAC) plus was used to determine all the events that met at least the IVAC criteria but still no Possible VAP (PVAP) criteria were met. In studies new rates were introduced as:

- Overall, VAE rate meaning all the events meeting at least the VAC definition per 1000 ventilation days.
- IVAC plus rate meaning all the events meeting at least the IVAC definition per 1000 ventilation days.

The EUVAE study (an international, multicenter cohort study, to assess the predictive accuracy for outcomes of VAEs defined by CDC) was published in 2018 and concluded that in adult patients on MV, most IVAC plus cases were due to atelectasis. Most significantly, it is reported that VAE algorithm identifying severe oxygenation deterioration of patients could miss a quarter of VAP cases and three quarters of VAT episodes [36, 58, 63]. The VAE algorithm has been extensively studied and applied mainly in adult patients. In the absence of a VAE definition tailored for children and the urgent need to improve outcomes in critically ill ventilated pediatric patients, the adult VAE algorithm has been uncritically applied to this population. In 2012, an attempt by the CDC with a Pediatric and Neonatal Ventilator Associated Event Working Group to develop the feasibility of VAE surveillance definitions for pediatric population was unsuccessful. The need to have an efficient metric customized for children was obvious for clinicians who require a metric to reflect the true quality of care; this is to measure and strengthen the efforts of quality improvement by using clinically relevant measurements. In 2016 and 2017 a pediatric approach to VAE surveillance was published by Cocoros *et al.* [64, 65]. In this study there is a suggestion of using the CDC terms of VAEs algorithm but with diagnostic criteria customized for pediatric patients in PICUs, NICUs and CICUs. There was an attempt to develop an objective surveillance metric that corresponds to meaningful patient outcomes. This group suggested mean airway pressure (MAP) values instead of positive end expiratory pressure (PEEP) values which are set by clinicians. MAP is the mean pressure exerted on the airway during the inspiration cycle and is determined by PEEP, peak inspiratory pressure (PIP), inspiration time and other parameters like flow or frequency and it reflects more accurately changes in lung compliance which is depleted in VAC accompanying reduced oxygenation. MAP criterion enables the surveillance definition to include patients on HFV, which are more commonly used in PICU and NICU compared to the adult population. They considered 12 different thresholds of MAP and FiO_2 value and found, as expected, different rates of VACs per 1000 ventilator days. Additionally, changes in FiO_2 threshold seemed to have significantly greater impact on rates in the CICUs than MAP, while changes in MAP threshold had greater impact on VAC rates in PICUs and NICUs. LOV, extubation, ICU LOS, ICU discharge, hospital mortality and

TABLE 5. UHL (NHS) diagnostic criteria for VAP in children (adapted from reference 23).

Condition	Patient current or within 48 hours of disconnection of MV (via ETT or tracheotomy)	
Age	<1 year	>1 year
Clinical criteria		
	Deterioration of gas exchange (*e.g.*, desaturation, increase FiO_2 requirements by ≥10% or increase ventilation support)	3 of 5
	PLUS	
	3 of 5	
	1. T °C > 38.5 °C or <36 °C	1. Deterioration of gas exchange (*e.g.*, desaturation, increase FiO_2 requirements by ≥10% or increase ventilation support)
	2. Leucopenia or leukocytosis defined by age	2. T °C > 38.5 °C or <36 °C
	3. New or increased purulent secretions	3. Leucopenia or leukocytosis defined by age
	4. New or increased respiratory distress, tachypnoea, or apneas	4. New or increased purulent secretions5. New or increased respiratory distress, tachypnoea, or apneas
	5. Tachycardia (>170 beats/min) or bradycardia <100 beats/min)	
Radiological criteria		
	≥1 CXRs with at least 1 of:	≥1 CXRs with at least 1 of:
	• New/progressive pulmonary infiltrates	• New/progressive pulmonary infiltrates
	• Consolidation	• Consolidation
	• Cavitation	• Cavitation
	• Pneumatoceles	If patient has pulmonary or cardiac disease ≥2 CXRs are needed
	If patient has pulmonary or cardiac disease ≥2 CXRs are needed	
Laboratory criteria[a] (differentiate VAP clinically defined by VAP with specific laboratory finding)		
	-Positive Laboratory Confirmed-Blood Stream Infection (LC-BSI) not related to another source of infection	
	-Positive pleural fluid culture	
	-Positive BAL ≥10^4 cfu/mL	
	-Pleural or pulmonary abscess with positive culture collected by needle aspiration	
	-Lung biopsy showing histological evidence of pneumonia or positive on culture	
	-Positive exams with virus or particular micro-organisms (Legionella, Aspergillus, Mycobacteria, mycoplasma, Pneumonocystis carinii):	
	○ Presence of viral antigen or PCR from respiratory secretions	
	○ Presence of virus in culture or visualization by immunofluorescence from bronchial secretions or tissue	
	○ four-fold increase in paired sera (IgG) (*e.g.*, influenza viruses, Legionella, Chlamydia)	
	○ detection of antigens in urine (Legionella)	
	If immunocompromised (including steroids >2 weeks):	
	-Matching positive blood & sputum cultures with Candida spp	
	-BAL evidence of fungi or Pneumocystis carinii (microscopy or culture)	

[a]*see to references of Table 2. UHL: University Hospital of Leicester; NHS: National Health Service; FiO_2: Fraction of inspired Oxygen; CXRs: Chest X-rays; VAP: ventilator associated pneumonia; BAL: bronchoalveolar lavage; PCR: Polymerase Chain Reaction.*

TABLE 6. Ventilator Associated Events tier for adults by CDC (adapted from reference 58).

Ventilator-Associated Condition(s) (VAC(s)), describing deterioration on ventilator after a period of stability or improvement	After ≥2 calendar days of stable or decreasing daily minimum FiO_2 or PEEP values: (a) Increase in daily minimum FiO_2 of ≥0.20 over the daily minimum FiO_2 of the first day in the baseline period, sustained for ≥2 calendar days. OR (b) Increase in daily minimum PEEP values of ≥3 cmH_2O over the daily minimum PEEP of the first day in the baseline period, sustained for ≥2 calendar days, (daily minimum PEEP values of 0–5 cmH_2O are considered equivalent for the purposes of VAE surveillance).
Infection-related VACs (IVACs), describing the VACs caused by infection	VAC criteria PLUS ● Temperature >38 °C or <36 °C, OR ● WBC ≥12,000 cells/mm^3 or ≤4000 cells/mm^3 AND ● A new antimicrobial agent(s) is started and is continued for ≥4 qualifying antimicrobial days within 2 days of the day of VAE.
Possible VAP(s) (PVAP(s)), describing VACs caused by pneumonia with laboratory criteria, (after 2015 update possible and probable VAP are named as pVAP).	IVAC criteria PLUS within 2 calendar days before or after the onset of deterioration of oxygenation, ONE of the following criteria is met: Criterion 1: Even without purulent respiratory secretions, one of the following cultures: ● ETA ≥10^5 CFU/mL or corresponding semi-quantitative result ● BAL ≥10^4 CFU/mL or corresponding semi-quantitative result ● Lung tissue ≥10^4 CFU/g or corresponding semi-quantitative result ● Protected specimen brush ≥10^3 CFU/mL or corresponding semi- quantitative result Criterion 2: Purulent respiratory secretions (defined as secretions from the lungs, bronchi, or trachea that contain ≥25 neutrophils and ≤10 squamous epithelial cells per low power field (lpf, ×100)) PLUS organism identified from one of the following specimens (qualitative or quantitative/semi-quantitative culture without sufficient growth to meet Criterion 1): ● Sputum ● Endotracheal aspirate ● Bronchoalveolar lavage ● Lung tissue ● Protected specimen brush Criterion 3: One of the following positive tests: ● Pathogens identified from pleural fluid collected only during thoracentesis or within 24 hours of chest tube placement (otherwise not eligible for PVAP) ● Lung histopathology defined as ○ Abscess or foci of consolidation with intense neutrophil accumulation in bronchioles and alveoli ○ Fungi infection evidence of lung parenchyma (hyphae, pseudohyphae, or yeast forms) ○ Viral infection evidence of the following viral pathogens (immunohistochemical assays, cytology, or microscopy performed on lung tissue) ○ Diagnostic test for Legionella species ○ Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus.

CDC: Centers for Disease Control and Prevention, FiO_2: Fraction of inspired Oxygen, PEEP: Possitive End-Expiratory Pressure, VAE: Ventilator Associated Event, VAC: Ventilator Associated Condition, IVAC: Infection related VAC, ETA: Endotracheal aspirate, BAL: Bronchoalveolar lavage, PVAP: Possible VAP.

hospital discharge to home, were studied and it was found that VAC events were associated with worse results. Again, the issue of one single pediatric VAC definition was arising and this time they proposed identification of VACs in these specific population using the FiO_2 0.25/MAP 4 definition as follows [65]:

FiO_2 0.25/MAP 4 definition of VAC by Cocoros *et al* [65]:

• an increase in daily minimum MAP by $\geq$4 cmH_2O.

OR

• an increase in daily minimum FiO_2 by $\geq$0.25 for $\geq$2 days following at least 2 days of stable or decreasing daily minimum MAP or FiO_2.

In another study there was an attempt to identify the reliability of application of the adult IVAC and PVAP criteria to patients with VAC in NICU and PICU [64]. In this study the VACs events were identified by the above proposed definition. For IVAC definition two different thresholds were used, temperature and WBC (the adult criteria and alternative thresholds), on day 3 of ventilation within 2 days before or after pediatric VAC onset. For PVAP definition they applied the same with the adult PVAP definition: a positive culture from respiratory specimen, purulent respiratory secretions plus a positive culture from respiratory specimen or pleural culture, lung histopathology or a diagnostic test for specific organisms. They also included in the study the requirement for new antimicrobial use for the VAC events. In this study it was obvious that when the metric of antibiotic use was met alone, results were nearly identical to the ones when both metric of abnormal temperature and WBC count were met (no matter which of the above thresholds were used). So, the authors proceeded to formulate the term pediatric AVAC for pediatric VAC with antimicrobial use instead of IVAC and separating it from the term pediatric Possible VAP which requires evidence of potentially pathogenic organisms via culture or other respiratory diagnostic tests. They observed that abnormal temperature and WBC count were associated with almost all pediatric VAC cases in PICU and CICU while in NICU these measurements are not evaluable for discrimination of infectious causes of pediatric VAC (as usually these values are associated with other interventions, for example thermoregulation in premature neonates). So, the proposed pediatric AVAC surveillance could be suggested as potential a better metric tool for monitoring antibiotic use in respiratory deteriorated pediatric population [64].

In recent years studies have been published about the different threshold of values used as criteria for the definition of pedVAE, [4, 17, 57, 61, 66–69]. Beardsley in 2016 suggested a VAE variation using PEEP value of at least 2 cmH_2O instead of 3 cmH_2O and Cirulis *et al.* [71] in 2016 suggested the same minimum daily PEEP value but sustained for at least 1 calendar day as follows [70, 71].

Definition of pedVAE by Cirulis *et al* [71]:

• an increase in daily PEEP by $\geq$2 cmH_2O.

OR

• an increase in daily minimum FiO_2 by $\geq$0.2 for $\geq$1 days following at least 2 days of stable or decreasing daily minimum PEEP or FiO_2.

In 2017, experts on VAE supported another variation in addition to the above for the definition of pedVAE, even less restrictive with pedVAC, pedIVAC-plus and pedPVAP included in the algorithm as described in Table 7 [72].

The difference between cases where VAE criteria were met and the VAP cases found by pediatric clinicians is remarkable in the literature. Although the VAEs tier is not a clinical diagnosis, it is helpful in further management of antibiotics. It is more obvious than ever that it is important and essential to find and establish a gold standard diagnostic tool with clearly objective and repetitive criteria for diagnosis and appropriate decision-making regarding management of antibiotic use in the pediatric population [4, 5, 73–77]. A distinction between infectious VARIs, (VAP and VAT included) and non-infectious VAEs is useful and should be clear so as to prevent the inappropriate administration of antibiotics [78–81]. This issue of both infective and noninfective events included in the VAE surveillance as is redefined by the CDC is challenging. The VARIs have diagnostic criteria that are more user-friendly and helpful for physicians at the time they need the diagnosis of VAT and VAP. On the other hand, VAE surveillance criteria seem to correlate with clinical outcomes, have good external comparability, are better for the diagnosis of non-infective events, are better for surveillance needs and are more objective as a good quality indicator. The subjectivity of interpretation of chest radiography have redirected on using more objective metrics like FiO_2, PEEP and MAP for respiratory deterioration However, although non-infectious respiratory complications (ARDS, fluid overload, atelectasis, pulmonary oedema, pulmonary embolism) may lead to misinterpretation of the findings on chest X-rays, the likelihood of having VAP without radiological findings is low [16, 18, 36, 82, 83].

In 2021 and 2022 CDC adopted the VAC definition of FiO_2 0.25/MAP 4 as described above and updated the pedVAE algorithm that is described in Table 8 [84].

If day 1 is the date of event (onset of oxygenation deterioration), then a new PedVAE cannot be recorded within 14 day-period [84]. But no further guidelines for IVAC or PVAP in children are published by CDC so far. The application of VAE algorithms using different criteria and different terms for the recognition of VARIs is mainly implemented and studied in ICUs but also in PICUs. Results are controversial and of course there is a need for the new parameters to be weighted in populations and subpopulations [3, 36, 64, 85–89]. Late studies have tried to review and analyze all the data on VAP and VAEs in children and neonates as in adults using clinical, radiological, laboratory findings concluding that a diagnostic gold standard is important but still wanting [2, 36, 63, 72, 82, 90–105]. To the direction of using the same language and having comparable VAEs analysis reports, in the field of research and surveillance, CDC recommends the use of the following terms of pedVAE measures [65, 84, 95]:

• pedVAE rates (ventilator days) as the ratio of the number of pedVAEs for a location to the number of ventilator days for a location by 1000.

• pedVAE rates Episodes for Mechanical Ventilation (EMV) as the ratio of the number of pedVAEs for a location to the number of EMV for a location by 100.

• DUR (Device Utilization Ratio) as the ratio of the ventilator days for a location to the patient days for the location.

TABLE 7. PedVAE tier for children by Peña-López *et al.* [72] (adapted from reference 72).

Definition of pedVAE by Peña-López *et al.* [72]:
pedVAE
After ≥2 calendar days of stable or decreasing daily minimum FiO_2 or PEEP
values:
• an increase in daily minimum FiO_2 by ≥0.2 or PEEP by ≥ 2 cmH_2O
OR
• an increase in daily minimum FiO_2 by ≥0.15 AND PEEP by ≥1 cmH_2O for ≥1 days following at least 2 days of stable or decreasing daily PEEP or FiO_2
ped-IVAC plus
IF this criterion is not met then it is pedVAC
pedVAE criteria PLUS the suspicion of infection AND a new antimicrobial agent(s) has been started and sustained for ≥4days
ped-PVAP
IF these criteria are not met then it is Ped-IVAC
Ped-IVAC plus criteria
PLUS
1 of 3:
1. Significative growth of respiratory pathogen in cultures
2. Insufficient growth of a pathogenic microorganism PLUS purulent sputum
3. Evidence of lung infection

PedVAE: pediatric definition of VAE; PEEP: positive end-expiratory pressure; FiO_2: Fraction of inspired Oxygen; VAC: Ventilator Associated Condition; IVAC: Infection related VAC; PVAP: Possible VAP.

TABLE 8. pedVAE algorithm CDC (adapted from reference 84).

PedVAE algorithm CDC
Condition
Baseline period of ≥2 calendar days of stable or decreasing daily minimum FiO_2 (the lowest value of FiO_2 documented during the calendar day that maintained for >1 hour) or MAP[a] values (the lowest value documented during the calendar day). Baseline period is defined as the 2 calendar days immediately preceding the first day of increased daily minimum MAP[a] or FiO_2
Criteria (indicators of worsening oxygenation)
1 of 2
1. Increase in daily minimum FiO_2 of ≥0.25 (25 points) over the daily minimum FiO_2 of the first day in the baseline period, sustained for ≥2 calendar days.
2. Increase in daily minimum MAP[a] values of ≥4 cmH_2O over the daily minimum MAP of the first day in the baseline period, sustained for ≥2 calendar days

[a] As MAP values of 0–8cmH_2O and 0–10cmH_2O for ages <30 days old, and ≥30 days old, respectively are considered equivalent, daily MAP value rise to at least 12 and 14 cmH_2O respectively, sustained for 2 calendar days are needed to meet the PedVAE definition. PedVAE: the pediatric definition of VAE; CDC: centers for disease control and prevention; FiO_2: Fraction of inspired Oxygen; MAP: mean airway pressure.

4. Conclusion

Despite the high incidence of VAP and its association to high morbidity and mortality, there is no gold standard for VAP definition in children. Both traditional and newer diagnostic algorithms have been used in children including special subgroups of populations. The value of diagnosis of VAP is essential for preventive strategies, treatment guidance and judicious use of antimicrobials. To prevent it we first need to define it clearly with proper tools driven by proper measurements that can lead the supervision of bundles of care against occurrence of VAP. The attempt to clarify the scope of VAP in PICUs is important. On one hand, the onset of antimicrobial prescription in a case of infective condition is crucial but on the other hand, the inappropriate use of antibiotics where they are not needed also increases mortality. The new definitions of pedVAEs may increase sensitivity and specificity of detecting infective and non-infective causes leading to clinical deterioration of the pediatric patient and increased respiratory support in the ventilator. New studies are expected to finetune these definitions and the impacts are waiting to be shown.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

SK—designed the research study, wrote original draft, reviewed and edited; AV—designed the research study, reviewed and edited; EI—reviewed, edited and corrected English; PEM—reviewed and edited; EK—reviewed and edited; NK—reviewed and edited; MS—supervised and reviewed; all authors contributed to editorial changes, read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Asimina Violaki and Maria Sdougka are serving as the Guest editors of this journal. We declare that Asimina Violaki and Maria Sdougka had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to SG.

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