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Original Article

Ventilator-associated events in children: A multicentre prospective cohort study

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ABSTRACT

Background: The Centres for Disease Control and Prevention (CDC) broadened the focus of surveillance from ventilator-associated pneumonia to ventilator-associated event (VAE) for quality purposes. No paediatric definition of VAE (PaedVAE) has been accurately validated. We aimed to analyse the incidence and impact on patient outcomes resulting from the application of the adult and two paediatric VAE (PaedVAE) criteria. Secondary objective: to evaluate VAE/PaedVAE as factors associated with increased duration of mechanical ventilation (MV) and Paediatric Intensive Care Unit (PICU) stay.
Methods: Multicentre observational prospective cohort study in 15 PICUs in Spain. VAEs were assessed using the 2013/2015 CDC classification. PaedVAE were assessed using the CDC definition based on mean airway pressure (MAP-PaedVAE) *versus* a paediatric definition based on positive end-expiratory pressure (PEEP-PaedVAE). Children who underwent MV $\geq$ 48 h were included.

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Results: A total of 3626 ventilator-days in 391 patients were analysed. The incidence of VAE, MAP-PaedVAE and PEEP-PaedVAE was 8.55, 5.24 and 20.96 per 1000 ventilator-days, respectively. The median time [IQR] for VAE, MAP-PaedVAE and PEEP-PaedVAE development from the MV onset was 4 [3–12.5], 4 [3–14], and 5 [3–7.75] days, respectively. Among survivors, all three were associated with increased MV duration (> 7 days) and PICU stay (> 10 days) at univariate analysis. Multivariate analysis showed that PEEP-PaedVAE was the only definition independently associated with MV above 7 days [OR = 4.86, 95% CI (2.41–10.11)] and PICU stay [OR = 3.49, 95% CI (1.68–7.80)] above ten days, respectively.
Conclusions: A VAE definition based on slight PEEP increases should be preferred for VAE surveillance in children.

1. Introduction

In 2013, the US Centers for Disease Control and Prevention (CDC) replaced surveillance definitions from ventilator-associated pneumonia (VAP) towards a broader concept of preventable conditions related to mechanical ventilation (ventilator-associated events: VAE) [1]. Previously, the use of specific care bundles to control infection in the intensive care unit (ICU) had demonstrated to be effective, but the lack of a gold standard definition for VAP, the difficulty in the classification of ventilator-associated respiratory infections, and the emergence of ventilator-associated tracheobronchitis as an independent source of morbidity, questioned zero VAP rates as an ICU quality indicator [2]. When shifting from VAP to VAE, the aim of the CDC was to increase the impact on outcomes and broaden the spectrum of complications related to mechanical ventilation for surveillance and preventive purposes [3]. It focused on respiratory worsening and removed subjective items from the algorithm. In Europe, a prospective multicentre study assessing VAEs and both respiratory infections (VAP and also ventilator-associated tracheobronchitis, often ignored in other studies) found that VAEs were associated with increased mortality, more days of mechanical ventilation, and greater hospital length of stay (LOS) than traditional CDC criteria, in line with the results of the meta-analysis performed by Fan et al. and other studies [4,5]. Currently, ventilatory bundles and preventive measures are turning on VAE [6,7].

The VAE surveillance definition algorithm implemented by the US National Healthcare Safety Network was initially available for only adult patients [1]. Shortly after, retrospective paediatric studies were conducted evaluating the application of VAE and it was noticed that the use of these new criteria in children would require an adaptation of the VAE definition in accordance with the peculiarities of the paediatric population [8–11]. The definition of paediatric VAE (PaedVAE) adopted by the US-CDC for children in 2017 emerged from a consensus of experts based on a retrospective study and a matched cohort analysis [12]. As the main items of the definition, they advocated for the use of mean airway pressure (MAP) instead of PEEP setting (MAP-PaedVAE) and a higher increase in the fraction of inspired oxygen (0.25 instead of 0.20). Concurrently, our group reported a paediatric VAE definition based on PEEP (PEEP-PaedVAE) that supported the use of slighter increases in PEEP/FiO_2 to make it less restrictive while maintaining its impact on outcomes [13] (Fig. 1). An update for adults has been released by January 2021 [14].

The aim of this study was to compare adult VAE criteria and both paediatric VAE definitions (MAP-PaedVAE and PEEP-PaedVAE) in terms of incidence and clinical outcomes. Our hypothesis was that PEEP-PaedVAE definition is the most sensitive while retaining the ability to discriminate episodes of mechanical ventilation with worse outcomes. The use of this less restrictive definition for surveillance might broaden the target population that could benefit from the application of preventive measures. Our secondary objective was to evaluate VAE/PaedVAE as variables associated with increased mechanical ventilation and duration of Paediatric Intensive Care Unit (PICU) hospitalisation.

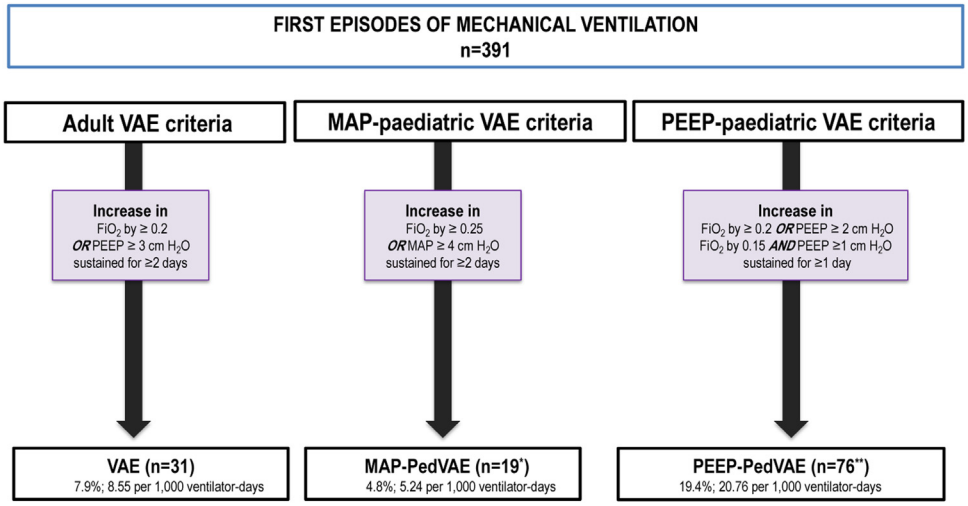

Fig. 1. Ventilator-Associated Event definitions.
VAE = Ventilator-Associated Event; MAP-PaedVAE = Paediatric Ventilator-Associated Event definition based on MAP; PEEP-PaedVAE = Paediatric Ventilator-Associated Event definition based on PEEP; **Nineteen MAP-PaedVAE were diagnosed during 18 episodes of mechanical ventilation; **Seventy-six PEEP-PaedVAE were diagnosed during 73 episodes of mechanical ventilation.

2. Material and methods

2.1. Study design, setting and participants

A multicentre, observational, prospective cohort study was conducted in 15 PICUs from Spain. Five out of 15 corresponded to IV-level PICUs and 10 to III-level PICUs, which account for the 60% and the 50% of the overall IV-level and III-level Spanish Paediatric Critical Health System, respectively, excluding neonatal ICUs. The study protocol was approved by the institutional review board on human research at Vall d'Hebron University Hospital, [PR(AMI)330/2018], who waived the need for a consent prior to participation in the study. Local researches were contacted by a member of the study team and participating hospitals obtained their local ethics committee approval. The study was conducted in a phased manner from the 17th of September 2018 to the 17th of March 2020, according to the date of each local ethics committee approval.

All consecutive children admitted to each PICU for a 12-month period from their inclusion in the study who received invasive mechanical ventilation (MV) for 48 h were eligible. Exclusion criteria were age $<$ 30 days, infants with a corrected gestational age of $<$ 44 weeks, and age $>$ 18 years, previous ventilation, extracorporeal life support, and right-to-left shunt or pulmonary hypertension. Subjects with missing data or incomplete follow-up were also excluded from the statistical analysis. Duration of MV was considered until extubation or PICU death. In patients with more than one episode of MV, only the first one was considered.

2.2. VAE definitions

An episode of MV was defined as one occurring during the period between tracheal intubation (day 1) and 24 h after successfully extubation. The current adult ventilator-associated event (VAE) [14], the MAP-PaedVAE [12], and PEEP-PaedVAE definitions were assessed, being reported elsewhere [13] (Fig. 1). According to both first definitions, the respiratory worsening had to be sustained for at least 2 calendar days to fulfil them. The PEEP-PaedVAE definition only needed $\geq$ 1 day-sustained respiratory worsening, lowered the threshold for PEEP increase from 3 to 2 cm H_2O, and also contemplated an increase of 1 cm PEEP plus 0.15 FiO2 [13].

2.3. Study variables

Medical, trauma, and surgical patients were included. Clinical and demographic information, including the Paediatric Risk of Mortality (PRISM) at ventilation onset and the Paediatric Logistic Organ Dysfunction score (PELOD) during the episode of MV were recorded. Multiorgan failure was defined as PELOD $>$ 13 [15]. Duration of ventilation was defined as number of days from the time ventilation was first initiated during a given ventilation episode. The following patients' outcomes were considered as end-points: duration of MV, PICU and hospital LOS, and the mortality during the episode of MV. Increased MV was defined as the need for invasive MV for seven or more days. Increased PICU LOS was defined as stay at PICU for ten or more days. Breakpoints were selected based on median duration of MV and hospitalisation from cohorts reported elsewhere [5,13].

Statistical analysis has been detailed at ESM-1.

3. Results

3.1. Study population

The study cohort comprised 391 children and 3,626 ventilator-days from a total of 530 eligible patients (**supplemental material Fig. 1**). Among them, only 12 (3%) patients underwent high frequency ventilation for some time during the episode of MV, corresponding to only 93 out of 3,626 ventilator-days (2.5%). Patients' baseline characteristics of the overall population are summarised in Table 1. Acute respiratory failure was the cause of intubation in 190 children (48.6%) and the presence of one or more comorbidities was identified in 241 children (61.7%). The median of PRIMS III score within the first 24 h of ventilation was 7 [3–13] and PELOD score was 11 [1–17.5]. A hundred and one of 391 patients (25.8%) developed multiorgan failure during the MV episode. The duration of the ventilation period [median, IQR], PICU, and hospital LOS from the MV onset were 7 [5–10], 11 [7–19] and 21 [14–39] days, respectively. Twenty-three of 391 patients (5.9%) died in the PICU, eighteen of them during the first episode of MV (4.6%).

3.2. Evaluation of three criteria

Thirty-one VAE (8.55 per 1000 ventilator-days, 7.9 per 100 episodes), 19 MAP-PaedVAE (5.24 per 1000 ventilator-days, 4.8 per 100 episodes), and 76 PEEP-PaedVAE (20.96 per 1000 ventilator-days, 19.4 per 100 episodes) were identified. Among them, three PEEP-PaedVAEs and one MAP-PaedVAE corresponded to second PaedVAEs during the same episode of mechanical ventilation (**supplemental material Fig. 1**). MAP-PaedVAE was more frequently reported by III-level PICUs *vs.* IV-level PICU (10.4 *vs*. 3 per 1000 ventilator-days, $p < 0{,}05$), whereas no statistically significant difference was found in the rate of VAE using PEEP-PaedVAE criteria.

Thirty-one VAEs (100%) fulfilled PEEP-PaedVAE criteria and 17 out of 19 MAP-PaedVAE (89.5%) fulfilled PEEP-PaedVAE criteria (**supplemental material Table 1**). Only 2 out of 19 MAP-PaedVAE (10.5%) were developed during high frequency ventilation. The other 17 MAP-PaedVAE developed on conventional mechanical mode and the respiratory worsening in four of them triggered the change from conventional mode to high frequency mode, also fulfilling VAE/PEEP-PaedVAE criteria.

The time for VAE, MAP-PaedVAE and PEEP-PaedVAE development from the MV onset were 4 [3–12.5], 4 [3–14], and 5 [3–7.75] days, respectively. Episodes fulfilling any of three criteria were significantly associated with $\geq$ 5 more days of MV and PICU LOS compared with those episodes not fulfilling VAE or any PaedVAE definition (**supplemental material Table 2**).

Among survivors, univariate analysis showed that intubation at PICU, reason for intubation, multiorgan failure and all three VAE criteria (VAE, MAP-PaedVAE, PEEP-PaedVAE) were significantly associated with MV $>$ 7 days. Multiorgan failure and all three VAE definitions were also significantly associated with PICU LOS $>$ 10 days in the univariate analysis. Among them, logistic multivariate analysis identified multiorgan failure [OR = 2.26, 95% CI (1.27–4.00); OR = 1.76, 95% CI (1.05–2.97)], and PEEP-PaedVAE [OR = 4.86, 95% CI (2.41–10.11); OR = 3.49, 95% CI (1.68–7.80)] as the only independent factors associated with more than 7 days of MV and more than 10 days of PICU LOS, respectively (Table 2 and Table 3). **Statistical analysis** has been reported as ESM.

4. Discussion

The last decade has seen an evolution of quality measures examining the practice of mechanical ventilation and probably a gentle transition from VAP to VAE surveillance. However, inconsistencies and lack of validation exist in the currently proposed models, and this work adds valuable information to the puzzle. This is the first prospective study assessing the performance of three different VAE definitions in children.

Table 1
Baseline patient characteristics.

	Total (n = 391)	VAE (n = 31)	MAP-PaedVAE (n = 18)	PEEP-PaedVAE (n = 73)
Male sex, n (%)	214 (54.7)	15 (48.4)	6 (33.3)	37 (50.6)
Age (yr) [median, IQR]	1.0 [0.2–5.3]	1.5 [0.3–5.8]	1.3 [0.3–4.6]	1.5 [0.3–6.4]
PRISM III score [median, IQR]	7 [3–13]	6 [3.5–13]	8.5 [5–16.5]	6 [3–13]
Comorbidities				
None	150 (38.3)	7 (22.6)	4 (22.2)	22 (30.1)
One	152 (38.9)	15 (48.4)	6 (33.3)	31 (42.5)
Two or more	89 (22.8)	9 (29.0)	8 (44.5)	20 (27.4)
Pre-existing conditions, n (%)				
Lung disease	19 (4.8)	3 (9.7)	2 (11.1)	4 (5.5)
Heart disease	71 (18.1)	8 (25.8)	4 (22.2)	16 (21.9)
Neurological disease	59 (15)	8 (25.8)	5 (27.8)	16 (21.9)
Kidney disease	13 (3.3)	0 (0)	1 (5.5)	1 (1.4)
GI-Liver disease	27 (6.9)	2 (6.4)	1 (5.5)	6 (8.2)
Haematological malignant disease	12 (3)	1 (3.2)	1 (5.5)	4 (5.5)
Solid cancer	17 (4.3)	1 (3.2)	1 (5.5)	2 (2.7)
Prematurity	45 (11.5)	4 (12.9)	3 (16.7)	7 (9.6)
Steam Cell Transplant	3 (0.8)	0 (0)	0 (0)	1 (1.4)
Solid transplant	5 (1.3)	1 (3.2)	1 (5.5)	2 (2.7)
Immunosuppression other	11 (2.9)	1 (3.2)	1 (5.5)	3 (4.1)
Other conditions	35 (8.9)	6 (19.3)	5 (27.8)	13 (17.8)
Place of intubation, n (%)				
Paediatric Intensive Care Unit	224 (57.3)	18 (58.1)	11 (61.1)	45 (61.6)
Operating theatre	96 (24.6)	6 (19.3)	4 (22.2)	13 (17.8)
Emergency room/Ward	27 (6.9)	3 (9.7)	1 (5.5)	7 (9.6)
Out-of-hospital setting	44 (11.2)	4 (12.9)	2 (11.2)	8 (11)
Type of patient				
Medical	270 (69)	23 (74.2)	14 (77.8)	53 (72.6)
Surgical	101 (25.8)	6 (19.3)	3 (16.7)	14 (19.2)
Trauma-burn	20 (5.2)	2 (6.5)	1 (5.5)	6 (8.2)
Reason for mechanical ventilation				
Respiratory failure	190 (48.6)	15 (48.4)	11 (61.1)	38 (52.0)
Surgery/other procedures	92 (23.5)	5 (16.1)	2 (11.1)	13 (17.8)
Septic shock	35 (9)	5 (16.1)	3 (16.7)	7 (9.6)
Cardiogenic shock/cardiac arrest	22 (5.6)	3 (9.7)	0 (0)	7 (9.6)
Altered level of consciousness	52 (13.3)	3 (9.7)	2 (11.1)	8 (11)

VAE = Ventilator-Associated Event; MAP-PaedVAE = Paediatric Ventilator-Associated Event definition based on MAP; PEEP-PaedVAE = Paediatric Ventilator-Associated Event definition based on PEEP; PRISM III score = Pediatric Risk Mortality score; IQR = Interquartile range.

Table 2
Factors associated with mechanical ventilation > 7 days in survivors: univariate and multivariate logistic regression models (N = 368).

	Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Sex, Male	0.98	0.63–1.52	0.931	–	–	–
Age, >1 year	0.79	0.51–1.22	0.304	–	–	–
PRISM III score >15	1.13	0.61–2.07	0.685	–	–	–
Type patient, non-medical	0.73	0.46–1.17	0.202	–	–	–
Comorbidities	1.23	0.79–1.90	0.353	–	–	–
Reason for MV, non-respiratory	0.59	0.38–0.91	0.019	0.59	0.32–1.06	0.079
Place of intubation, PICU	1.71	1.10–2.70	0.019	1.30	0.72–2.35	0.379
Multiorgan failure	2.07	1.26–3.39	0.004	**2.26**	**1.27–4.00**	**0.005**
VAE	12.23	4.52–42.72	< 0.001	2.15	0.61–13.32	0.229
MAP-PaedVAE	12.96	3.46–84.21	<0.001	1.15	0.16–9.97	0.887
PEEP-PaedVAE	6.74	3.78–12.46	< 0.001	**4.86**	**2.41–10.11**	< **0.001**

CI = Confidence Interval; OR = Odds Ratio; PRISM III score = Paediatric Risk Mortality score; MV: Mechanical Ventilation; PICU = Paediatric Intensive Care Unit; VAE = Ventilator-Associated Event; MAP-PaedVAE = Paediatric Ventilator-Associated Event definition based on MAP; PEEP-PaedVAE = Paediatric Ventilator-Associated Event definition based on PEEP.
Number in bold indicate statistically significant results

Interestingly, our findings highlight that a paediatric definition of VAE based on PEEP was associated with significantly higher sensitivity. Our data show that patients who developed VAE with either of the definitions were significantly associated with MV above 7 days and PICU LOS above 10 days, at the univariate analysis. However, when adjusted in the multivariate analysis by confounding factors, only the definition based on slight PEEP increases remained independently associated with worse outcomes. Our multicentre study suggests that the paediatric VAE definition based on slight PEEP increases should be preferred for VAE surveillance in children.

Our results are consistent with other studies in which MV episodes fulfilling VAE criteria were associated with increased mortality, longer ventilator periods and hospitalisation [4,5,8,11,13]. In addition, our data also confirm that the implementation of adult VAE criteria in children resulted too restrictive, as it had been previously reported [8,16]. Surprisingly, use of MAP-PaedVAE criteria in our paediatric population resulted

Table 3
Factors associated with PICU length of stay > 10 days in survivors: univariate and multivariate logistic regression models (N = 368).

	Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Sex, Male	1.05	0.70–1.59	0.802	–	–	–
Age, > 1 year	0.92	0.60–1.38	0.679	–	–	–
PRISM III score > 15	0.96	0.54–1.73	0.907	–	–	–
Type patient, non-medical	1.20	0.78–1.87	0.408	–	–	–
Comorbidities, yes	1.05	0.81–1.36	0.710	–	–	–
Reason for MV, non-respiratory	0.98	0.65–1.47	0.911	–	–	–
Place of intubation, PICU	1.36	0.90–2.06	0.142	–	–	–
Multiorgan failure	1.88	1.15–3.10	0.012	**1.76**	**1.05–2.97**	**0.031**
VAE	5.34	1.98–18.60	0.002	1.36	0.31–7.48	0.693
MAP-PaedVAE	5.86	1.57–38.05	0.022	1.32	0.19–11.36	0.774
PEEP-PaedVAE	4.13	2.24–8.05	< 0.001	**3.49**	**1.68–7.80**	**0.001**

CI = Confidence Interval; OR = Odds Ratio; PRISM III score = Paediatric Risk Mortality score; MV = Mechanical Ventilation; PICU = Paediatric Intensive Care Unit; VAE = Ventilator-Associated Event; MAP-PaedVAE = Paediatric Ventilator-Associated Event definition based on MAP; PEEP-PaedVAE = Paediatric Ventilator-Associated Event definition based on PEEP.
Number in bold indicate statistically significant results

even more restrictive than the adults VAE definition. This issue is a limitation that makes difficult the use of MAP-PaedVAE in the current practice, as it has been advertised elsewhere [17]. This limitation can be explained in part by the increase of FiO_2 threshold from 0.20 to 0.25 and the increase of MAP by $\geq$ 4 cm *versus* the increase of PEEP by $\geq$ 3 cm H_2O compared with the VAE adult definition.

The use of MAP rather than PEEP was initially accepted by paediatric intensivists due to their more conservative use of PEEP than adult intensivists [12,17], the great accuracy of MAP to reflect changes in lung compliance, and the need to allow high frequency ventilated patients to be included in the surveillance definition, given the use of this ventilatory mode in neonatal and paediatric populations [12]. However, MAP is a function of numerous variables and is not specifically set on any conventional ventilator (this control is only available on high-frequency oscillators). Moreover, the greatest effect on oxygenation is generally achieved by increasing PEEP, because MAP will increase in direct proportion to the increase in PEEP (depending on the I/E ratio) [18]. Furthermore, PEEP is part of the standard of care in paediatric ventilated patients, most of them on conventional mode; although MAP may be the preferred monitoring criteria in high-frequency ventilation, this ventilator strategy is usually limited to neonates or as a rescue therapy in children, like in our population [19]. Besides, our results show that clinical deterioration frequently fulfils other VAE criteria based on PEEP or FiO_2 when the patient is still on conventional mechanical ventilation and just this VAE episode triggers the need to change respiratory support from conventional mode of ventilation to high frequency mode.

The PEEP-PaedVAE definition maintained a greater impact on outcomes. This definition [13], apart from requiring a lower increase in PEEP/FiO2 than in the other two definitions, also contemplates a shorter duration of respiratory worsening (sustained only during one calendar day instead of two). In all of three definitions, VAE/PaedVAE were defined for a 14-day period, starting on the day of worsening oxygenation (the event day). Based on the reported rules, a new VAE/PaedVAE cannot be identified or reported until this 14-day period has elapsed. Events identified with the PEEP-PaedVAE definition were associated with a median of above five extra days of ventilation and PICU stay, when compared with those ventilator episodes in which no VAE was identified. Whereas it can be speculated that sicker children had their PEEP elevated to a greater extent, which may be harmful, these are not randomised trial data, and we cannot comment in the extent to which PEEP was harmful or beneficial. We can only state that the multivariate model (Table 2 and Table 3) identified the PEEP-PaedVAE criteria as independently associated with worse outcomes, when adjusted by variables reflecting patient's status. In contrast, the other definitions did not show a statistically significant association.

Therefore, apart from the preferred use of PEEP instead of MAP described above to monitor VAEs, the PEEP-PaedVAE has the advantage of its higher incidence, which represents a considerable scope for improvement with the implementation of a VAE bundle in children. But most significantly, the major benefit of the implementation of the PEEP-PaedVAE definition for prevention would be the translation of lower PEEP-PaedVAE rates into better patient outcomes. This represents a new opportunity to overcome many of the weaknesses of the traditional ventilator-associated pneumonia surveillance and broadens the focus of surveillance to encompass other preventable conditions related to MV. However, from the authors' point of view, both classifications (VAP and PEEP-PaedVAE) should be complementary, not mutually exclusive [20].

VAEs have many potential causes. Most common are pneumonia, fluid overload, atelectasis and ARDS [21]. How these different causes of VAEs impact on the different definitions remains unknown. Similarly, the impact of VAEs in patients in the COVID-19 era remains uncertain. VAE surveillance provides an opportunity for hospitals to rethink their ventilator bundles. Selected interventions that reduce the duration of MV and that target the common causes of VAEs, such as minimising sedation, awakening, and breathing trials, early mobility or conservative fluid management, between others, may have different impact on these definitions [22–25]. Traditional bundles are missing some of these potentially helpful interventions. Due to the differences between VAP and VAE, it is likely that VAE prevention requires a distinctive approach. The introduction of VAE definitions provides an invitation to the intensivists to rethink ventilator bundles. The ideal VAE bundle is likely one that targets the variables which most frequently trigger VAEs and minimises time that children undergo mechanical ventilation.

Next steps in this line of research will be focused on validation with larger datasets to fine-tune the score, possibly even the current version of the CDC VAE algorithm. Further studies should assess the applicability of the PEEP-PaedVAE criteria for clinical purposes. It is needed to implement guidelines to reduce variability in increasing PEEP in ventilated children, to identify whether it is a true VAE or just an over-reaction, as well as educational programs to learn on the importance to acknowledge and prevent VAE among children. A gap of information exists about the effects on VAEs in children with multiple admissions or re-intubated. This is an issue for the entire VAE concept, also in adults,

and need to be investigated. Effect of VAEs in patients with tracheotomy, which are unlikely in children, is another gap for further research. Short-acting sedatives, conservative fluid management and spontaneous awaking and breathing trials have been protective against VAEs [22,26]. Further research is required to assess whether implementation of a ventilator bundle can reduce the number of children requiring increases of PEEP and can be extubated and discharged earlier.

This study has the following strengths in methodology. Firstly, this study was prospectively designed and carried out; possible predictors were deliberately collected with quality control procedures, making the data more reliable. Moreover, investigators were blinded to definitions. Secondly, this was a multicentre study involving many paediatric ICUs, making the findings more generalisable than in single centres. Third, to assess the performance of each definition on patient outcomes, length of stay was considering the period only from MV onset until PICU or hospital discharge. Our study has also several limitations. First, this study was conducted in Spain and findings may not be representative outside Spain, due to variations in therapeutic strategies, case mix, or duration of MV. Therefore, a multinational study is recommended. Second, exclusion of previous ventilated patients seriously limits generalisation to tracheotomised patients or who are re-intubated. That is consistent with other reports on VAE, and the investigation of this subset requires further research. Third, the severity of each organ dysfunction was not measured daily but comprised the whole ventilator period. Fourth, these data are not generated by a randomised clinical trial. We cannot infer causation regarding whether PEEP was harmful or beneficial because findings might well have been the result of unmeasured confounders. Lastly, given the low incidence of some of the events, the power to demonstrate statistical differences is sometimes limited by small cohort size.

5. Conclusions

Our study confirms that even slight sustained increments of respiratory support have impact on outcomes. Among ventilated children, a respiratory deterioration requiring a slight increase in PEEP/FiO_2 sustained for $\geq$ 1 day was independently associated with 4.9-fold risk increase for ventilation time above 7 days and a 3.6-fold increase for PICU hospitalisation periods. Therefore, a VAE definition based on slight PEEP increases might have greater utility for VAE surveillance in children. Further validation with larger datasets and more diverse population including registry data will be required. Our multicentre study suggests the need to test new ventilatory bundles among ventilated children with the goal to reduce time to extubation and to ICU discharge.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

Disclosure of interest

JR has served on the speakers' board and as a consultant for ROCHE, Pfizer, and MSD. The remaining authors have disclosed that they do not have any conflicts of interest.

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Glossary

ARDS	Acute Respiratory Distress Syndrome.
CDC	Centres for Disease Control and Prevention.
COVID-19	Coronavirus-19 disease.
ICU	Intensive Care Unit.
LOS	Length of stay.
MAP	Mean Airway Pressure
MAP-PaedVAE	Paediatric Ventilator-Associated Event based on MAP.
PaedVAE	Paediatric Ventilator-Associated Event
PEEP	Positive End-Expiratory Pressure.
PEEP-PaedVAE	Paediatric Ventilator-Associated Event based on PEEP
PELOD score	Paediatric Logistic Organ Dysfunction score
PICU	Paediatric Intensive Care Unit
PRISM score	Paediatric Risk of Mortality score.
VAE	Ventilator-Associated Event
VAP	Ventilator-Associated Pneumonia

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.accpm.2022.101072.

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