

## META-ANALYSIS

# Endotracheal intubation during chest compressions in the pediatric simulation setting: a systematic review and meta-analysis

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**Abstract**

Endotracheal intubation (ETI) in the pediatric setting is a complex skill and performing ETI during pediatric cardiopulmonary resuscitation is even more challenging. Simulation studies have investigated the performances of several devices for ETI. We undertook a systematic review and meta-analysis to evaluate the performances of devices for ETI during simulated pediatric on-going chest compressions. Devices were divided in four groups: direct laryngoscopy (DL) with Macintosh or Miller blade, or video-laryngoscopy with screen-on-device (VLS-SoD) or with distant monitor (VLS-DM). Primary outcomes were overall success rate (SR) and time-to-intubation (TTI). Results are expressed as Risk Ratio (RR) or Mean Difference (MD) with 95% confidence interval. We included 12 studies comparing at least two devices. The SR was greater for VLS as compared to DL-Miller (RR: 0.83 (0.78; 0.89),  $p < 0.00001$ ) or DL-Macintosh (RR: 0.81 (0.77; 0.85),  $p < 0.00001$ ). Subgroup analyses confirmed that both types of VLS were superior to DL-Miller (VLS-DM:  $p = 0.03$ ; VLS-SoD:  $p < 0.00001$ ) or DL-Macintosh (both VLSs:  $p < 0.00001$ ). As compared with VLS, TTI was longer with both DL blades: Miller (MD: 8.26 seconds (5.30; 11.21),  $p < 0.00001$ ) or Macintosh blade (MD: 7.63 seconds (4.14; 11.12),  $p < 0.00001$ ). In the subgroup analyses, VLS-SoD was superior to DL-Miller or DL-Macintosh (both  $p < 0.00001$ ), while VLS-DM was superior to DL-Macintosh ( $p < 0.00001$ ), possibly not to DL-Miller ( $p = 0.06$ ). Under simulated conditions of ongoing pediatric resuscitation, use of VLS guarantees higher overall SR and shorter TTI as compared to DL performed with Miller or Macintosh blade. Among VLSs, those with screen-on-device may have better performances than those with distant monitor.

**Keywords**

Direct laryngoscopy; Video-laryngoscopy; Manikin; Orotracheal intubation; Children

## 1. Introduction

Over 20,000 children per year have a cardiac arrest (CA) in the United States, with almost half of out-of-hospital CA of presumed respiratory nature [1–4]. Currently, both adult and pediatric resuscitation guidelines [5, 6] emphasize the need for high quality chest compressions with minimal interruption and early defibrillation, whilst the best strategy for airway management remains more debatable.

In fact, some differences can be seen regarding advanced airway management between the European Resuscitation Council (ERC) and the American Heart Association (AHA) resuscitation guidelines [5] in the pediatric setting. The ERC panel advice to use bag-mask ventilation (BMV) during CPR and to perform the ETI (or insertion of a supraglottic airway device—SAD) only once return of spontaneous circulation is achieved [6]. Conversely, the AHA committee leaves the

decision regarding advanced airway management or BMV to the operators [5].

The Macintosh and Miller blades for direct laryngoscopy (DL) are considered the first line approach for ETI under normal conditions, but the additional difficulties encountered during cardiopulmonary resuscitation (CPR) may warrant a different approach. Whether the use of video-laryngoscopy (VLS) may increase the effectiveness of pediatric ETI during ongoing chest compressions is still unclear, and the potential advantages of VLS over DL have not been clinically studied. However, several simulation studies have attempted to address this question. In order to compare the performances of devices for pediatric ETI during ongoing chest compressions, we performed a systematic review and meta-analysis of simulation studies.

**TABLE 1. PICOS criteria.**

PICOS CRITERIA	
Population	Participants performing any type of laryngoscopy for ETI during simulated on-going chest compressions
Intervention and Comparison	Tracheal Intubation performed with at least two devices for ETI by participants (regardless their prior airway experience or professional background)
Outcome(s)	Time-to-Intubation and/or overall Success Rate
Study design	Prospective studies conducted in simulated pediatric scenario enrolling at least 10 participants

*PICOS: Population, Intervention, Comparison, Outcomes, Study design. ETI: endotracheal intubation.*

## 2. Material and methods

We performed a systematic web-based advanced literature search through the NHS Library Evidence tool on the management of pediatric airways under simulated CPR conditions. We followed the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) statement for reporting systematic reviews and meta-analyses [7] and the relative PRISMA checklist is reported as **Supplementary Table 1**. A registration of our protocol on PROSPERO registry was attempted, but this database does not support the registration of simulation studies.

### 2.1 Search and inclusion criteria

The initial computerized search was conducted on PubMed and EMBASE on August 12th 2021 to identify relevant abstracts. EMBASE search was restricted to 2016, in order to identify conference abstracts not yet peer-reviewed and published. In our systematic search, we identified four subgroups of terms. The first group included the terms (simulation) OR (manikin); the second included only (airway); the third was used to identify pediatric studies ((pediatric) OR (children) OR (infant) OR (neonate\*)) and the last to select CA scenarios ((resuscitation) OR (chest compression\*) OR (ROSC) OR (cardiopulmonary) OR (cardiac arrest)).

Articles were assessed for eligibility according to the PICOS criteria (Table 1). Studies were included regardless of the operator’s skills on airway management. In order to evaluate the performances of devices for ETI, the two primary outcomes were time-to-intubation (TTI) and/or overall success rate (SR). In the primary analysis we included studies where the only difficulty was the performance of ETI during ongoing chest compressions; studies where the manikin was set with a difficult airway scenario were included in sensitivity analyses.

### 2.2 Screening and data acquisition

Eligible articles were downloaded and data were recorded. Two further searches were performed manually and independently by three authors (SM, FM, MA). Studies evaluating performances of SADs were excluded; similarly, we excluded studies where the authors report data only on a single airway device for ETI. We also excluded book chapters, reviews, editorials and letters to editor. English language restrictions were applied. For prospective studies published in other languages, we read the abstract and, if necessary, contacted the authors for further information. Study selection for determining the eligi-

bility for inclusion in the systematic review and data extraction were performed independently by four reviewers (FS, SM, FM, LLV). Discordances were resolved involving one senior author (MA).

### 2.3 Quality assessment, publication bias and GRADE of evidence

Risk of bias assessment for case-control studies was performed using the Newcastle-Ottawa scale (NOS) [8–10]. Presence of publication bias was investigated by visual inspection of funnel plots for the primary outcomes. Grade of evidence was performed according to the recommendations of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group by two authors (LLV, FS) using the GRADEpro GDT (GRADEpro Guideline Development Tool (Software). McMaster University and Evidence Prime, 2021) available from [gradepr.org](http://gradepr.org).

### 2.4 Statistical analysis

The Inverse variance method was used to analyze the two primary outcomes. Results are reported as risk ratios (RR) or as Mean difference (MD), using 95% Confidence Intervals (CI), and two tailed *p* values. *P* values were considered significant if  $<0.05$ . The presence of statistical heterogeneity was assessed using the  $\chi^2$  (Cochran Q) test. Heterogeneity was likely if  $Q > df$  (degrees of freedom) suggested and confirmed if  $p \leq 0.10$ . Quantification of heterogeneity was performed and values of  $I^2$  ranging 0–24.9%, 25–49.9%, 50–74.9% and  $>75\%$  were considered as none, low, moderate and high heterogeneity, respectively. A random effect model was used by default [11].

Two sensitivity analyses were planned. The first one was performed including also the studies evaluating intubation under a difficult airway scenario on top of ongoing CPR. The second sensitivity analysis was carried out with “leave one study out at time” approach.

## 3. Results

Our systematic search yielded 259 results in PubMed. Further 49 studies were found on EMBASE. No other studies were retrieved manually. As shown in the PRISMA flow diagram (**Supplementary Fig. 2**), after the evaluation of all findings, we initially included sixteen studies reporting TTI and/or SR data with at least two devices, but one was subsequently excluded as it did not have a group performing ETI with devices

from two groups of devices [12], one because participants wore personal protective equipment and focused on this additional difficulty [13] and another two since the device used was not classified as a laryngoscope [14, 15].

Characteristics of the remaining 12 included studies are reported in Table 2 (Ref. [16–27]). Of the included studies, three evaluated the performances of devices for ETI both under simulated normal and difficult airway conditions [20, 22, 23]. Most studies were conducted on paramedics ( $n = 7$ ), followed by doctors of different specialty ( $n = 4$ ), nurses ( $n = 1$ ) and a mixed population (paramedic + nurses,  $n = 1$ ). The time to declare failure in ETI was not clearly specified by seven studies, while most of the remaining had a cut-off of 60 seconds ( $n = 5$ ), with only one allowing longer time for each intubation attempt (120 seconds). Regarding the standard CPR scenario, most studies ( $n = 8/13$ , 62%) used automated ongoing chest compressions with a mechanical device. The simulation studies that included a “CPR-difficult” scenario reproduced different additional challenges for airway management. The reproduced difficulty was reproduced by inflation of the tongue (to simulate edema and a Mallampati score of 3) in two studies [20, 22] or by positioning a standard fitting immobilization collar [23].

### 3.1 Overall SR

The SR with VLS approach was compared to the DL with Miller blade in 8 studies, while 4 reported SR comparing VLS to DL with Macintosh blade. The overall SR was significantly greater for VLS as compared to DL with Miller (RR 0.83 (95% CI: 0.78; 0.89),  $p < 0.00001$ ;  $I^2 = 69\%$ ; Fig. 1a) or Macintosh blade (RR 0.81 (95% CI: 0.77; 0.85),  $p < 0.00001$ ;  $I^2 = 0\%$ ; Fig. 1b).

Subgroup analyses comparing VLS and DL with Miller blade showed no subgroup differences ( $p = 0.07$ ,  $I^2 = 69.5\%$ ), and both types of VLS were significantly superior to DL Miller: VLS-DM: RR 0.89 (95% CI: 0.80, 0.99),  $p = 0.03$ ,  $I^2 = 73\%$ ; VLS-SoD: RR 0.78 (95% CI: 0.71, 0.86),  $p < 0.00001$ ,  $I^2 = 63\%$ . The other subgroup analysis comparing VLS and DL with Macintosh blade showed no subgroup differences ( $p = 0.69$ ,  $I^2 = 0\%$ ), and both types of VLS were significantly superior to DL Macintosh: VLS-DM: RR 0.82 (95% CI: 0.76, 0.88),  $p < 0.00001$ ,  $I^2 = 0\%$ ; VLS-SoD: RR 0.80 (95% CI: 0.75, 0.86),  $p < 0.00001$ ,  $I^2 = 0\%$ .

We conducted sensitivity analyses after inclusion of studies where the authors included in the simulated scenario of ongoing chest compression also a further element of difficult airway management. We included further three studies [20, 22, 23] per each analysis (VLS vs. DL Miller or Macintosh). The inclusion of these studies did not meaningfully change the result from primary analysis (overall and subgroups). No sensitivity analyses performed with “leave one out at time” approach changed the statistical significance of the primary analysis results.

The inspection of funnel plots did not reveal evidence of publication bias (Supplementary Fig. 2 and Supplementary Fig. 4).

### 3.2 TTI

The TTI with VLS approach was compared to DL with Miller blade in 8 studies and to Macintosh blade in 4 studies. As compared with VLS, TTI was significantly longer with both DL blades: Miller (MD 8.26 s (95% CI: 5.30, 11.21),  $p < 0.00001$ ;  $I^2 = 91\%$ ; Fig. 2a) or Macintosh blade (MD 7.63 s (95% CI: 4.14, 11.12),  $p < 0.00001$ ;  $I^2 = 91\%$ ; Fig. 2b).

Subgroup analyses comparing VLS and DL with Miller blade showed no subgroup differences ( $p = 0.24$ ,  $I^2 = 28.2\%$ ), but only VLS-SoD was significantly faster than DL Miller (MD 9.82 s (95% CI: 6.34, 13.30),  $p < 0.00001$ ;  $I^2 = 89\%$ ), whilst VLS-DM had a trend towards faster TTI (MD 5.67 s (95% CI: 0.29, 11.62),  $p = 0.06$ ,  $I^2 = 94\%$ ).

The other subgroup analysis comparing VLS and DL with Macintosh blade showed significant subgroup differences ( $p < 0.00001$ ,  $I^2 = 97.6\%$ ). As compared to DL Macintosh, both types of VLS were significantly superior in terms of TTI (VLS-DM, MD 4.07s (95% CI: 2.57, 5.56),  $p < 0.00001$ ,  $I^2 = 0\%$ ; VLS-SoD, MD 10.53 s (95% CI: 9.28, 11.79),  $p < 0.00001$ ,  $I^2 = 0\%$ ).

The sensitivity analyses included further three studies [20, 22, 23] per each analysis (VLS vs. DL Miller or Macintosh). The inclusion of these studies did not meaningfully change the result from primary analysis, apart from the comparison between the DL Miller and the subgroup of VLS-DM that became significantly different (from  $p = 0.06$  to  $p = 0.02$ ). No sensitivity analyses performed with “leave one out at time” approach changed the statistical significance of the primary analysis results.

Funnel plots inspection did not reveal evidence of publication bias (Supplementary Fig. 3 and Supplementary Fig. 5).

A table with summary of the overall results is provided as Supplementary Table 2.

### 3.3 Risk of bias assessment and GRADE of evidence assessment

The assessment of risk of bias with the NOS for case-control studies included in our meta-analysis showed that all studies had low risk of bias, with scores ranging from 6 to 8 points out of a maximum of 9 (Supplementary Table 3). In particular, all studies did not perform multivariate analyses looking for factors influencing the performance of the operators. About half of the included studies had lost of data above 5% of participants.

Evidence according to the GRADE working group was regarded as very low since indirectness was assessed as very serious because the included studies were performed in the simulated environment (Supplementary Table 4).

## 4. Discussion

To the best of our knowledge, the present meta-analysis represents the first attempt to compare the performances of devices for ETI under the challenging conditions of simulated ongoing pediatric CPR. Our study divided devices in two main groups (DL and VLS), with two subgroups each. The DL devices were divided according to the type of blade used (Macintosh’s or

**TABLE 2. Characteristics of the included studies.**

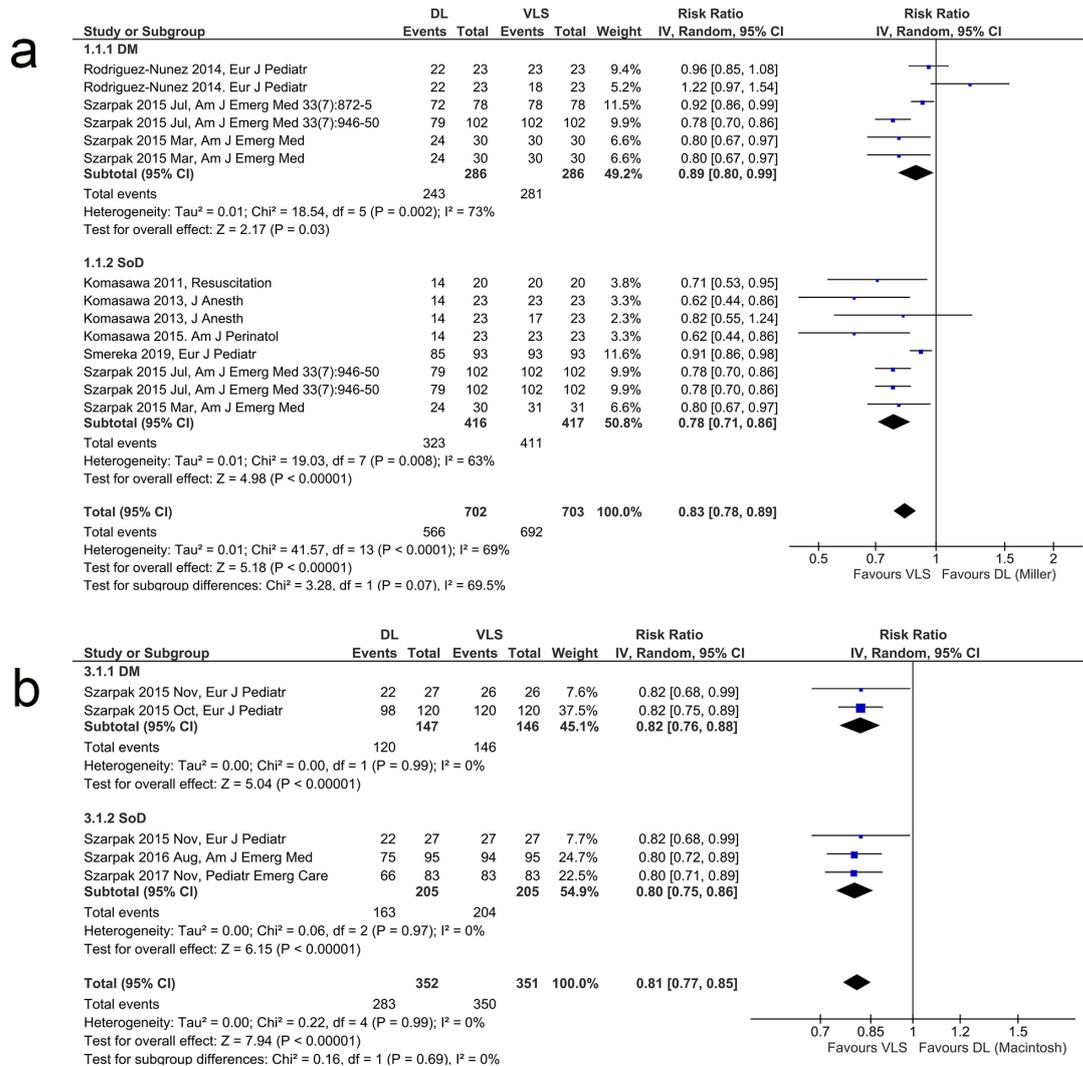
First year	Author	N =	Simulator Chest compression	Setting	Devices: DL. Devices: VLS.	Time to declare failure	Experience in Pediatric Airways	Graduation-Diploma	Ref.
2011,	Komasawa Resuscitation	20	ALS Baby Trainer, infant Manual	CPR	DL-Miller. Airtraq.	NS	Experienced	Doctors (pICU/EM)	[16]
2013,	Komasawa J Anesth	23	ALS Baby Trainer, infant Manual	CPR	DL-Miller. Airtraq; AWS.	NS	None	Doctors (Anaesthesia)	[18]
2014,	Rodriguez-Nunez Eur J Pediatr	23	Megacode Junior, Megacode Baby Manual	CPR	DL-Miller. Glidescope.	60 s	None	Doctors (Pediatrics)	[19]
2015,	Komasawa Am J Perinatol	23	NewBorn Anne manikin, infant Manual	CPR	DL-Miller. AWS.	NS	None	Doctors (Anaesthesia)	[17]
2015 Mar,	Szarpak Am J Emerg Med	120	PediaSIM CPR Lucas-2®	CPR	DL-Miller. AWS; Truview; Glidescope.	NS	None	Paramedics + Nurses	[25]
2015 Jul,	Szarpak Am J Emerg Med 33(7):872–5	78	ALS Baby Trainer, infant Manual	CPR	DL-Miller. Truview.	60 s	None	Paramedics	[27]
2015 Jul,	Szarpak Am J Emerg Med 33(7):946–50	102	PediaSIM CPR Lucas-2®	CPR	DL-Miller. McGrath; Airtraq; Glidescope.	NS	None	Paramedics	[26]
2015 Oct,	Szarpak Eur J Pediatr	120	PediaSIM CPR Lucas-2®	CPR CPR+D	DL-Macintosh. Truview	NS	None	Paramedics	[23]
2015 Nov,	Szarpak Eur J Pediatr	107	PediaSIM CPR Lucas-2®	CPR	DL-Macintosh. Intubrite; Coopedeck; CoPilot.	NS	None	Paramedics	[24]
2016 Aug,	Szarpak Am J Emerg Med	95	PediaSIM CPR Lucas-2®	CPR	DL-Macintosh. McGrath	60 s	None	Paramedics	[21]
2017 Nov,	Szarpak Pediatr Emerg Care	83	PediaSIM CPR Lucas-2®	CPR CPR+D	DL-Macintosh. Airtraq	60 s	None	Nurses	[22]
2019,	Smereka Eur J Pediatr	93	Pediatric HAL® S3005 Corpulus System®	CPR CPR+D	DL-Miller. UEScope	120 s	None	Paramedics	[20]

*CPR: cardiopulmonary resuscitation; CPR + D: cardiopulmonary resuscitation + difficult airways; DL: direct laryngoscopy; VLS: video-laryngoscopy. EM: Emergency Medicine; pICU: pediatric Intensive Care Unit staff. NS: not specified by the authors.*

Miller’s), while VLSs were separated according to the position of the screen/monitor (VLS-SoD and VLS-DM).

We initially hypothesized significant advantages of VLS over DL, both in terms of SR and TTI; our results support this

initial hypothesis of superiority of VLS approaches for both primary outcomes. Moreover, this finding was confirmed also in the sensitivity analyses where we added simulation studies with the manikin set with a difficult airway scenario, and by



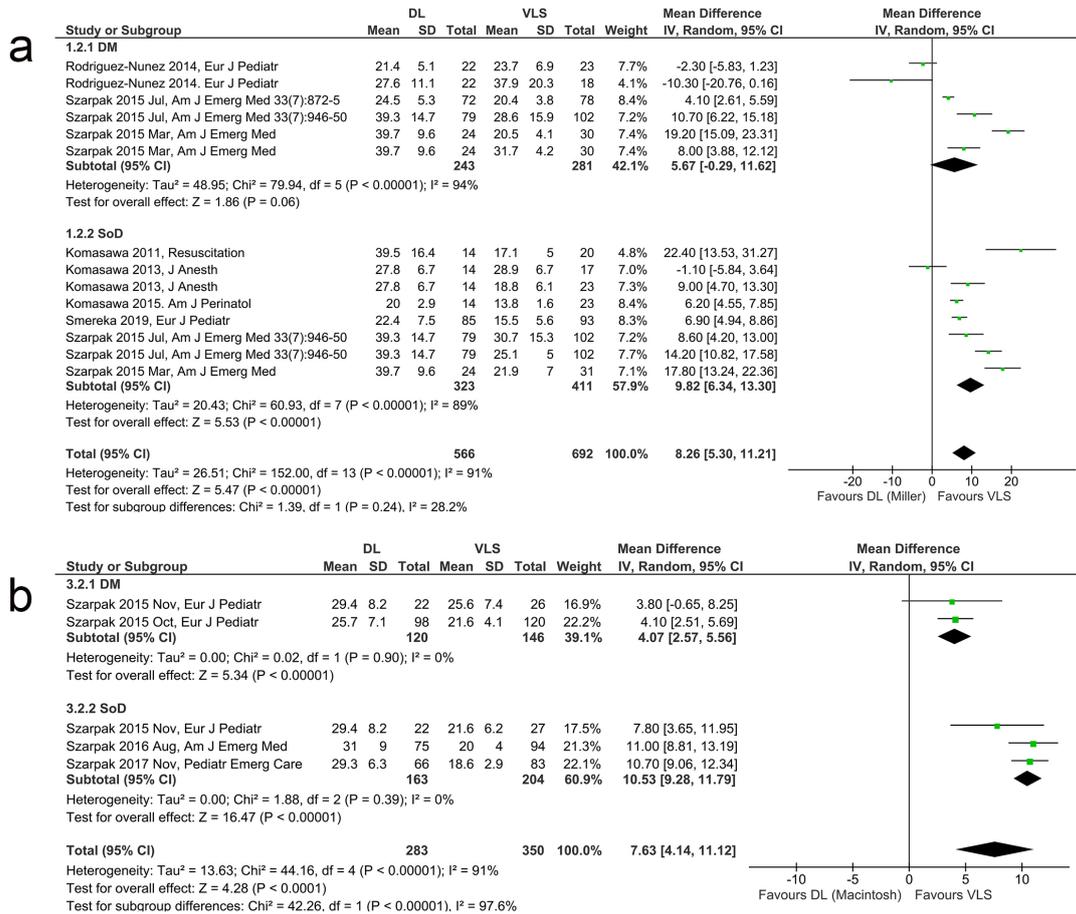
**FIGURE 1. Forest plot on the success rate of videolaryngoscopy (VLS) as compared to direct laryngoscopy (DL) with Miller blade (a) or Macintosh blade (b) under simulated conditions of pediatric resuscitation. CI: confidence interval; DM: distant monitor; IV: inverse variance; SoD: screen on device.**

all the sensitivity analyses conducted excluding one study at time. Apart from a significantly higher overall SR, the VLS devices ensured faster ETI than DL blades. In particular, VLS achieved ETI around 8 seconds faster than DL with Miller or Macintosh blades. Interestingly, when looking at the two types of VLS, our results indirectly suggest better performances of the VLS-SoD over VLS-DM. Such observation come from the evaluation of RR, MD, 95% CI and *p* values in multiple comparisons. Overall, it must be noted that a mean difference of 7 to 8 seconds between VLS and the two standard laryngoscopy blades may not be clinically relevant on oxygenation. Conversely, one may argue also that such timeframe is long enough to significantly increase the risk of aspiration.

From clinical perspectives, the available evidence on the best airway management strategy in critically ill children is relatively limited and sometimes conflicting. Two systematic reviews suggested prolonged intubation time and lower success rate with VLS [28, 29], but recent studies suggest benefits from VLSs [30–34]. However, the advantages of VLS over DL in the ongoing pediatric CPR setting have not been clinically studied. This aspect is not surprising since de-

signing a study for the best technique for airway management is challenging, and this challenge is probably brought at the highest level under very stressful conditions of ongoing pediatric resuscitation. These methodological difficulties, and the consequent gap in knowledge, could be partially compensated by results from simulation studies. Although the simulation in the field of airway management cannot entirely reproduce all real-life difficulties encountered during ETI (secretions and bleeding among others), simulation still represents an extremely valid training tool, and a recent meta-analysis [35] found that simulation-based curriculum for advanced airway management is significantly superior to no intervention and to non-simulation interventions.

Several studies have already shown that VLS may increase the effectiveness of ETI in emergency scenarios [36–38], so that some authors already suggested that VLS may be considered “plan A” for pediatric ETI during CPR. In clinical practice, performing ETI during ongoing chest compression impairs the steadiness of the airway visualization; under these conditions, VLSs have the advantages of producing not only a better visualization, but also a magnification of the glottis



**FIGURE 2. Forest plot on the time to intubation of videolaryngoscopy (VLS) as compared to direct laryngoscopy (DL) with Miller blade (a) or Macintosh blade (b) under simulated conditions of pediatric resuscitation. CI: confidence interval; DL: direct laryngoscopy; DM: distant monitor; IV: inverse variance; SoD: screen on device; VLS: video-laryngoscopy.**

region. This aspect is further amplified in the context of pediatric resuscitation where several operators care for a small patient.

Our indirect observation of better performances of the VLS-SoD over VLS-DM may be partially explained by the difficulty for the operator to keep the VLS in a steady position, whilst looking in another direction in the context of the unsteadiness produced by ongoing CPR. Indeed, moving the gaze towards the DM, the operator may partially lose control of the VLS positioning during chest compressions. Moreover, from clinical and practical perspectives one should consider that use of VLS-DM may be challenging during ongoing CPR. Indeed, adding a mobile column with the monitor for VLS may generate crowding around the small pediatric patient in presence of several operators and instruments (*i.e.*, emergency trolley with defibrillator). Although we do not suggest to over-interpret these sub-group results, it seems reasonable to prefer VLS-SoD also in consideration of their spatial arrangement.

Our study may provide some support to the guidelines for pediatric resuscitation, giving a boost to the use of VLS. However, it is important to note that our meta-analysis should not be interpreted as a support towards the use of ETI in pediatric resuscitation protocols, but just as an attempt to evaluate the performances of different devices for ETI. Currently, the AHA Committee does not discuss the choice of device for ETI during

CPR. Conversely, the ERC guidelines leave the decision on the device to the operator considering that benefits of VLS are operator-dependent and require training, and suggesting the use of VLS in case of expected additional difficulty (*i.e.*, immobilization of cervical spine). During ongoing resuscitation, the superiority of ETI as compared to airway management with SAD or BMV has not been demonstrated, for both adults and pediatric patients. In the adult population, a large randomized controlled trial found that among patients with out-of-hospital CA advanced airway management with SADs does not improve functional outcome as compared with ETI [39]. Regarding the pediatric patients, there are limited data on in-hospital CA, while studies on out-of-hospital CA suggests that ETI, SADs and BMV strategies achieve similar survival and favorable neurological function [40–42]. Therefore, operators should balance the risks of BMV strategy with the benefits and difficulties of ETI and/or SAD.

#### 4.1 Strengths and limitations

The main strength of our study is the systematic approach to detect and analyze evidence in the field with the attempt to group devices. We also included studies at low risk of bias and in most cases, participants had no significant experience in pediatric airway, thus decreasing the clinical heterogeneity in the participants analyzed. Therefore, the validity of our

results is certainly limited to the personnel without experience in pediatric airway management. However, our study has significant intrinsic limitations, mainly related to the simulation environment of the included studies. The role of simulation cannot be over-emphasized in the field of airways and a recent meta-analysis [35] supports the role of advanced airway management with simulation training in medical education. Moreover, simulation is invaluable for the approach to difficult scenarios; indeed, it would be ethically and methodologically difficult randomizing a patient to the use of one device over another in the context of unexpected difficult airways or during CA (or both). Nonetheless, simulation-based studies on airways have gross limitations and difficulty to fully reproduce all features of real-life. For instance, the presence of airway secretions and bleeding not only crucially influences the operator's performance, but these are very frequent in the difficult scenarios, especially after repeated ETI attempts. Moreover, comparability between manikins and human anatomy has been repeatedly questioned, both for adults and pediatric studies [43–45]. One study evaluated the anatomic features of the SimBaby simulator with the magnetic resonance images of 20 infants, and found that the simulator does not adequately reproduce upper airway anatomy [44]. For the above discussed reasons, the overall results in terms of TTI and SR summarized by our meta-analysis may not be applicable to real-life and may overestimate actual clinical performances. Indeed, in the setting of simulation it is already known that difficult scenarios may fail, and a greater-than-expected number of participants may achieve the difficult objective [46, 47]. In case of airway scenarios, guidelines recommend against “blind” insertion of endotracheal tube (or bougie) for the risk of trauma/bleeding and the low chances of success. However, achieving blind intubation in simulated studies is possible as participants could try to blindly pass the endotracheal tube as they do not perceive the risk to harm a manikin.

A part from the limitations due to the simulation environment, there are other issues in our meta-analysis. First, despite a reasonable number of studies included, we found that a limited number of scientific groups approached this topic. Indeed, one study group performed 9 of the 13 included studies and another group conducted 3 studies. This finding decreases the external validity of our findings. Second, the cut-off for declaring a failed attempt was not declared by half studies. Third, conducting a meta-analysis without grouping VLS would have not been feasible because of the vast number of devices available on the market. Considering the data available, we chose not to perform a trial sequential analysis to evaluate the robustness of our findings as there was heterogeneity in the device used [48].

## 5. Conclusions

Under simulated conditions of ongoing pediatric CPR, the use of VLSs guarantees higher overall SR and shorter TTI as compared to DL performed with Miller or Macintosh blade. Among VLSs, those with screen-on-device seem to have better performances than those with distant monitor. However, further studies are warranted to confirm this results in a clinical scenario.

## AUTHOR CONTRIBUTIONS

FS and ST—conceptualization; AD—methodology; AD and LLV—software; MA, SF and LLV—validation; SM and FM—formal analysis; SM—investigation; MA—resources; FM—data curation; SM and FM—writing—original draft preparation; SF—writing—review and editing; ST—visualization; LLV—supervision; FS—project administration. All authors have read and agreed to the published version of the manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest. Filippo Sanfilippo is serving as one of the Editorial Board members of this journal. We declare that Filippo Sanfilippo 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 MS.

## SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.signavitae.com/mre-signavitae/article/1523591859122651136/attachment/Supplementary%20material.docx>.

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