Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe

*Walid Habre, Nicola Disma, Katalin Virag, Karin Becke, Tom G Hansen, Martin Jöhr, Brigitte Leva, Neil S Morton, Petronella M Vermeulen, Marzena Zielinska, Krisztina Boda, Francis Veyckemans, for the APRICOT Group of the European Society of Anaesthesiology Clinical Trial Network**

Summary

Background Little is known about the incidence of severe critical events in children undergoing general anaesthesia in Europe. We aimed to identify the incidence, nature, and outcome of severe critical events in children undergoing anaesthesia, and the associated potential risk factors.

Methods The APRICOT study was a prospective observational multicentre cohort study of children from birth to 15 years of age undergoing elective or urgent anaesthesia for diagnostic or surgical procedures. Children were eligible for inclusion during a 2-week period determined prospectively by each centre. There were 261 participating centres across 33 European countries. The primary endpoint was the occurence of perioperative severe critical events requiring immediate intervention. A severe critical event was defined as the occurrence of respiratory, cardiac, allergic, or neurological complications requiring immediate intervention and that led (or could have led) to major disability or death. This study is registered with ClinicalTrials.gov, number NCT01878760.

Findings Between April 1, 2014, and Jan 31, 2015, 31 127 anaesthetic procedures in 30 874 children with a mean age of 6·35 years (SD 4·50) were included. The incidence of perioperative severe critical events was 5·2% (95% CI 5·0–5·5) with an incidence of respiratory critical events of 3·1% (2·9–3·3). Cardiovascular instability occurred in 1·9% (1·7–2·1), with an immediate poor outcome in 5·4% (3·7–7·5) of these cases. The all-cause 30-day in-hospital mortality rate was 10 in 10 000. This was independent of type of anaesthesia. Age (relative risk 0·88, 95% CI 0·86–0·90; p<0·0001), medical history, and physical condition (1·60, 1·40–1·82; p<0·0001) were the major risk factors for a serious critical event. Multivariate analysis revealed evidence for the beneficial effect of years of experience of the most senior anaesthesia team member (0·99, 0·981–0·997; p<0·0048 for respiratory critical events, and 0·98, 0·97–0·99; p=0·0039 for cardiovascular critical events), rather than the type of health institution or providers.

Interpretation This study highlights a relatively high rate of severe critical events during the anaesthesia management of children for surgical or diagnostic procedures in Europe, and a large variability in the practice of paediatric anaesthesia. These findings are substantial enough to warrant attention from national, regional, and specialist societies to target education of anaesthesiologists and their teams and implement strategies for quality improvement in paediatric anaesthesia.

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*Investigators listed at the end of the Article

Department of Anaesthesia, Pharmacology and Intensive Care, University Hospitals of Geneva, Geneva, Switzerland (Prof W Habre MD); University of Geneva, Geneva, Switzerland (Prof W Habre); Department of Anaesthesia, Istituto Giannina Gaslini, Genova, Italy (N Disma MD); Bolyai Institute (K Virag MSc) and Department of Medical Physics and Informatics (Prof K Boda PhD), University of Szeged, Szeged, Hungary; Department of Anaesthesia and Intensive Care, Cnopf´sche Kinderklinik/Klinik Hallerwiese, Nürnberg, Germany (K Becke MD); Department of Anaesthesia and Intensive Care, Odense University Hospital, Odense, Denmark (T G Hansen MD); Department of Clinical Research, The University of Southern Denmark, Odense, Denmark (T G Hansen); Department of Anaesthesia, Luzerner Kantonsspital, Luzern, Switzerland (M Jöhr MD); Research Department, European Society of Anaesthesiology, Brussels, Belgium (B Leva MT); Department of Anaesthesia, Royal Hospital For Children, Glasgow, UK (N S Morton MD); University of Glasgow, Glasgow, UK (N S Morton); Department of Anaesthesiology, Maastricht University Medical Centre, Maastricht, Netherlands (P M Vermeulen PhD); Department of Anaesthesiology and Intensive

Introduction

Guidelines for paediatric anaesthesia management and structured programmes for specific training have been developed in Europe during the past decade to standardise practice and improve patient safety. The incidence, nature, and outcome of severe critical events in children during and immediately after anaesthesia in Europe, and the effects of variability in practice are unknown. Most of the literature on paediatric anaesthesia morbidity and mortality comprises clinical audits focusing on a single institution or country,[1–3] which were not sufficiently powered to study rare, severe complications or mortality.[4] Moreover, differences in study design and in the definitions of severe complications make comparisons between the studies problematic.

In 2014, a large North American register was initiated as part of a safety and quality improvement programme that revealed an incidence of severe critical events in paediatric anaesthesia of 0·14%.[5] This finding is in line with previous reports from single centres or countries, the findings of which show that the rate of major perioperative complications causing severe morbidity, mortality, or both, after general[3,6] or regional anaesthesia,[7–10] is low. Most studies have highlighted respiratory complications as the primary cause of severe adverse outcome following sedation or general anaesthesia in children.[11–13] Other publications have pointed out a significant increase in haemodynamic-related severe critical events as a consequence of bleeding or inadequate fluid management.[5,14] Although most of these studies attempted to identify major risk factors (such as age <1 year, the presence of comorbidities, and specific surgical procedures), identification of predictable and preventable risks is of paramount importance as the basis

Care, Wroclaw Medical University, Wroclaw, Poland (M Zielinska MD); and Département d'Anesthésie-Réanimation pédiatrique, Hôpital Jeanne de Flandre, CHRU de Lille, Lille, France (F Veyckemans MD)

Correspondence to: Prof Walid Habre, Department of Anaesthesiology, Pharmacology and Intensive Care, University Hospitals of Geneva, Geneva CH-1206, Switzerland
walid.habre@hcuge.ch

See Online for appendix

Research in context

Evidence before this study

There is no clear information about the morbidity and mortality associated with anaesthesia management in children in Europe. We used the MeSH terms "morbidity", "mortality", "severe complications", "adverse events", "children", "anaesthesia", and "perioperative", to search MEDLINE and we limited the results to include studies done in Europe only. Most studies about paediatric anaesthesia morbidity and mortality that have been published between Jan 1, 1971, and Jan 1, 2014, are the results of clinical audits focusing on a single institution or country.

Moreover, studies focusing on adverse events in the perioperative period have used a variety of definitions for the occurrence of severe adverse events, which makes any benchmarking comparison difficult. Although respiratory complications were considered to be the primary cause of perioperative complications in Europe, reports from outside Europe suggested a significant increase in haemodynamic-related severe adverse events leading to poor outcomes, such as perioperative cardiac arrest. A registry in the USA included morbidity and mortality data from larger specialist institutions and has confirmed the evolving role of cardiovascular events in these outcomes while documenting a rate of serious adverse perioperative events of approximately 0·14%. Age, comorbidities, and physical status of the child have been recognised as risk factors.

Added value of this study

Our study was prospective, multicentre, multinational, and pan-European in scope, and we used detailed definitions of severe critical events. The critical events were captured with a high degree of fidelity in a large cohort of paediatric cases from a range of institutions. A high rate of severe critical events was revealed, with a large variable incidence across Europe. The nature of events and their outcomes are described in detail. We identified new risk factors for severe critical events, including inexperience of the anaesthesiology team, especially in the management of the youngest and most ill patients. The discovery of widely variable clinical practice among the participating centres in Europe, and even within countries, advocates for the establishment of a European register to monitor peri-anaesthetic morbidity and mortality in children. A cutoff age of 3 years was estimated, below which children should be managed by more specialist services to reduce risk of adverse events and improve outcomes.

Implications of all the available evidence

These findings warrant attention from national, regional, and specialist scientific societies, and provide a basis to identify areas for further training, clinical research, and for quality improvement initiatives. Moreover, some centralisation of care for the youngest and most ill infants is needed to allow access to more experienced health-care teams to reduce the adverse event rate and improve outcomes.

for implementation of paediatric practice standards to improve the quality and safety of anaesthesia for children throughout Europe.

This prospective observational multicentre cohort study was designed to identify the incidence and nature of severe critical events and their outcomes in children undergoing any type of anaesthesia in Europe. These events were defined as the occurrence of respiratory, cardiac, allergic, or neurological complications requiring immediate intervention and that led (or could have led) to major disability or death. We also aimed to identify the risk factors contributing to these severe critical events, and to describe the variations in paediatric anaesthesia practice throughout Europe.

Methods

Study design

We prospectively collected perioperative data that described the anaesthesia management of consecutive children admitted to 261 participating centres across 33 European countries. Children were recruited during a consecutive 2-week period, which was determined in advance by each participating centre, between April 1, 2014, and Jan 31, 2015. Patients were followed for up to 60 min after anaesthesia or sedation, and the child's status at discharge or at 30 days, if still in hospital, was reported. All children from birth to 15 years of age undergoing an inpatient or outpatient diagnostic or surgical procedure, whether elective, urgent or emergency, in-hours or out-of-hours, under sedation or general anaesthesia, with or without regional analgesia, or under regional anaesthesia alone, were eligible for inclusion. Children were excluded from the study if they were aged 16 years and older, were admitted directly to the operating room already intubated, or anaesthesia procedures were done in the neonatal or paediatric intensive care unit.

Participating investigators registered on a voluntary basis through a call for centres sent to active members of the European Society of Anaesthesiology (ESA) and the European Society for Paediatric Anaesthesiology (ESPA). Ethics requirements differed among countries and even within a given country. All participating centres applied for formal ethics approval or a waiver, as appropriate (appendix p 1).

Procedures

Before starting to recruit patients, each local investigator provided details of their hospital's paediatric anaesthesia activity, perioperative care facilities, annual number of procedures, and the number of certified or dedicated anaesthesiologists for paediatric practice. Data obtained from the recruited children were collected on data acquisition sheets, which were then entered anonymously on a secure internet-based electronic case record form (OpenClinica, Boston, MA, USA).

All severe critical events, including their time of occurrence (during anaesthesia induction, maintenance, or emergence, or in the post-anaesthetia care unit), the treatment needed, and the immediate outcome were documented. These severe critical events included all episodes of laryngospasm, bronchospasm, pulmonary aspiration, drug error, anaphylaxis, cardiovascular instability, neurological damage, perioperative cardiac arrest, and the occurrence of stridor at emergence from anaesthesia or in the post-anaesthesia care unit.

We defined the primary endpoint as the occurrence of any severe critical event requiring immediate intervention that led, or could have led, to major disabilities or death. Secondary outcome measures were the potential consequences of those severe critical events (ie, no harm, minor sequelae, major sequelae, in-hospital mortality) at discharge from the hospital or at 30 days post-anaesthesia or sedation.

Full details of the patient history, type of procedure, anaesthetic and airway management, regional analgesia, the experience of the anaesthetic team in charge, and postoperative care (up to 60 min) were also recorded (appendix p 2–4).

For more on the **definition of critical events** see http://www.esahq.org/research/clinical-trial-network/ongoing-trials/apricot/documents

Statistical analysis

On the basis of the largest retrospective study in a referral centre in Europe,[3] and considering the probability of occurrence of any of the severe critical events studied as a primary endpoint, we anticipated that a minimum of approximately 25 000 patients would provide a 95% CI for the overall incidence of severe critical events with an acceptable confidence width assuming that the lowest incidence of severe critical events is 0·1%, (ie, 95% exact CI is 0·065–0·147). We identified a similar minimum number of subjects when estimating the sample size on the comparisons between institutions. We defined an a priori detailed statistical analysis plan in the initial protocol.

We did statistical analysis with SPSS (version 24) and SAS (version 9.4) statistical software. Data are expressed as mean (SD) for continuous variables and percentages for categorical variables. Univariate and multivariate methods were used to test factors associated with the endpoints. We used these methods on all available data and when all risk factors were present. We considered that multiple procedures were sometimes done on the same individuals, so we did univariate analysis with a generalised linear model, using binomial distribution for the dependent variable, log-link function, and unstructured covariance structure for correlated observations. We estimated univariate relative risks (RRs) and 95% CIs from the model.

We did receiver operating characteristic analysis, using age as a continuous variable, to identify a cutoff age where the overlap of the distribution of ages with and without a complication was minimal.

We did multivariate analyses with a hierarchical RR regression model with log-link function and binomial dependent variable, taking the participating centre as a random factor. To avoid multicollinearity, we examined correlations between the independent variables by factor analysis with principal component method, and by correspondence analysis. The factor analysis showed that grouping some variables were in line with the medical and clinical considerations. We collapsed mostly correlated binary or dichotomised categorical variables into one variable using the OR logical operator. We used these collapsed variables in the multivariate analyses with the remaining nominal and continuous variables. Some variables, which were clearly insignificant by the univariate methods or not medically meaningful, were not included in the multivariate models. We tested medically plausible interactions and model fit, and we calculated estimated RRs with 95% CIs and p values. Despite the collapsed variables, multivariate models did not include all cases, so we compared all covariates for complete cases and for groups with missing data by descriptive statistics. In all cases, we used two-sided tests.

This study is registered with ClinicalTrials.gov, number NCT01878760.

Role of the funding source

The funding source provided the infrastructure for the trial, identified the national study coordinating investigators, liaised with the local investigators regarding their ethics submission process and the inclusion period, and monitored the data entry and cleaning. WH, FV, KV, BL, and KB had access to the raw data. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit the manuscript for publication.

Results

For the **protocol and case report form** see http://www.esahq.org/research/clinical-trial-network/ongoing-trials/apricot/documents

The final APRICOT exported dataset, dated March 24, 2016, included 30 874 participants and 31 127 anaesthetic procedures, with 188 children having more than one anaesthetic procedure during the 2-week inclusion period (from two to ten anaesthetic procedures; figure 1). The dataset represented 88% of all procedures done in the participating centres during the 2-week inclusion period (appendix p 1).

The mean age of the enrolled children was 6·35 years (SD 4·5) comprising 361 (1·2%) neonates, 2912 (9·4%) infants (aged 28 days to 1 year-old), 13 463 (43·6%) pre-school children (1–5 years), 9229 (29·9%) schoolchildren (6–12 years), and 4908 (15·9%) adolescents (13–15 years). The age (but not the weight) of one child was not reported. A history of prematurity was reported in 2344 (7·6%) of the children with a mean gestational age at birth of 32·3 weeks (SD 3·5) weeks, but these data were missing in 11% (n=3461) of cases.

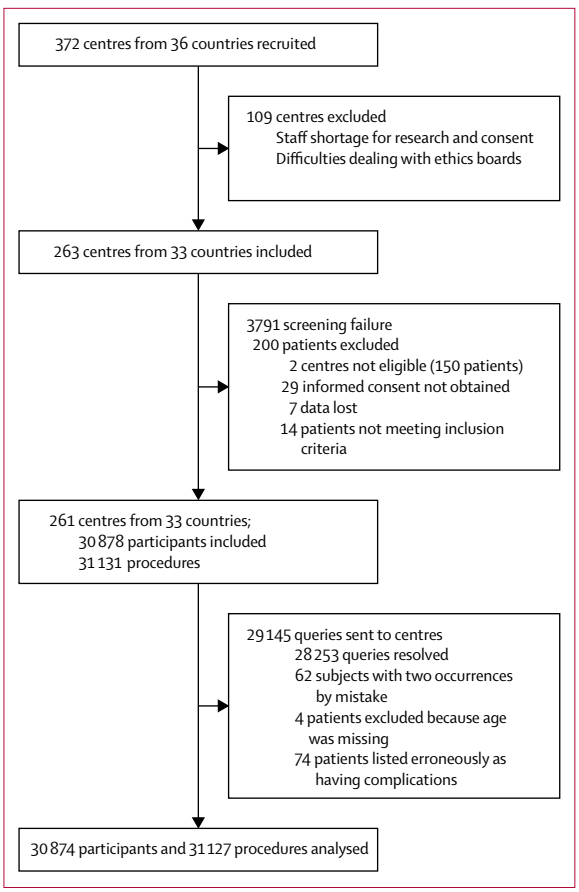

Figure 1: **APRICOT trial profile**

Applying receiver operating characteristic analysis with age showed a threshold cutoff age of 3·77 years for the occurrence of severe critical events, when the sum of sensitivity and specificity was at a maximum.

Table 1 lists the American Society of Anesthesiology Physical Status (ASA-PS) distribution of the patients, and patient characteristics and relevant medical history are summarised in the appendix (p 2).

Details of the anaesthesia plans and the scheduled times of the procedures are shown in the appendix (pp 3–4). 40 different drug combinations were used for premedication, and 100 different drug combinations were used for induction of anaesthesia. Inhalational induction was used in younger children (mean age 4·87 years [SD 3·8]) compared with intravenous induction (7·99 [4·6]; p<0·001). Indication, mean age, and outpatient and inpatient distribution, as well as the schedule type of all procedures performed, are shown in the appendix (pp 5–6). The composition of the anaesthesia team taking care of the child during the procedures is also shown (appendix p 7).

1478 children (4·8%) had severe critical events. The total number of reported severe critical events occurring during or immediately after anaesthesia was 1637 (5·3% of the 31127 procedures), with 1335 children having one severe critical event, 127 children having two, 14 children having three, and two having four. The estimated incidence of perioperative severe critical events was 5·2% (95% CI 5·0–5·5). This incidence was significantly higher during general anaesthesia than under sedation (RR 2·69, 95% CI 1·38–5·26; p<0·0001), and was lower when anaesthesia was done outside of the operating room (eg, MRI, radiotherapy) than when inside (RR 0·57, 0·47–0·70; p<0·0001). Of the reported severe critical events, 283 (17·3%) of 1637 resulted in additional post-anaesthesia treatments, prolonged treatment in hospital, or both.

Tables 2–4 summarise the incidence of respiratory severe critical events (laryngospasm, bronchospasm, bronchial aspiration, and post-anaesthesia stridor), cardiovascular severe critical events, drug errors and their time of occurrence, the applied treatments, and the immediate outcome.

The incidence of severe laryngospasm was 1·2% (95% CI 1·1–1·3) and of bronchospasm, 1·2% (1·1–1·3). Bronchial aspiration was reported in 29 patients (with two having episodes at two different times of the anaesthesia), corresponding to an incidence of 9·3 per 10000 cases or 0·1% (0·06–0·13). Finally, the incidence of post-anaesthetic stridor was 0·7% (0·6–0·8) for the whole population studied, and 1·1% (0·9–1·3) for those who had undergone tracheal intubation. The incidence of cardiovascular instability requiring an intervention was 1·9% (95% CI 1·7–2·0). In 32 (5·5%) of the cases, the outcome was poor: haemodynamic instability resulted in cardiac arrest in eight patients, coagulopathy in 19, and rescue treatments (extracorporeal membrane oxygenation, re-operation, etc) in nine others.

Ten episodes of cardiac arrest occurred in nine patients out of 30874, or 0·03% (95% CI 0·01–0·05; table 5). Hypoxaemia was the plausible cause for cardiac arrest in four cases, while low cardiac output occurred in four patients, and hypotension in two others. None of the children died during the perioperative period but at 30 days, three children had died and three others were still in hospital.

The incidence of drug errors (eg, wrong dose, drug, or site of administration) was 49 (0·2%, 95% CI 0·1–0·2) (table 4). Drug error (epinephrine) led to a severe immediate adverse outcome in one patient.

Figure 2 shows the distribution of the main respiratory and cardiovascular critical events according to age category. The incidence of cardiovascular and respiratory critical events was significantly higher in neonates (0–1 month) and infants (1 month to 1 year), with neonates having the highest rate of cardiovascular complications (12·1%, 95% CI 8·9–15·9; p<0·0001).

Severe critical events occurred significantly more frequently with increasing ASA risk category: ASA I, 3·5% (95% CI 3·2–3·7); ASA II, 5·7% (5·0–5·7); ASA III, 9·0% (8·0–10·0); ASA IV and V, 15·0% (12·1–18·5); overall p<0·0001.

	n (%)	Mean age (SD), 95% CI	Anaesthesia team, n (%)			
			Specialist anaesthesiologist with mainly (>80%) paediatric cases	Specialist anaesthesiologist with frequent (50–80%) paediatric anaesthesia cases	Specialist anaesthesiologist with occasional (<50%) paediatric anaesthesia cases	Anaesthesiologist in training, anaesthetic nurse, or technician
ASA I	18 883 (60·7%)	6·6 (4·4), 6·5–6·6	10 182 (53·9%)	2863 (15·2%)	4234 (22·4%)	1601 (8·5%)
ASA II	8739 (28·1%)	6·2 (4·6), 6·1–6·3	5629 (64·4%)	1128 (12·9%)	1374 (15·7%)	608 (7·0%)
ASA III	2987 (9·6%)	5·6 (4·7), 5·5–5·8	2149 (72·0%)	318 (10·6%)	315 (10·6%)	204 (6·8%)
ASA IV	498 (1·6%)	4·4 (4·6), 4·0–4·8	393 (78·9%)	48 (9·6%)	44 (8·8%)	13 (2·6%)
ASA V	12 (0·04%)	1·5 (3·2), –0·5 to 3·6	11 (91·7%)	1 (8·3%)	0 (0·0%)	0 (0·0%)
Total	31 119 (100%)	6·3 (4·5), 6·3–6·4	18 364 (59·0%)	4358 (14·0%)	5967 (19·2%)	2426 (7·8%)

Values missing for eight procedures. ASA I: normal healthy patient. ASA II: mild systemic distress. ASA III: severe systemic distress. ASA IV: severe systemic distress that is a constant threat to life. ASA V: moribund patient who is not expected to survive without surgical intervention. ASA=American Society of Anesthesiologists.

Table 1: **Mean patient age in years (standard deviation; 95% confidence interval) and distribution among anaesthesia teams according to ASA physical status**

The incidence of severe critical events significantly differed between the anaesthesia teams only when individuals in ASA-PS III, IV, and V were grouped: compared with dedicated providers, the incidence was 1·34-times higher for frequent providers (RR=1·34, 95% CI 1·00–1·79; p=0·051), and 1·48-times higher for occasional providers (1·48, 1·11–1·96; p=0·007). This difference was only evident for cardiovascular critical events, where the risk was higher for frequent providers (1·47, 1·03–2·09; p=0·035) and for occasional providers (1·79, 1·29–2·50, p=0·001), compared with dedicated providers.

Table 5 describes the details of the patients who had a neurological event, with an incidence of 1·6 per 10 000 cases or 0·02% (95% CI 0·002–0·03), and those with anaphylaxis, with an incidence of 1 per 10 000 cases or 0·01% (0·002–0·025). No neurological critical events were reported after regional analgesia, and most of the others could not be related to anaesthesia management.

Figure 3 illustrates the incidence of severe critical events occurring in the participating centres across 33 European countries, and the relative contribution of respiratory and cardiovascular complications to the total incidence of severe critical events in each country. We observed a large range (0·4–13·3%) for the incidence of severe respiratory critical events (0·2–6·7% for laryngospasm, 0·3–3·2% for bronchospasm, 0·3–6·7% for stridor, and 0·1–0·4% for bronchial aspiration), cardiovascular critical events (0·2–6·7%), and for the incidence of the other events (0·1–4·4 %).

After univariate and multivariate analyses, age (considered as a continuous variable) was a risk factor for respiratory critical events (table 6), with a decreased risk of 12% for respiratory severe critical events for each increasing year of age. Univariate analysis revealed that history of prematurity increased the relative risk for the occurrence of these respiratory complications by a factor of almost two (table 6). Multivariate analysis with collapsed variables

	Laryngospasm (n=368)	Bronchospasm (n=371)	Bronchial aspiration (n=29)	Stridor (n=208)
Time of occurrence, n (%)				
Induction	132 (35·0%)	118 (29·5%)	13 (41·9%)	..
Maintenance	69 (18·2%)	99 (24·7%)	8 (25·8%)	..
Awakening	165 (43·6%)	167 (41·7%)	8 (25·8%)	157 (70%)
Post-anaesthesia care unit	12 (3·2%)	16 (4·0%)	2 (6·5%)	67 (30%)
Treatment, n (%)				
Propofol	255 (52·5%)	..	..	..
Succinylcholine	69 (14·2%)	..	..	..
Intubation/prolonged intubation	73 (15·1%)	56 (12·1%)	4 (9·3%)	..
Bronchodilators	..	224 (48·3%)	13 (30·2%)	..
Epinephrine	..	19 (4·1%)	..	54 (23·3%)
Deepening anaesthesia	..	85 (18·3%)	..	..
Bronchotracheal suction	..	..	23 (53·5%)	..
Antibiotics	..	..	2 (4·7%)	..
CPAP	..	..	1 (2·3%)	84 (36·2%)
Intravenous steroids	..	..	..	31 (13·4%)
Other treatments	88 (18·1%)	80 (37·3%)	..	63 (27·1%)
Outcome, n (%)				
Uneventful	358 (97·1%)	216 (57·0%)	18 (54·6%)	198 (95·2%)
Intubation/prolonged intubation	9 (2·4%)	11 (2·9%)	4 (12·1%)	9 (4·3%)
Pulmonary oedema	1 (0·3%)	..	..	..
Hypoxaemia	..	145 (38·3%)*	10 (30·3%)	..
Admission to intensive care unit	..	2 (0·5%)	..	..
Pneumonia	..	..	1 (3·0%)	..
Tracheostomy	..	..	..	1 (0·5%)
Other	..	5 (1·3%)	..	..

Data are n (%); there were some repeated events. Airway interventions include application of CPAP, PEEP, or oxygen. CPAP=continuous positive airway pressure. PEEP=positive end-expiratory pressure.*Hypoxaemia defined as oxygen saturation less than 90%.

Table 2: **Time of occurrence, treatment, and outcome of perioperative respiratory severe critical events**

	Severe cardiovascular events (n=549)
Time of occurrence, n (%)*	
Induction	143 (21·9%)
Maintenance	454 (69·4%)
Awakening	32 (4·9%)
Post-anaesthesia care unit	25 (3·8%)
Type of event,n (%)†	
Bleeding	112 (16·0%)
Arrhythmia (all)	136 (19·5%)
Arrhythmia (bradycardia)	86 (12·3%)
Arrhythmia (ventricular tachycardia)	2 (0·3%)
Arrhythmia (ventricular fibrillation)	1 (0·2%)
Hypotension	384 (54·9%)
Vasodilation	37 (5·3%)
Hypertension	7 (1·0%)
Cardiac dysfunction	4 (0·7%)
Myocardial ischaemia	2 (0·3%)
Miscellaneous	14 (2·0%)
Treatment, n (%)‡	
Fluid resuscitation	316 (33·7%)
Blood products	124 (13·3%)
Fluids and blood products§	29 (3·1%)
Vasopressors	301 (32·4%)
Fluids/blood products and vasopressors§	185 (19·7%)
Atropine	138 (14·7%)
Defibrillation	8 (0·9%)
Other treatments	51 (5·5%)
Outcome, n (%)¶	
Uneventful	560 (94%)
Cardiac arrest	8 (1·3%)
Coagulopathy	19 (3·2%)
Extracorporeal membrane oxygenation	2 (0·3%)
Myocardial ischaemia	1 (0·2%)
Admission to intensive care unit	5 (0·8%)
Reoperation for haemostasis	2 (0·3%)

Data are n (%).*n=654. †n=696. ‡n=938. §Subgroup of children who received both interventions for cardiovascular critical events. ¶n=597.

Table 3: **Time of occurrence, type of severe cardiovascular critical events, treatment applied, and outcome**

	Drug errors (n=49)
Time of occurrence, n (%)*	
Induction	22 (44%)
Maintenance	22 (44%)
Awakening	5 (10%)
Post-anaesthetic care unit	1 (2%)
Type of events, n (%)	
Wrong dose	29 (59·2%)
Wrong drug	8 (16·3%)
Wrong site of administration	12 (24·5%)
Wrong site of femoral block	1 (2·0%)
Subcutaneous administration of drugs	7 (14·0%)
Fluid extravasations	4 (8·0%)
Treatment, n (%)	
None	42 (85·7%)
Naloxone	5 (10·2%)
Diuretics	1 (2·0%)
Fluid resuscitation	1 (2·0%)
Outcome, n (%)	
No sequelae	16 (32·7%)
Minor sequelae	32 (65·3%)
Major sequelae†	1 (2·0%)

*For one patient, drug error was reported during induction and maintenance and for another, during maintenance and awakening. †Patient was admitted to the intensive care unit after receiving epinephrine instead of atropine with neostigmine.

Table 4: **Time of occurrence, type of drug error, treatment applied, and outcome**

revealed that the presence of sensitised airways (defined as airways with acute or chronic inflammation) and physical condition (prematurity, fever, handicap, snoring, medication, or ASA-PS >2) are important risk factors for the occurrence of respiratory severe critical events (table 6).

Although there was no evidence for an effect of the type of health institution or anaesthesia team on the occurrence of respiratory severe critical events, we found weak evidence for the potential protective role of an experienced anaesthesiologist (1% decrease in occurrence per year of experience; table 5). Both inhalation induction and airway management (use of endotracheal tube, supraglottic airway, or both) were significantly associated with a higher risk of respiratory severe critical events.

Table 7 summarises the risk factors for cardiac severe critical events. The risk was significantly higher for surgical procedures compared to non-surgical procedures, specifically cardiac surgery (RR 16·92 [95% CI 13·67–20·93]) and cardiac catheterisation (3·20 [1·71–5·85]). Multivariate analysis confirmed the significant effect of physical condition and the protective role of an experienced anaesthesiologist (2% decrease in risk of cardiac severe critical events per year of experience; table 7).

Considering the low occurrence of other critical events (ie, anaphylaxis, neurological events, drug errors, and bronchial aspiration), identifying risk factors in a univariate and multivariate analysis was only possible for bronchial aspiration (appendix, p 8), which occurred more frequently in emergency situations (RR 8·43 [95% CI 1·97–36·10]).

There were 38 participating centres from 14 countries that did not report any severe critical events. A subgroup analysis revealed that children included from these centres were significantly older, were more likely to be normal healthy patients (ASA-PS I), fewer had a history of prematurity and handicap, fewer underwent tracheal intubation, and more were managed by more experienced anaesthesiologists (p<0·001; data not

	Age	ASA category	Procedure	Timing	Clinical signs	Perioperative severe adverse event	Plausible cause	Treatment	Outcome	Status at 30 days
Children with perioperative cardiac arrest (n=9)										
Case 1	8m	II	Trauma	Maintenance	..	Hypotension, hypoxaemia	Displacement endotracheal tube during endoscopic thoracic surgery, severe hypoxaemia, and hypotension	CCM, atropine, ephedrine, re-intubation	Uneventful	Discharged home
Case 2	4y 6m	II	ENT	PACU	..	Hypoxaemia	Pneumothorax under tension (closure tracheostomy)	CCM, epinephrine	Uneventful	Still in hospital
Case 3a	4y 3m	IV	Cardiac catheterism (eg, DORV, VSD, ASD, pulmonary stenosis)	Induction (ketamine)	..	Arrhythmia, hypotension	Low cardiac output at induction	CCM, epinephrine	Recovered; admitted to ICU for 24 hours	Death from cardiopathy
Case 3b	4y 3m	V	Cardiac surgery	Induction (etomidate and ketamine)	..	Arrhythmia, hypotension	Low cardiac output at induction from complex cardiopathy	CCM, OCM, defibrillation, epinephrine, calcium, bicarbonate	Bypass in urgent situation; admitted to ICU (for 19 days)	Death from cardiopathy
Case 4	14y 8m	II	Trauma	Maintenance	..	Hypoxaemia, haemodynamic instability, bradycardia	Trachea blocked by endobronchial blocker	CCM, atropine	Uneventful	Discharged home
Case 5	1m	II	Gastrointestinal surgery	Induction	..	Severe hypoxaemia (SpO_2<85% for >2 min), bradycardia, asystole	Difficult ventilation; no intubation	CCM, epinephrine	Haemodynamic instability; neurological controls normal	Discharged home
Case 6	5d	IV	Cardiac surgery	Maintenance	..	Haemodynamic instability	Norwood operation	CCM, defibrillation, extracorporeal membrane oxygenation	Multiple organ failure and death	Death
Case 7	10y 10m	V	Gastrointestinal surgery	Induction (rapid sequence induction with propofol-atracurium)	..	Bleeding, hypotension, transfusion	..	CCM, epinephrine, phenylephrine	Death from sepsis	Death
Case 8	2m	III	Gastroenterology endoscopy	Induction	..	Hypotension, severe hypoxaemia (SpO_2 about 60%)	Cardiac dysfunction in a complex patient; low cardiac output	CCM, epinephrine, phenylephrine	Uneventful	Still in hospital
Case 9	29d; born at 36 weeks	IV	Thoracic	Maintenance	..	Hypotension, bradycardia	Under ACE inhibitors for coarctation	CCM, atropine	Uneventful	Discharged to acute centre

(Table 5 continues on next page)

shown). Thus, a Spearman rank correlation analysis was done on the subgroup of patients included in the 223 centres that reported any severe critical events to characterise a potential relationship between the incidence of severe critical events and the number of patients recruited from each centre. There was some evidence for a lower incidence of respiratory and cardiovascular severe critical events in the centres with high caseload (appendix p 9).

24789 (80·3%) patients were admitted to the post-anaesthesia care unit (recovery room), while 4040 (13·1%) were sent directly to the ward. 603 (1·9%) children were admitted to an intermediate care unit, and 1435 (4·7%) were admitted to an intensive care unit. Oxygen was delivered systematically in 43·7% of cases. The mean duration of stay was 2·1 h (SD 23·0) hours in the post-anaesthesia care unit, 1·1 days (3·9) in the intermediate care unit, and 4·3 days (7·5) in the intensive care unit.

Status at 30 days post-anaesthesia or post-sedation was available in 29 094 cases. 27 943 children were discharged home (96%), with 305 (1·1%) sent to a convalescent centre, and 171 (0·6%) to an acute centre; 640 (2·2%) patients were still in hospital.

	Age	ASA category	Procedure	Timing	Clinical signs	Perioperative severe adverse event	Plausible cause	Treatment	Outcome	Status at 30 days
(Continued from previous page)										
Children with neurological symptoms (n=5)										
Case 1	7y 10m	III	..	Awakening	Seizures	..	Known complex epilepsy; seizure at extubation	Barbiturates	Seizures	Discharged home
Case	2y 5m	III	..	Induction	Transient seizures during sevoflurane induction	..	Not related to anaesthesia; patient with leukaemia on vincristine therapy	None	Uneventful	Discharged home
Case 3	7y 1m	IV	..	Awakening	Loss of motor movements after scoliosis surgery with difficult interpretation of somatosensory evoked potential	..	Not related to anaesthesia	Reoperation with decompressive laminectomy	No neurological deficit	Still in hospital
Case 4	14y 5m	II	..	Maintenance	Grand mal seizure before awakening	..	Unknown—all investigations negative	None	Uneventful	Discharged home
Case 5	1y 4m	I	..	Awakening/ PACU	Unreported, despite query		Unreported	Benzodiazepines	Psychomotor agitation	Discharged home
Children with anaphylaxis (n=3)										
Case 1	8y 4m	I	..	Maintenance	Hypotension	..	Erythromycin (confirmed)	Fluid resuscitation, phenylephrine	Uneventful	Discharged home
Case 2	9y 9m	I	..	PACU	Not reported	..	Neostigmine (suspected)	Intravenous steroids, H_1 receptor antagonist	Uneventful	Discharged home
Case 3	2y 11m	II	..	Maintenance	Hypotension	..	Latex allergy (confirmed)	Epinephrine	Admitted to intensive care	Discharged home

Age is in years (y), months (m), and days (d). One patient (case 3) had two distinguished episodes on two different days. ASA=American Society of Anesthesiology. CCM=closed chest massage. ENT=ear, nose, and throat surgery. PACU=post-anaesthesia care unit. DORV=double outlet right ventricle. VSD=ventricular septal defect. ASD=atrial septal defect. ICU=intensive care unit. OCM=open chest massage. SpO_2=pulse oximeter oxygen saturation. ACE=angiotensin-converting enzyme.

Table 5: **Details of the children with perioperative cardiac arrest, neurological symptoms, or anaphylaxis**

The overall mortality rate at 30 days was 30, or 0·1% (95% CI 0·07–0·14). None of the reported deaths were anaesthesia-related. Sepsis was reported as the most frequent cause of death (eight patients), while multiple organ failure (three), congenital abnormalities (three), viral encephalitis (four), congenital heart disease (three), respiratory distress syndrome (two), haematological diseases (two), chemotherapy-associated lung haemorrhage (one), pulmonary embolism (one), and epidermolysis bullosa (one) were also reported. For two cases the cause of death was unknown.

Discussion

We did a large prospective multicentre cohort study to determine the incidence and nature of severe critical events in children undergoing anaesthesia in Europe. The results show a large variability across the participating centres in 33 European countries. Respiratory-related severe critical events were the most frequent complications reported in all age groups, whereas cardiovascular incidents were predominantly reported in neonates and infants. Although the outcome of most severe critical events was uneventful, additional treatment strategies or prolonged hospitalisation was needed in one in six patients who had a critical event. Large variations in paediatric anaesthesia practice in Europe were documented, highlighting the urgent need for more widespread implementation of good clinical practice guidelines and standards of paediatric anaesthesia management across Europe.

The design of this study was an anonymised observational audit of current paediatric anaesthesia practice, with anaesthesia management left entirely at the discretion of the health-care provider. Local ethics committees differed in their opinion regarding the need for individual written parental informed consent, and thus we were unable to include all children anaesthetised during each 2-week inclusion period, since permission was not sought from or given by some parents to include their child's data. However, data were available for 89% of children anaesthetised within 2 weeks at 261 institutions, with a balanced distribution between hospital categories and anaesthesiologists. There were very few missing values,

which imply that the findings are readily generalisable. However, we cannot infer what happened in non-participating centres; since centres voluntarily participated in the study, the results might be applicable only to the sample of included centres across Europe. The participant centres were not aware of the outcome of the study because they did not perform pre-analysis of their own data. Thus, we can declare with confidence that their participation was not biased by a personal or institutional motivation.

We used a validated and uniform definition of the recorded adverse events to decrease variations in interpretation of a given adverse event. Each definition specifically required that a non-planned intervention was necessary to treat or reverse the complication. Although we cannot completely exclude that some occurrences might have been interpreted differently by the anaesthesiologist in charge, two independent data cleaning procedures generated over 29 000 queries, which were sent to the participating centres to ensure full objectivity of the reporting. Additionally, all complications were reviewed by the two principal investigators (WH and FV) independently and details were confirmed, when necessary, by the local investigators.

Our results show a higher incidence of severe critical events than previously reported in the literature.[1,2,15,16] Most of these reports were based on retrospective analysis[3,6,13] or voluntary self-reporting,[5,17,18] which might have underestimated paediatric anaesthesia morbidity. However, the overall 30-day in-hospital mortality in our cohort study was lower than reported by de Bruin and colleagues.[19] This discrepancy in the high incidence of severe critical events and lower mortality might be explained in part by the nature of the case load and case mix of the institutions involved in our study.

There were significant differences in the occurrence and nature of severe critical events among participating countries (figure 3). Countries were deliberately not identified in this report, but we hope the data will form the basis for a range of quality improvement initiatives across Europe. This need is further substantiated by the various non-evidence-based strategies applied to treat a given complication (tables 2, 3). Our sample size calculation was based on the incidence of severe critical events occurring in a dedicated paediatric centre,[3] thus this study might not be adequately powered to identify the risk factors based on individual institutions or to study risk factors for specific types of severe critical events.

It has been suggested that a low volume of paediatric cases might be associated with a higher incidence of cardiac arrest;[20] in a subgroup analysis of centres reporting respiratory and cardiovascular severe critical events, there was some evidence for such a relationship, suggesting that the caseload, and potentially the experience it provides, could be more relevant than the type of institution. The composition of the anaesthesia team has been reported to decrease perioperative morbidity.[21] We found that in more than 55% of cases, one single anaesthesiologist performed the anaesthesia procedure, which reflects the variable provision in Europe of paediatric anaesthesia nurses.[22] Nevertheless, the results did not show any difference in the incidence of severe critical events when comparing size or composition of the anaesthesia team (data not shown).

In line with previous studies published in the literature, age was found to be a significant risk factor for the occurrence of severe critical events.[1–3,14,23,24] Although cardiovascular severe critical events were significantly more frequent in neonates (figure 2), respiratory severe critical events were more frequent in

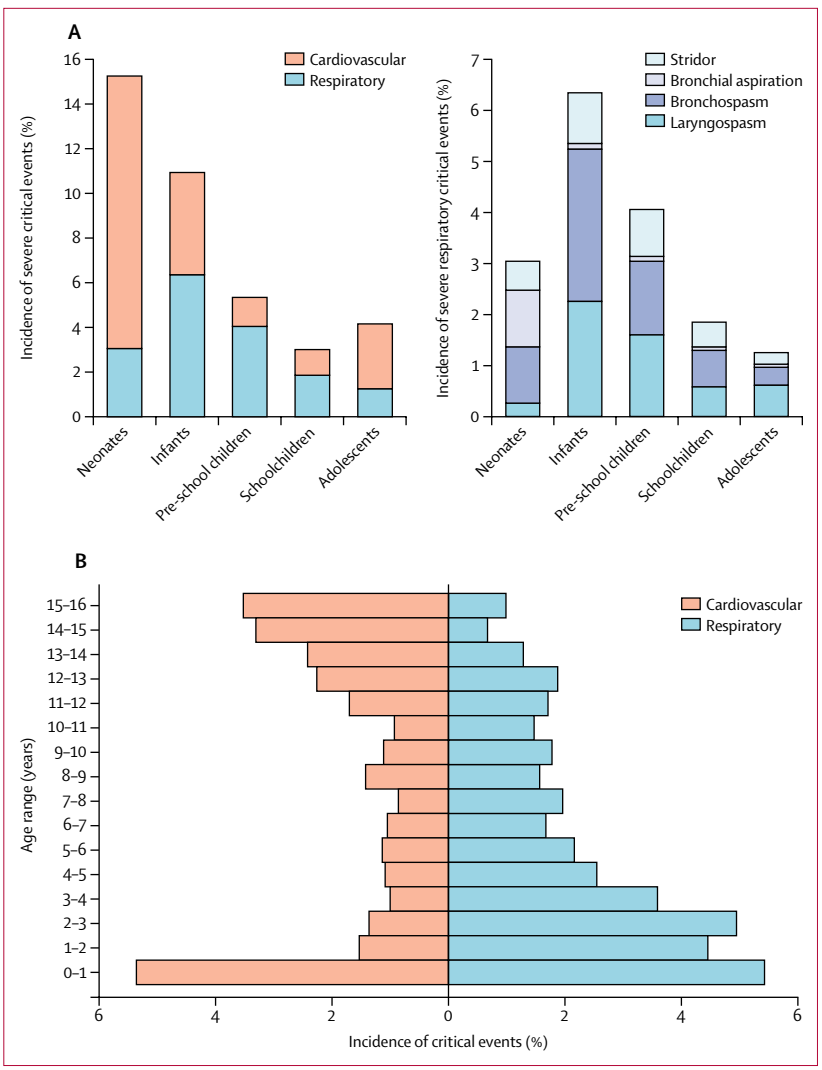

Figure 2: **Distribution of severe critical events throughout the age groups**
(A) Relative incidence and of respiratory and cardiovascular events (%) and the relative distribution of the four respiratory critical events (%). (B) Age distribution of cardiovascular (orange) and respiratory (blue) critical events.

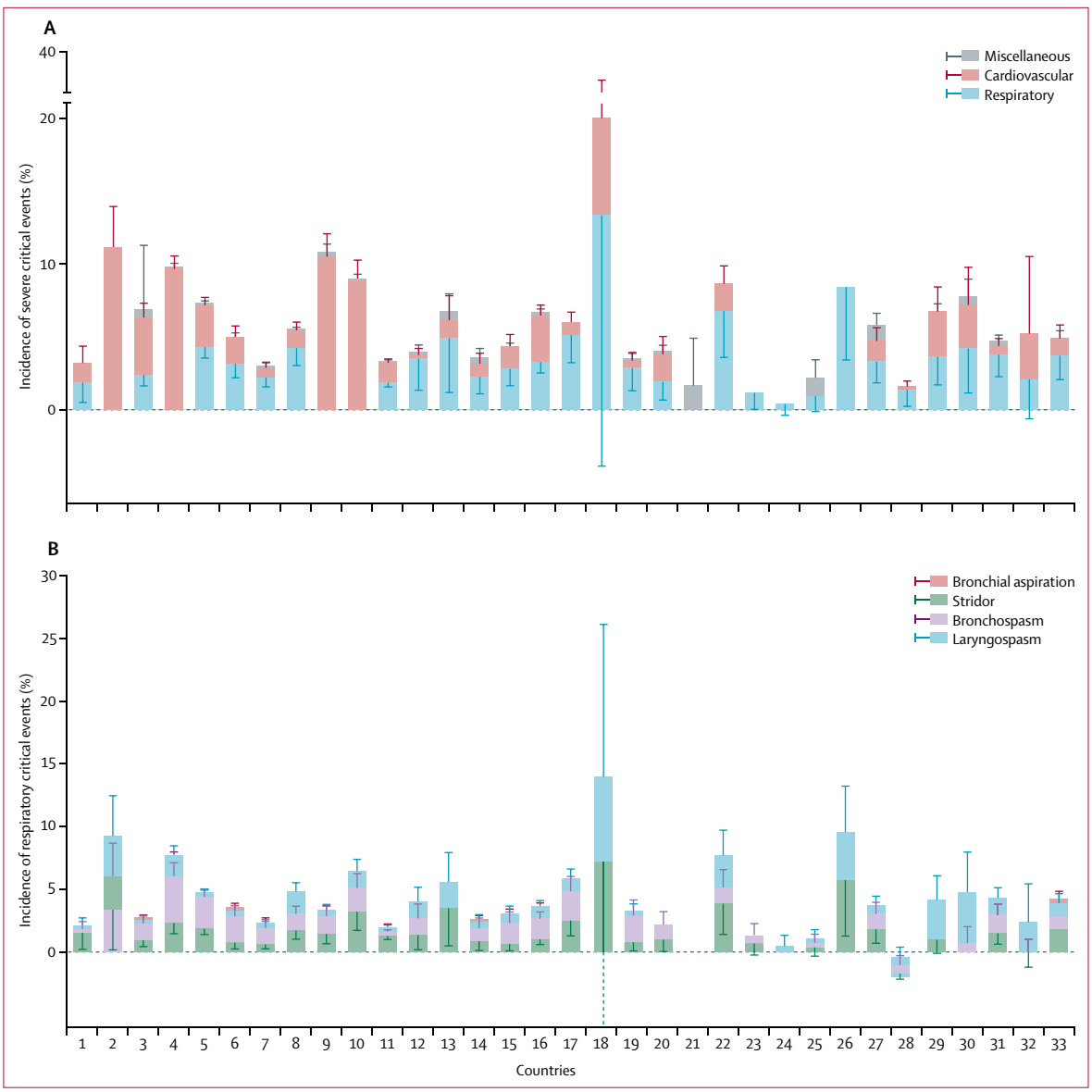

Figure 3: **Distribution of severe critical events throughout the 33 European countries**
(A) Relative incidence and 95% CIs of respiratory (bronchospasm, laryngospasm, bronchial aspiration, stridor), cardiovascular (cardiovascular instability and cardiac arrest), and miscellaneous severe critical events (anaphylaxis, neurological events, and drug errors). (B) Relative incidence and 95% CIs of the four respiratory critical events.

infants and pre-school children. There are no accepted normative ranges for physiological parameters in neonates, so one could expect a higher incidence of cardiovascular events, which might affect subsequent neurological development.[25] An ongoing European multicentre clinical trial aims to identify the out-of-range physiological parameters that lead to unplanned therapeutic interventions during anaesthesia management in neonates.[26]

The results of our study reveal a significantly higher incidence of both respiratory and cardiac severe critical events in children up to 6 years of age. The receiver operating characteristic analysis suggests that children younger than 3–3·5 years should be managed by tertiary care providers or by anaesthesiologists with specific paediatric training to reduce the occurrence and improve the outcome of peri-anaesthetic severe critical events. Identifying an age that might be considered as a threshold for allocating children to centres with specialist paediatric practices or paediatric anaesthesiologists is a matter of debate in many European countries and anaesthesia societies.[27,28]

Although the predictive value and the rating consistency of ASA physical status has been questioned in

children,[23,29] including it in the risk stratification in this study of severe critical events was useful.[20,30,31] The results of our study show that ASA-PS used alone, or as a collapsed variable in addition to the presence of history of handicap (including congenital heart disease), fever, and snoring, was associated with a higher incidence of severe critical events. Considering that the role of the anaesthesiologist was relevant regarding severe critical events in our study, particularly severe cardiovascular instability when ASA-PS was greater than III, management of such cases by an experienced paediatric anaesthesiologist can be recommended.

As expected, snoring appeared as a risk factor for the occurrence of severe critical events, independently of ear, nose, and throat surgery. This finding highlights the importance of recognising the presence of this risk factor during the pre-anaesthesia assessment of the child.[32]

In line with previous reports,[1] anaesthesia management had an important effect on the incidence of respiratory severe critical events (table 6). Our results highlight an extremely large variability in anaesthesia practice in Europe with the use of numerous drug combinations and analgesia techniques (appendix pp 3–4). There is a need to harmonise paediatric anaesthesia management in Europe as illustrated by the variety of anaesthesia plans (eg, those regarding tracheal intubation). Intubation without muscle relaxant significantly increased the risk for bronchospasm, and there was a reassuring absence of reports of anaphylaxis associated with muscle relaxants, which encourages their more widespread integration into clinical guidelines for airway management in children.

In summary, the results of the present study provide insight into the paediatric anaesthesia practice across 33 European countries, and allow an estimation of the incidence, nature, and outcome of severe critical events in the participating centres. While anaphylaxis and neurological events occurred rarely, the incidence of cardiac arrests was similar to that reported in the literature. However, the overall incidence of respiratory and cardiac severe critical events was higher than previously published, with a large variability among the participating centres across Europe. The most important risk factors for severe critical events are young age, medical history, comorbidities, and physical

	Univariate (n=31 127)					Multivariate* (n=28 512)
	Yes		No		Relative risk (95% CI); p value	Relative risk (95% CI); p value
	Total	SD or n (%)	Total	SD or n (%)		
Mean age (years)	4·2	3·8	6·4	4·5	0·88 (0·86–0·90); p<0·0001	0·88 (0·86–0·90); p<0·0001
Sex (male *vs* female)	19 017	542 (2·9%)	12 110	317 (2·6%)	1·09 (0·95–1·25); p=0·21	1·00 (0·88–1·14); p=0·96
Airway sensitivity						
Upper respiratory tract infection in the past 2 weeks	4200	265 (6·3%)	26 046	582 (2·2%)	2·82 (2·45–3·25); p<0·0001	..
Wheezing in the past 12 months	1967	164 (8·3%)	27 398	646 (2·4%)	3·53 (2·99–4·17); p<0·0001	..
Asthma diagnosis	1886	86 (4·6%)	28 645	764 (2·7%)	1·71 (1·38–2·13); p<0·0001	..
Passive smoking	3400	128 (3·8%)	18 114	492 (2·7%)	1·39 (1·15–1·69); p=0·00065	..
Airway sensitivity†	8821	426 (4·8%)	22 058	430 (1·9%)	2·38 (2·09–2·72); p<0·0001	2·23 (1·93–2·57); p<0·0001
Environmental sensitivity						
Allergy	3831	112 (2·92%)	27 059	741 (2·7%)	1·07 (0·88–1·30); p=0·49	..
Atopy	2330	84 (3·6%)	27 362	726 (2·7%)	1·36 (1·09–1·70); p=0·0067	..
Environmental sensitivity‡	5203	160 (3·1%)	25 806	697 (2·7%)	1·14 (0·96–1·35); p=0·13	1·09 (0·93–1·28); p=0·27
Physical condition						
Prematurity	2363	121 (5·1%)	25 272	666 (2·6%)	1·94 (1·61–2·35); p<0·0001	..
Fever	904	44 (4·9%)	29 522	801 (2·7%)	1·79 (1·33–2·41); p=0·00012	..
Handicap	4083	121 (3·0%)	26 672	732 (2·7%)	1·08 (0·90–1·31); p=0·42	..
Snoring	4429	217 (4·9%)	21 814	510 (2·3%)	2·09 (1·79–2·45); p<0·0001	..
Medication	7242	222 (3·1%)	23 611	633 (2·7%)	1·15 (0·99–1·33); p=0·077	..
ASA status (p<0·0001§)						
ASA status II	8739	300 (3·4%)	18 883	448 (2·4%)	1·45 (1·25–1·67); p<0·0001	..
ASA status III-IV-V	3497	111 (3·2%)	18 883	448 (2·4%)	1·34 (1·09–1·65); p=0·0052	..
Physical condition¶	14 253	493 (3·5%)	16 872	366 (2·2%)	1·60 (1·40–1·82); p<0·0001	1·21 (1·05–1·39); p=0·0067
Anaesthesia plan						
Surgical *vs* non-surgical	22 225	643 (2·9%)	8902	216 (2·4%)	1·19 (1·02–1·39); p=0·025	..

(Table 6 continues on next page)

	Univariate (n=31 127)					Multivariate* (n=28 512)
	Yes		No		Relative risk (95% CI); p value	Relative risk (95% CI); p value
	Total	SD or n (%)	Total	SD or n (%)		
(Continued from the previous page)						
General anaesthesia *vs* sedation	29 064	841 (2·9%)	1961	18 (0·9%)	3·15 (1·98–5·02); p<0·0001	..
Urgent-emergency *vs* elective anaesthesia	5893	168 (2·9%)	25 232	691 (2·7%)	1·04 (0·88–1·23); p=0·65	..
After hours *vs* during opening hours	3133	79 (2·5%)	27 993	780 (2·8%)	0·91 (0·72–1·14); p=0·39	..
Premedication	15 263	420 (2·7%)	15 862	439 (2·8%)	0·99 (0·87–1·13); p=0·91	..
Inpatient *vs* outpatient	18 670	590 (3·2%)	12 455	269 (2·2%)	1·46 (1·27–1·69); p<0·0001	..
Consultation >24 h	18 525	541 (2·9%)	12 600	318 (2·5%)	1·16 (1·01–1·33); p=0·036	..
Ear-nose-throat surgery	5707	224 (3·9%)	25 412	635 (2·5%)	1·57 (1·35–1·82); p<0·0001	..
Type of centres (p=0·039§)						
Mixed adult-paediatric *vs* paediatric	14 626	440 (3·0%)	12 966	333 (2·6%)	1·14 (0·99–1·31); p=0·071	..
Community or private hospital *vs* paediatric	3535	86 (2·4%)	12 966	333 (2·6%)	0·92 (0·73–1·16); p=0·49	..
Anaesthesia team (p=0·045§)						
Frequent *vs* specialist	4359	147 (3·4%)	18 367	476 (2·6%)	1·30 (1·08–1·56); p=0·0047	..
Occasional *vs* specialist	5969	169 (2·8%)	18 367	476 (2·6%)	1·10 (0·92–1·30); p=0·30	..
Trainee *vs* specialist	2428	67 (2·8%)	18 367	476 (2·6%)	1·07 (0·83–1·37); p=0·62	..
Type of centres combined with anaesthesia team‖ (p=0·98§)						
Occasional *vs* paediatric	6704	187 (2·8%)	21 991	605 (2·8%)	1·02 (0·86–1·20); p=0·84	..
Trainee *vs* paediatric	2428	67 (2·8%)	21991	605 (2·8%)	1·00 (0·78–1·29); p=0·97	..
Years of experience of most senior team member	13·85	9·0	14·80	9·4	0·989 (0·982–0·996); p=0·0029	0·99 (0·981–0·997); p=0·0048
Anaesthesia plan**	27 119	793 (2·9%)	4008	66 (1·6%)	1·72 (1·34–2·21); p<0·0001	1·46 (1·12–1·89); p=0·0047
Anaesthesia management						
Induction type (intravenous *vs* inhalation)††	13 906	303 (2·2%)	15 105	538 (3·6%)	0·85 (0·74–0·98); p=0·024	0·78 (0·66–0·93); p=0·0043
Interface for airway management	..	..	..	..	<0·0001§	<0·0001
ETT *vs* facial mask	13 671	554 (4·1%)	4970	61 (1·2%)	3·31 (2·54–4·30); p<0·0001	3·36 (2·41–4·67); p<0·0001
SGAW *vs* facial mask	10 919	223 (2·0%)	4970	61 (1·2%)	1·67 (1·26–2·21); p=0·00036	2·00 (1·40–2·85); p=0·0001
Other *vs* facial mask	573	16 (2·8%)	4970	61 (1·2%)	2·29 (1·33–3·95); p=0·0028	2·65 (1·49–4·74); p=0·0001
Rapid sequence	1372	37 (2·7%)	12 295	516 (4·2%)	0·64 (0·46–0·89); p=0·0084	..
Uncuffed *vs* cuffed	3843	169 (4·4%)	9828	386 (3·9%)	1·12 (0·94–1·34); p=0·21	..
Monitored cuff pressure	4667	201 (4·3%)	5144	184 (3·6%)	1·20 (0·99–1·46); p=0·063	..
Vocal cords sprayed	1134	56 (4·9%)	12 535	498 (4·0%)	1·24 (0·95–1·63); p=0·11	..
Deep *vs* awake extubation	3562	167 (4·7%)	9370	367 (3·9%)	1·20 (1·00–1·43); p=0·049	..
Deep *vs* awake removal SGAW	4600	107 (2·3%)	6211	114 (1·8%)	1·26 (0·97–1·63); p=0·089	..
Myorelaxant for intubation	8382	305 (3·6%)	5284	248 (4·7%)	0·78 (0·66–0·91); p=0·0023	..

ASA=American Society of Anesthesiology. ETT=endotracheal intubation. SGAW=supraglottic airway. *Variables in the multivariate model: age, gender, airway sensitivity, environmental sensitivity, physical condition, anaesthesia plan, years of experience of senior person, induction type, interface for airway management. †Airway sensitivity: upper respiratory tract infection in the past 2 weeks, wheezing, asthma, or passive smoking. ‡Allergy or atopy. §The overall effect of a categorical variable on the risk of severe respiratory critical events. ¶Prematurity, fever, handicap, snoring, medication, or ASA status greater than II. ||Paediatric: all specialist and frequent in paediatric or mixed hospital; occasional: all occasional and frequent in community or private institution. **Urgent or emergency, after hours, inpatient, consultation >24 h, or ear, nose, and throat surgery. ††Adjusted for age.

Table 6: **Relative risk and 95% CIs for the risk factors associated with the occurrence for severe respiratory critical events (perioperative laryngospasm, bronchospasm, or postoperative stridor)**

status. Accordingly, children younger than 3 years and those with a medical history including prematurity, handicap (metabolic or genetic disorder, or neurological impairment), snoring, airway hypersensitivity, and a medical condition with fever or under medication are at increased risk of severe critical events and should be anaesthetised by an adequately experienced anaesthesiologist with sufficient paediatric training and

	Univariate (n=31 127)					Multivariate* (n=31 062)
	Yes		No		RR (95% CI); p value	RR (95% CI); p value
	Total	SD or n (%)	Total	SD or n (%)		
Mean age (years)	5·96	5·6	6·35	4·5	0·99 (0·96–1·01); p=0·11	0·99 (0·97–1·02); p=0·568
Sex (male)	19 017	319 (1·7%)	12 110	275 (2·3%)	0·74 (0·63–0·87); p<0·0001	0·74 (0·64–0·87); p=0·0002
Physical condition						
Prematurity	2363	92 (3·9%)	25 272	437 (1·7%)	2·24 (1·79–2·80); p<0·0001	..
Fever	904	23 (2·5%)	29 522	556 (1·9%)	1·32 (0·86–2·03); p=0·20	..
Handicap	4083	153 (3·8%)	26 672	434 (1·6%)	2·33 (1·94–2·79); p<0·0001	..
Medication	7242	241 (3·3%)	23 611	345 (1·5%)	2·26 (1·92–2·67); p<0·0001	..
ASA status II	8739	169 (1·9%)	18 883	191 (1·0%)	1·90 (1·55–2·34); p<0·0001	..
ASA status III-IV-V	3497	233 (6·7%)	18 883	191 (1·0%)	6·56 (5·44–7·92); p<0·0001	..
Physical condition†	11 526	383 (3·3%)	19 599	211 (1·1%)	3·07 (2·60–3·63); p<0·0001	2·65 (2·20–3·19); p<0·0001
Surgical and anaesthesia plans						
Surgical *vs* non-surgical	22 225	516 (2·3%)	8902	78 (0·9%)	4·20 (3·22–5·49); p<0·0001	..
General anaesthesia *vs* sedation	29 064	587 (2·0%)	1961	5 (0·3%)	8·30 (3·56–19·35); p<0·0001	..
Urgent-emergency *vs* elective anaesthesia	5893	161 (2·7%)	25 232	433 (1·7%)	1·54 (1·28–1·865); p<0·0001	..
After hours *vs* opening hours	3133	52 (1·7%)	27 993	542 (1·9%)	0·80 (0·58–1·09); p=0·16	..
Premedication	15 263	267 (1·8%)	15 862	327 (2·1%)	0·86 (0·73–1·01); p=0·067	..
Inpatient *vs* outpatient	18 670	519 (2·8%)	12 455	75 (0·6%)	4·54 (3·57–5·78); p<0·0001	..
Consultation >24 h	18 525	415 (2·2%)	12 600	179 (1·4%)	1·53 (1·25–1·88); p<0·0001	..
Cardiac surgery	256	74 (28·9%)	30 863	520 (1·7%)	16·92 (13·67–20·93); p<0·0001	..
Cardiac catheterism	243	18 (7·4%)	30 882	576 (1·9%)	3·20 (1·71–5·85); p<0·0001	1·85 (1·17–2·92); p=0·0088
Type of centres (p=0·0091‡)						
Mixed adult-paediatric/ paediatric	14 626	291 (2·0%)	12 966	260 (2·0%)	0·99 (0·84–1·17); p=0·94	..
Community private hospital/paediatric	3535	43 (1·2%)	12 966	260 (2·0%)	0·62 (0·45–0·85); p=0·003	..
Anaesthesia team§ (p=0·027‡)						
Frequent *vs* specialist	4359	79 (1·8%)	18 367	371 (2·0%)	0·87 (0·68–1·11); p=0·26	..
Occasional *vs* specialist	5969	119 (2·0%)	18 367	371 (2·0%)	0·99 (0·79–1·21); p=0·83	..
Trainee *vs* specialist	2428	25 (1·0%)	18 367	371 (2·0%)	0·50 (0·31–0·79); p=0·004	..
Type of centres combined with anaesthesia team¶ (p=0·013‡)						
Occasional *vs* paediatric	6704	129 (1·9%)	21 991	440 (2·0%)	0·96 (0·79–1·17); p=0·69	0·96 (0·73–1·25); p=0·741
Trainee *vs* paediatric	2428	25 (1·0%)	21 991	440 (2·0%)	0·50 (0·32–0·80); p=0·003	0·43 (0·28–0·67); p=0·0002
Years of experience of most senior team member	13·98	8·9	14·79	9·4	0·99 (0·98–1·00); p=0·052	0·98 (0·97–0·99); p=0·0039
Anaesthesia plan‖	28 480	582 (2·04%)	2647	12 (0·45%)	4·085 (2·27–7·35); p<0·0001	4·65 (2·27–9·55); p<0·0001
Anaesthesia management						
Induction type (intravenous *vs* inhalation)	13 906	295 (2·1%)	15 105	291 (1·9%)	0·99 (0·80–1·24); p=0·98	..
Myorelaxant	8382	361 (4·3%)	5284	125 (2·4%)	2·34 (0·88–6·20); p=0·087	..
Rapid sequence	1372	52 (3·8%)	12 295	434 (3·5%)	1·01 (0·32–3·22); p=0·98	..

ASA=American Society of Anesthesiology. *Variables in the multivariate model: age, gender, airway sensitivity, environmental sensitivity, physical condition, anaesthesia plan, years of experience of senior person, induction type, interface for airway management †Prematurity, fever, handicap, medication, or ASA status greater than II. ‡The overall effect of a categorical variable on the risk of cardiovascular instability. §Paediatric specialist as reference value. ¶Paediatric: all specialist and frequent in paediatric or mixed hospital; occasional: all occasional and frequent in community or private institution. ||Urgent or emergency, after hours, premedication, inpatient, or consultation >24 h.

Table 7: **Relative risk and 95% CIs for the risk factors associated with the occurrence of perioperative cardiovascular instability**

ongoing paediatric experience or, if possible, postponed. The findings from APRICOT will help local institutions and national societies to establish standards of care and implement patient safety and quality improvement projects aimed at reducing the risk of severe critical events.

Contributors

WH and FV were the coordinating investigators, and were involved in the study design, literature search, data cleaning, data analysis, data interpretation, coordination of the team, and manuscript writing. ND was involved in data interpretation and manuscript writing. KV and KBo were the statisticians and did data analysis, data interpretation, and manuscript writing. KBe, TGH, MJ, PMV, and MZ are members of the steering committee, and were involved in study design, data interpretation, and manuscript reviewing. BL was involved in protocol writing, ethics approval coordination, study monitoring, data management, cleaning of the data, and final reports. NSM was involved in study design, data interpretation, manuscript writing, and language editing.

Declaration of interests

We declare no competing interests.

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