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# Unexpected death in children with severe congenital heart defects in Norway 2004–2016

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## ABSTRACT

**Aims** Updated knowledge on the rates and causes of death among children with severe congenital heart defects (CHDs) is needed to further improve treatment and survival. This study investigated nationwide mortality rates in children with severe CHDs with an emphasis on unexpected mortality unrelated to cardiac intervention.

**Methods and results** Data on all pregnancies and live-born children in Norway from 2004 to 2016 were obtained from national registries, the Oslo University Hospital's Clinical Registry for CHDs and medical records. Among 2359 live-born children with severe CHDs, 234 (10%) died before 2 years of age. Of these, 109 (46%) died in palliative care, 58 (25%) died of causes related to a cardiac intervention and 67 (29%) died unexpectedly and unrelated to a cardiac intervention, either before (n=26) or following (n=41) discharge after a cardiac intervention. Comorbidity (38/67, 57%), persistent low oxygen saturation (SaO<sub>2</sub>; <95%; 41/67, 61%), staged surgery (21/41, 51%), residual cardiac defects (22/41, 54%) and infection (36/67, 54%) were frequent in children who died unexpectedly unrelated to an intervention. Two or more of these factors were present in 62 children (93%). The medical reports at hospital discharge lacked information on follow-up in many patients who died unexpectedly.

**Conclusions** The numbers of unexpected deaths unrelated to cardiac intervention in children <2 years of age without comorbidity were low in Norway. However, close follow-up is recommended for infants with comorbidities, persistent low oxygen saturation, staged surgery or residual cardiac defects, particularly when an infection occurs.

## INTRODUCTION

Congenital heart defects (CHDs) are the most common birth defects, affecting approximately 1% of all newborns.<sup>1–4</sup> One-quarter requires early treatment.<sup>3,5</sup> However, some children receive palliative care without a surgical approach and others die unexpectedly before intervention.<sup>6,7</sup> Recently, a more active surgical approach in children with complex CHDs and severe comorbidity has been adopted.<sup>6,8,9</sup> Despite major improvements in diagnostics and treatment modalities, CHDs still represent a major cause of mortality.<sup>10–12</sup> Complex CHDs and severe comorbidity are frequent findings in deceased children.<sup>1</sup> The risk factors for perioperative and postoperative mortality include prematurity, comorbidity, univentricular heart and complex surgical procedures.<sup>13–16</sup> To further improve treatment and survival of children with severe CHDs,

## What is already known on this topic?

- ▶ Univentricular heart, complex surgical procedures and comorbidity are risk factors for perioperative and postoperative mortality in infants with severe congenital heart defects (CHDs).
- ▶ Approximately half of all deaths after a cardiac intervention occur following hospital discharge.

## What this study adds?

- ▶ This study presents nationwide data on mortality in children (<2 years of age) with severe CHDs.
- ▶ Unexpected deaths unrelated to a cardiac intervention were infrequent in children (<2 years of age) with severe CHDs and without comorbidity.
- ▶ Children with comorbidities, low oxygen saturation (<95%), staged cardiac surgery, residual cardiac defects and infections were at an increased risk of unexpected death and should be closely followed up after discharge from hospitals.

updated knowledge on the rates and causes of mortality is needed. Information on adverse outcomes in children discharged from the hospital after cardiac surgery is particularly limited.<sup>17–20</sup>

The present study investigates the rates and clinical details of all deaths before 2 years of age in children with severe CHDs during 2004–2016 in Norway. Secondary, it describes the time trends of unexpected mortality, especially that unrelated to cardiac intervention.

## METHODS

### CHD classification

Heterotaxia, transposition of the great arteries, tetralogy of Fallot, double-outlet right ventricle, truncus arteriosus, hypoplastic aortic arch, coarctation of the aorta, atrioventricular septal defects (AVSD), anomalous pulmonary venous return, hypoplastic left heart syndrome, aortic valve stenosis, pulmonary valve atresia, tricuspid valve atresia, Ebstein's anomaly, coronary artery anomalies and other complex defects were classified as severe.<sup>21,22</sup> Ventricular septal defects (VSD) were classified as severe if treated by intervention or if



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a child with a non-restrictive VSD died in palliative care. This study did not include non-severe CHDs. All individuals were assigned one main CHD diagnosis according to the International Paediatric and Congenital Cardiac Code (IPCCC).<sup>23</sup>

### Data sources

Data on all pregnancies from 1 January 2004 to 31 December 2016 were extracted from the Medical Birth Registry of Norway<sup>24</sup> containing information on all live births, stillbirths and terminations of pregnancies after 12 weeks of gestation. Oslo University Hospital is the national centre for invasive treatment of children with CHDs in Norway; information on live-born children with severe CHDs was retrieved from Oslo University Hospital's Clinical Registry for Congenital Heart Defects. Data from this registry were linked to the mandatory Norwegian Cause of Death Registry, containing information about the date and causes of death. The medical records of all deceased infants were reviewed.

### Definitions

*Palliative care* included children without a feasible surgical option and children who did not receive cardiac surgery due to complex morbidity and expected quality of life.<sup>7</sup> *Staged surgery* encompassed cardiac interventions as part of staged surgical treatment for four-chamber or univentricular solutions. *Residual defects* were defined as non-surgical shunts, outlet obstruction/valvar stenosis or regurgitation of expected clinical relevance after cardiac surgery. *Peroperative/postoperative in-hospital mortality* included deaths occurring during an intervention or before hospital discharge after a cardiac intervention. *Unexpected death* was defined as death occurring in children with planned active treatment, before, during or after the cardiac intervention. *Death after deterioration* was defined as death

occurring more than 24 hours after the occurrence of new symptoms or signs. The infants were presumed to have died of *cardiac death* if the symptoms leading to death were primarily cardiac, and there was no other evident cause of death. *Persistent low oxygen saturation* included all children with persistent oxygen saturation below 95%, regardless of cyanotic CHD or a condition with presumed normal oxygen saturation. *Comorbidity* encompassed non-cardiac conditions with significant effects on the child's health and/or development, such as genetic disorders, multiple malformations and organ failure. *Small for gestational age* was defined as birth weight below the 10th percentile for gestational age.<sup>25 26</sup> *Infection at the time of death* was defined as documented clinical or biochemical signs of infection related to death (not necessarily the cause of death).

### Statistical analysis

Continuous variables are presented as median (range) and categorical variables as numbers and proportions. Time trends were analysed (log-linear model) using the Joinpoint Regression Program (V.4.0; SEER software, National Cancer Institute, USA) and are presented as the expected annual percent changes with 95% CI. Other statistical analyses were performed using STATA/SE V.15.0 (StataCorp, College Station, Texas, USA). Based on previous literature, we analysed the presence of anticipated risk factors.

## RESULTS

### Mortality in infants with severe CHDs

Figure 1 presents an overview of all pregnancies (n=789 345) and live-born children with severe CHDs (n=2359) in Norway from 2004 to 2016, and the classification of 236 (10%) children who died before 2 years of age.

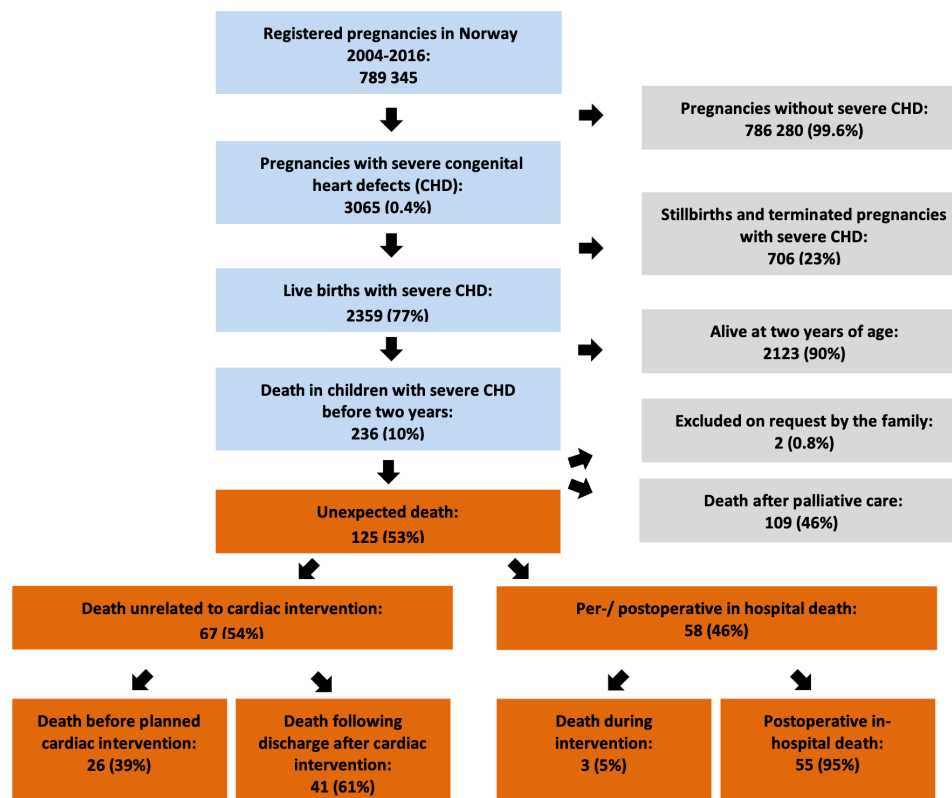
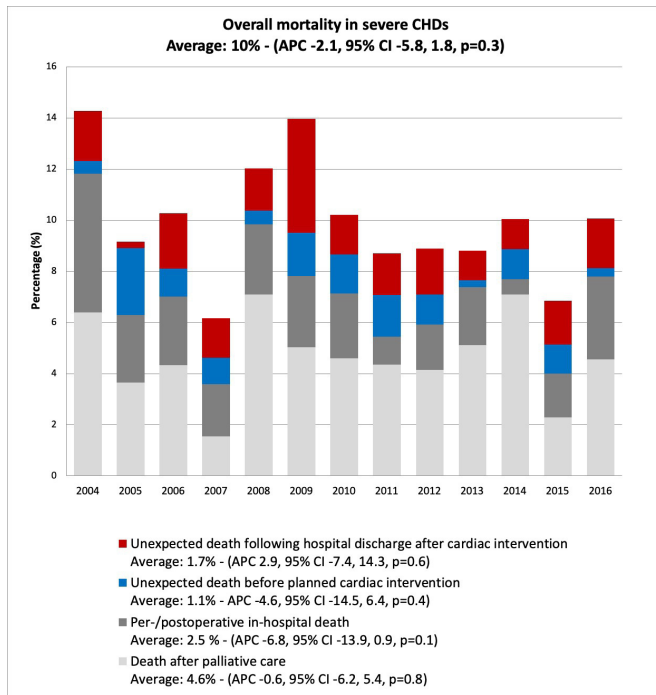


Figure 1 Pregnancies and severe congenital heart defects (CHDs) in Norway, 2004–2016.

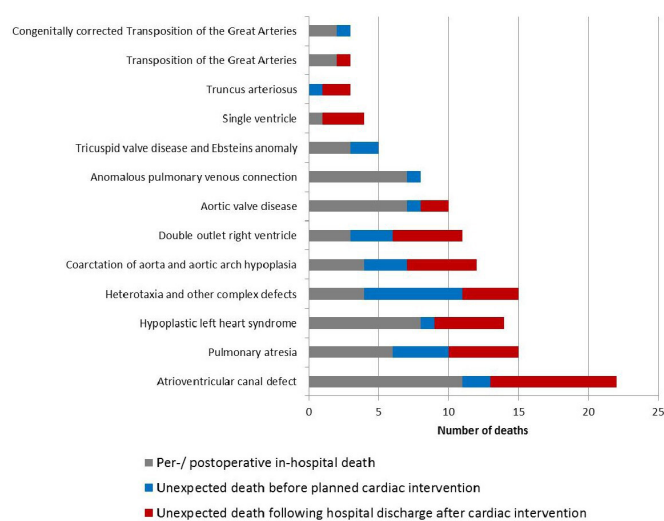


**Figure 2** Annual proportions of death in children below 2 years of age with severe congenital heart defects (CHDs) in Norway, 2004–2016. APC, annual percent changes.

The prevalence of severe CHDs in pregnancy was 0.4%; approximately one-quarter of which resulted in stillbirths or terminations. Most (n=2123, 90%) children born with severe CHDs were alive until 2 years of age.

Deaths after palliative approach in the study population have been described previously.<sup>7</sup> The annual proportions of unexpected deaths before 2 years of age in children with severe CHDs are presented in figure 2. We found no significant time trends during the study period.

Unexpected deaths unrelated to a cardiac intervention occurred after deterioration in 70% (47/67) of cases. The IPCCC



**Figure 3** International Paediatric and Congenital Cardiac Codes in children with severe congenital heart defects and unexpected death before 2 years of age in Norway, 2004–2016.

**Table 1** Factors associated with presumed increased risk for adverse outcome in children with severe congenital heart defects who died unexpectedly before cardiac intervention <2 years of age in Norway, 2004–2016 (n=26)

	Number (%)
Prematurity (<37 weeks)	11 (42)
Small for gestational age	10 (38)
Comorbidity	16 (62)
Undetected heart defect at deterioration	3 (12)
Persistent low oxygen saturation (<95%)	18 (69)
Infection at the time of death	10 (38)

diagnoses in children with CHDs and unexpected death before 2 years of age are presented in figure 3.

AVSD was the most frequent diagnosis (n=22, 18%) in children with unexpected deaths. Two of these children died before planned interventions, 11 in relation to an intervention and 9 following hospital discharge after a cardiac intervention.

### Unexpected death before a planned cardiac intervention

Unexpected deaths unrelated to cardiac intervention occurred before planned cardiac intervention in 26 of 67 (39%) children. This heterogeneous group included 17 different IPCCC diagnoses (figure 3). Sixteen (62%) children were never discharged from the hospital. In three children discharged from the hospital, the CHD was previously undetected (total anomalous pulmonary venous connection, hypoplastic left heart syndrome and anomalous left coronary artery from the pulmonary artery). The causes of death were presumed to be cardiac in 11 (42%) children, due to comorbidity in three (12%) children, due to infection in seven (27%) children and due to a combination of comorbidity and cardiac cause in five (19%) children. The median survival time was 19 days (range: 0–208 days, IQR: 2–68 days). Factors associated with presumed increased risk for adverse outcomes are presented in table 1. All 26 children had at least one of these risk factors and 24 (92%) had two risk factors or more.

### Unexpected death in children discharged from the hospital after the cardiac intervention

A total of 41 of 67 (61%) unexpected deaths unrelated to cardiac intervention occurred following hospital discharge after a cardiac intervention. The IPCCC diagnoses are reported in figure 3. The causes of death were presumed to be cardiac in 15 (37%) children, infection in 23 (56%) children (lower respiratory tract infection in 17 children), aspiration in two children and multimorbidity in one child. The cardiac deaths were caused by heart failure worsening (n=7), sudden cardiac arrest (n=3), central shunt occlusion (n=3) and multiorgan failure after surgery for undetected coarctation of the aorta (n=2). Single ventricle palliation was initiated in 13 of the 41 children, staged four-chamber surgery in eight children and corrective surgery in 20 children. Staged surgery as part of either a univentricular (n=8) or a four-chamber (n=4) solution was performed in 12 of 15 cardiac deaths. Only five (12%) deaths occurred in children without comorbidities or significant residual heart defects. Thirty (73%) children deteriorated outside of the hospital and 13 died before hospital arrival. The median survival time was 175 days (IQR 8–561 days), and the median time to death after cardiac intervention was 67 days postdischarge (IQR 20–159 days). Six (15%) of these 41 children died within the first 30 postoperative days. Factors associated with presumed increased risk for adverse

**Table 2** Factors associated with presumed increased risk for adverse outcomes in children with severe congenital heart defects who died unexpectedly following discharge from hospital after a cardiac intervention before 2 years of age in Norway, 2004–2016 (n=41)

	Number (%)
Prematurity (<37 weeks)	8 (20)
Small for gestational age	10 (24)
Comorbidity	22 (54)
Undetected heart defect at deterioration	2 (5)
Persisting low oxygen saturation (<95%) after intervention	23 (56)
Infection at the time of death	26 (63)
Staged surgery	21 (51)
Significant residual defect after cardiac surgery at last examination before death	21 (51)
Shunt dependent circulation	10 (24)

outcomes are presented in table 2. Every child had at least one risk factor and 36 children (88%) had three or more risk factors. AVSD was the main IPCCC diagnosis in nine children (22%), all of whom had corrective surgery and causes of death were pneumonia (n=5), gastroenteritis (n=3) or aspiration (n=1). Down syndrome was diagnosed in 8 (89%) children with AVSD.

We reviewed the clinical reports from the last contact with Oslo University Hospital before clinical deterioration leading to death of 37 (90%) children. The reports are routinely sent to parents, local hospitals, general practitioners and child health centres responsible for local follow-up of these children. There was a documented plan for the next contact at Oslo University Hospital in 18 cases (49%), local follow-up was planned in nine cases (24%) and no defined plan in the remaining 10 (27%) cases. Only half of these reports (n=18, 49%) described the next treatment step. There was no information on warning signs in 29 (78%) cases, no description of expected clinical and echocardiographic course in 30 (81%) cases, and no guidance for echocardiographic follow-up in 33 (89%) cases.

## DISCUSSION

This nationwide study showed a stable 2-year mortality rate of 10% (n=236) in live-born children with severe CHDs during 2004–2016 in Norway. Of these, 46% (n=109) children died in a palliative care setting, 11% (n=26) died unexpectedly before a cardiac intervention, 25% (n=58) died in relation to a cardiac intervention and 17% (n=41) died unexpectedly after a cardiac intervention. Five children died because of a previously undetected CHD. Most children who died unexpectedly had complex conditions and the majority more risk factors such as small for gestational age, premature birth, comorbidity, low oxygen saturation, staged surgery or residual defects after surgery. Infection was the most frequent cause of death in children who died unexpectedly following hospital discharge after a cardiac intervention.

This study verified the decreasing trends in preoperative and postoperative mortality reported in other studies.<sup>2 8 19</sup> The high proportion of palliative care is contrasted with those of other reports in recent years reporting a trend towards more cardiac surgery in infants with complex CHDs and severe comorbidity.<sup>6 8 9</sup> We have previously discussed how palliative care may affect morbidity and mortality rates in these children.<sup>7</sup> Nevertheless, the mortality rate for the entire group of children with severe CHD was low compared with previous reports.<sup>2 3 6</sup>

Advances in prenatal and postnatal screening for CHDs and preoperative management have resulted in improved preoperative outcomes.<sup>27–29</sup> However, recent publications indicate that preoperative deaths still account for more than 50% of early mortality in children with severe CHDs. Comorbidity is a commonly reported risk factor.<sup>1 2 6</sup> We reported a similar proportion of preoperative mortality in Norway, mainly due to palliative care. Half of these cases had no feasible surgical option.<sup>7</sup> Increased access to organs and advancements in neonatal heart transplantation may further improve preoperative survival.<sup>30</sup> In the present study, small for gestational age (38%), prematurity (42%), comorbidity (62%) and persistent low SaO<sub>2</sub> (69%) occurred frequently in children with unexpected preoperative death. Most children (92%) had two or more risk factors, and the majority were never discharged from hospital after birth. However, the 10 children who were discharged died after deterioration at home.

Unexpected deaths following hospital discharge after cardiac intervention accounted for 18% of all deaths in children with severe CHDs before 2 years of age, a rate similar to those in previous reports.<sup>18 19</sup> The risk factors include univentricular heart, specific types of procedure, comorbidity, prematurity, non-Caucasian ethnicity, low weight, neurodevelopmental conditions, age at surgery and preoperative clinical deterioration.<sup>17 20</sup> Our findings confirm several of these; however, their relative importance cannot be determined owing to the heterogeneity of the patients. The most important finding in the present study was that most of the deaths occurred among particularly vulnerable children with several risk factors. The causes of death were either cardiac or infectious in almost all cases (93%). Lower respiratory tract infection was a common cause of death and more than two-thirds of these children had comorbidities, including a genetic disorder. However, our data also suggested that unexpected deaths before 2 years of age rarely occurred in operated children without significant residual defects and comorbidity.

Children with AVSD accounted for 18% of unexpected deaths before 2 years of age among children with severe CHDs. Of unexpected deaths following discharge after cardiac intervention, 22% occurred in children with AVSD. All of these deaths were related to an infection, and 89% had Down syndrome. Infection, particularly pneumonia, is a common cause of death in children with Down syndrome.<sup>31 32</sup> Consequently, parents and local healthcare professionals should be well informed about the symptoms and signs of infection in this group and early hospitalisation should be considered.

Most small children with severe CHDs are vulnerable and require close follow-up, particularly those with combined risk factors. The early signs of clinical and echocardiographic deterioration are important. Most of the medical records in the present study lacked information about treatment plans and expected clinical and echocardiographic courses. Information about clinical and echocardiographic warning signs and echocardiographic guidance was also missing. We lacked detailed information about contacts between the family and healthcare services, but most children had gradual deterioration. In Norway, most children with CHDs are followed up by local hospitals, general practitioners and child health centres with varying competence and experience. Although our findings do not provide a causality, it is possible that detailed, individual and documented follow-up plans from the surgical centre may reduce the risk for adverse outcomes; however, the education of parents and local healthcare professionals is also important. A wide range of discharge programmes has been developed for this purpose, including

home monitoring, electronic resources and video consultations.<sup>33–36</sup> Such strategies have to be adapted to existing local health services and are difficult to compare. Further studies are needed to elucidate their costs and benefits.

The main strength of this study was the analysis of a national cohort of severe CHDs, including both live-born children and terminated pregnancies. The use of national registries and access to medical records ensured the inclusion of nearly all cases of severe CHDs with detailed medical information.

The present study has some limitations. The observational design prevented the demonstration of causal associations between the findings and outcomes. The number of cases was limited, and the time trends should be cautiously interpreted. We cannot exclude the possibility that some patients died before surgery without being recorded in the Oslo University Hospital's Clinical Registry for CHDs. The risk of low SaO<sub>2</sub> should be interpreted with caution. Our data did not allow for a precise classification of saturation levels, and the results may not reflect the true effect. The risk of desaturation may thus be underestimated, particularly in infants with a recent fall from their habitual saturation level. However, the risk may be overestimated in those with complex defects and a stable low oxygen saturation. Moreover, we used arbitrary definitions of comorbidity, and the classifications were based on our assessments. Finally, risk stratification was difficult to perform due to the heterogeneity of the study population and the lack of detailed medical information about the surviving children. An international prospective register of children with severe CHDs could provide the knowledge needed to further improve survival and outcome.

In conclusion, unexpected deaths unrelated to cardiac interventions were infrequent in children younger than 2 years with severe CHDs and without comorbidity. Children with complex conditions and combined risk factors such as small for gestational age, premature birth, comorbidities, staged cardiac surgery, residual cardiac defects and persistent low SaO<sub>2</sub> were at risk and should be followed closely, particularly when an intercurrent infection occurs. Medical reports should include detailed, individualised follow-up plans. Targeted discharge strategies, including parental education, may also be of value. Finally, we emphasise the need for prospective, multicentre registries for improved risk stratification.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

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**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are stored in 'eReg Versjon 2.4.0 OUS-HF' and are available on reasonable request. They are not to be reused without approval from the Regional Committee for Medical and Health Research Ethics South East Norway.

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