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Population-Based Outcome Data of Extremely Preterm Infants in Germany during 2010–2017

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Keywords
Mortality · Retinopathy of prematurity · Bronchopulmonary dysplasia · Extreme prematurity

Abstract
Background and Objective: Results of five randomized controlled trials (RCT) sequentially published in 2010–2013 suggested that aiming for higher, as opposed to lower oxygen saturation targets, reduces rates of mortality in infants <28 weeks of gestation, while increasing rates of severe retinopathy of prematurity (ROP). Two further RCTs published in 2011 and 2015 demonstrated that avoiding endotracheal intubation by minimally invasive surfactant administration reduces respiratory morbidity. Assuming that such data are likely to affect clinical practice and ultimate outcome, we analyzed population-level results in extremely preterm infants born across Germany during 2010–2017. ***Methods:*** We used mandatory German quality surveillance data to compare mortality and morbidities in preterm infants born between 24 weeks 0 days and 27 weeks 6 days of gestation in 2010–2013 versus 2014–2017. ***Results:*** Mortality decreased from 15.1% (1,366/9,058) in 2010–2013 to 12.7% (1,385/10,924) in 2014–2017, risk ratio (RR) 0.845 (95% confidence interval [CI], 0.784–0.901). Rates of severe ROP (≥grade 3) per survivor increased from 12.1% (930/7,692) to 13.3% (1.269/9,539), RR 1.100 (95% CI: 1.017–1.191). The lowest mortality and highest ROP rates were found in infants born in 2014. There was no change in rates of necrotizing enterocolitis, while those of bronchopulmonary dysplasia (BPD) decreased steadily between 2010 and 2017, alongside the increased proportion of infants who were never intubated. ***Conclusions:*** There was a moderate decline in mortality, an insignificant increase in severe ROP, and a steady decline of BPD in Germany during 2010–2017. Avoiding endotracheal intubation may have contributed to lowered BPD rates.

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Introduction

The association between oxygen treatment and retinopathy of prematurity (ROP) had been the subject of the first randomized controlled trials (RCTs) ever conducted in very preterm infants [1]. However, the ensuing policy of restrictive oxygen administration contributed to excess mortality and cases of cerebral palsy [2]. The care of very preterm infants changed profoundly after the advent of respiratory support by mechanical ventilation and continuous positive airway pressure, antenatal steroids, ex-

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ogenous surfactant replacement, and pulse oximetry monitoring. The majority of observational studies conducted thereafter pointed to a continued association between lower oxygen saturation and rates of severe ROP without increased rates of death or cerebral palsy [3]. While acknowledging uncertainties regarding how best to balance these competing risks, recommendations made in European consensus guidelines published in 2007 [4] and reaffirmed in 2010 [5] and 2013 [6] stated that oxygen saturation targets in preterm babies receiving supplemental oxygen should be maintained below 93% and never exceed 95%, without specifying a lower limit.

The optimum target range for oxygenation was addressed by five large RCTs that used masked pulse oximeters, comparing 85%–89% versus 91%–95%: The "Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial" (SUPPORT) in the USA [7, 8], the "Canadian Oxygen Trial" (COT) conducted in Canada, Argentina, Germany, Finland, and Israel [9], and the three "Benefits Of Oxygen Saturation Targeting" (BOOST) II trials conducted in New Zealand, Australia, and the UK [10]. SUPPORT pointed to an increased rate of death and found a significantly reduced rate of severe ROP associated with a low oxygenation target range in 2010. A subsequent joint analysis of all five trials revealed increased rates of mortality and necrotizing enterocolitis (NEC), alongside decreased rates of severe ROP, associated with low oxygenation target ranges [11]. These findings were upheld by a subsequent Cochrane meta-analysis of aggregate data [12] and a pre-planned meta-analysis of individual participant data [13] which also revealed high oxygen saturation targets being significantly associated with increased rates of infants with bronchopulmonary dysplasia (BPD), as defined by supplemental oxygen at 36 weeks postmenstrual age.

Oxygen saturation targets were also a major topic at the annual meeting of the German Society for Neonatology and Pediatric Intensive Care in 2014, with the first authors of the BOOST-II trials publication and the first meta-analysis published being present as invited speakers. A survey among European neonatal intensive care units reported that more than 80% of respondents had changed their oxygenation saturation targets between 2010 and 2015 [14]. The annual rate of units that reported a change of oxygenation saturation policy peaked in 2014. The new targets were on average 3%–5% higher than the former targets, but there was extensive variation as to the precise limits.

SUPPORT, the first of the large oxygen saturation target trials, also investigated early continuous positive airway pressure, as opposed to endotracheal intubation and exogenous surfactant administration [15]. While rates of death and BPD did not differ between groups, infants in the early continuous positive airway pressure groups had lower rates of treatment with postnatal corticosteroids and required fewer days of mechanical ventilation. A subsequent meta-analysis found lower rates of BPD associated with strategies that aimed to avoid endotracheal intubation [16]. The beneficial effects of early surfactant and avoiding endotracheal intubation may be combined by less invasive surfactant administration (LISA) techniques. This approach has steadily gained acceptance in Germany since first described in 2007 [17], boosted by two RCTs that showed efficacy in reducing the length of mechanical ventilation [18, 19]. A meta-analysis [20] and a recent further large RCT in infants with a gestational age of 25–28 weeks confirmed the association between surfactant administration without endotracheal intubation and reduced rates of BPD [21]. Assuming that published results of large RCTs are likely to influence clinical practice and ultimate outcome, we investigated changes in mortality and morbidities in preterm infants of 24–27 weeks' gestation born during 2010–2017 in Germany on a population level.

Methods

By federal regulation, all neonatal intensive care units in Germany are subject to federal quality surveillance. This implies a mandatory central collection of minimum perinatal data sets for all newborn infants born after December 31, 2009. In Germany, funding of public and private hospitals relies on reimbursements of running costs by health insurance companies and subsidies for equipment by the federal states. About 90% of the population is covered by statutory health insurance. We used the aggregate data of federal quality surveillance reports published annually by the institutes entrusted with the national data collection (2010–2014: aQua – Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen, Göttingen; 2015–2017: Institut für Qualität und Transparenz im Gesundheitswesen, Berlin) which list mortality and major morbidities separately for each week of gestation ≤32 weeks. In the perinatal data sets, ROP was graded according to the International Committee for the Classification of Retinopathy [22], and ROP ≥grade 3 was considered severe. Intraventricular hemorrhage (IVH) was graded according to Papile et al. [23], NEC according to Bell et al. [24]. BPD was diagnosed as moderate or severe in infants with a postmenstrual age of 36 weeks requiring more than 21% or 30% of oxygen, respectively, to achieve arterial oxygenation of 90% or more [25]. Sepsis was diagnosed according to the definitions of the German national reference center for nosocomial infections [26]. Data on ROP treatment could not be evaluated in 2012–2015 because the data collection had been slow to react to the advent of intravitreal bevacizumab administration [27]. Only surgical treatment (laser or cryotherapy) was reg-

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Table 1. Mortality and morbidities of preterm infants 24–27 weeks' gestation

	2010–2013		2014–2017				
	n	rate, %	*n*	rate, %	RR	95% CI	*p* value
Admitted	9,058		10,924				
Death prior to discharge	1,366	15.1	1,385	12.7	0.841	0.784–0.901	<0.0001
SGA							
Yes	367	4.0	306	3.1	0.753	0.685–0.874	0.0002
No	999	11.0	1,039	10.4	0.939	0.865–1.020	0.1408
Age at death							
1–7 days	799	8.8	722	7.2	0.816	0.741–0.899	<0.0001
8–28 days	337	3.7	373	3.7	1.000	0.865–1.155	1.0000
>28 days	230	2.5	249	2.5	0.978	0.819–1.167	0.8169
IVH grade 3 or 4	1,217	13.4	1,489	13.6	1.015	0.946–1.089	0.6932
NEC stage 2 or 3	649	7.2	765	7.0	0.977	0.884–1.081	0.6576
Sepsis							
Before 72 h of life	1,512	16.7	1,216	12.1	0.726	0.677–0.779	<0.0001
After 72 h of life	2,485	27.4	2,348	23.4	0.853	0.813–0.896	<0.0001
BPD (moderate/severe)	2,687	34.9	2,310	24.2	0.693	0.662–0.727	<0.0001
ROP stage 3 or more	930		1,269				
By survivors		12.1		13.3	1.100	1.017–1.191	0.0180
In infants examined		11.5		12.4	1.075	0.993–1.164	0.0734

istered until 2015 but not intravitreal injections which already outnumbered surgical treatment when first registered in 2016. We restricted the analysis to infants born between 24 weeks 0 days and 27 weeks 6 days of gestation, as resuscitation of infants below 24 weeks is optional in Germany, without any change during the 8-year observation period [28]. Epi Info 7.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA) was employed to compare proportions using Fisher exact test, to compute RRs with 95% confidence intervals (CIs), and to calculate extended Mantel-Haenszel Chi-square (χ^2) for linear trend statistics, with p values below 0.05 considered significant.

Results

The number of preterm infants with a gestational age of 24 weeks 0 days and 27 weeks 6 days admitted to neonatal intensive care increased from 9,058 born in 2010–2013 to 10,924 born in 2014–2017. This was associated with an increased ratio of secondary to primary admissions, from 15.3% to 17.2% ($p = 0.0003$), reflecting a higher rate of transfer between hospitals. The ratio of infants born at 24 and 25 versus 26 and 27 weeks remained similar (3,726/5,332 vs. 4,597/6,327, $p = 0.1801$).

Mortality decreased significantly from 15.1% to 12.7% (χ^2 for trend 22.7, $p < 0.00001$) (Table 1). The decrease in mortality was restricted to deaths occurring during the first week of life (χ^2 24.9, $p < 0.00001$) and in small for gestational age (SGA) infants (birth weight below the 10th percentile) (χ^2 19.6, $p = 0.00001$).

There was no change in rates of severe (grade 3 or 4) IVH (χ^2 0.01, $p = 0.9970$) or NEC (stage 2 or 3) (χ^2 0.03, $p = 0.8567$) while rates of sepsis diagnosed within first 72 h life (χ^2 152.6, $p < 0.000001$) and after 72 h of life declined consistently (χ^2 96.8, $p < 0.000001$). Rates of severe ROP ≥(grade 3) per survivor increased moderately from 12.1% to 13.3% (χ^2 4.13, $p = 0.0423$) while there was no significant increase in the rates of severe ROP in infants examined (χ^2 2.16, $p = 0.1417$). Total rates of invasive ROP treatment (laser coagulation and intravitreal bevacizumab combined) did not differ between 2010/2011 and 2015/2017 ($p = 0.4409$). Both the nadir of mortality and the peak of ROP were observed for infants born in 2014 (Fig. 1).

Rates of moderate or severe BPD per survivor fell continuously (χ^2 313.0, $p < 0.000001$), from 34.9% to 24.2% (Fig. 2). This was accompanied by a steady increase in the fraction of infants admitted who received respiratory support without ever having been endotracheally intubated (χ^2 146.6, $p < 0.000001$), from 20.7% to 27.8% (RR 1.342, 95% CI: 1.276–1.411). At the same time, there was a small increase in the proportion of infants born alive with a gestational age of 24–33 weeks who had received antenatal steroids (χ^2 103.4, $p < 0.000001$), from 83.8% to 85.8% (RR 1.023, 95 CI: 1.018–1.028).

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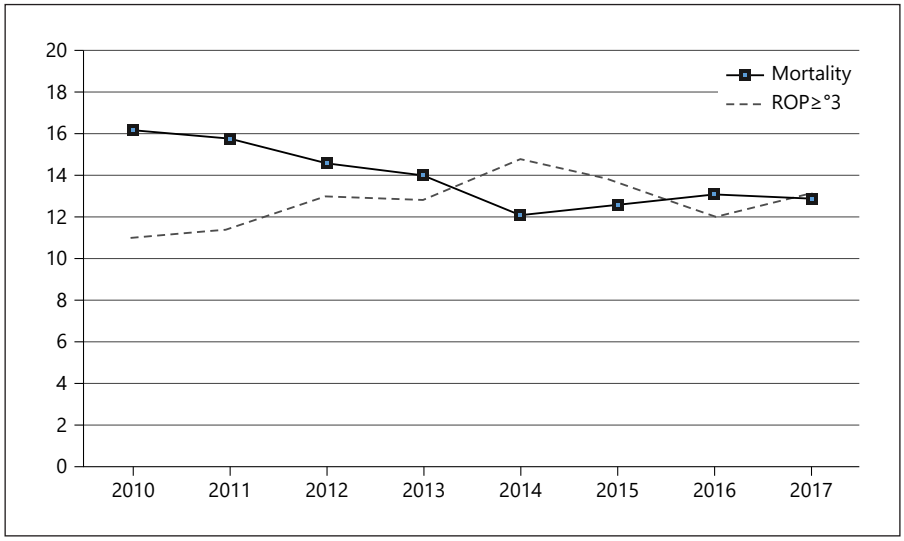

Fig. 1. Mortality (as a percentage of infants admitted) and severe ROP (per survivor) during 2010–2017.

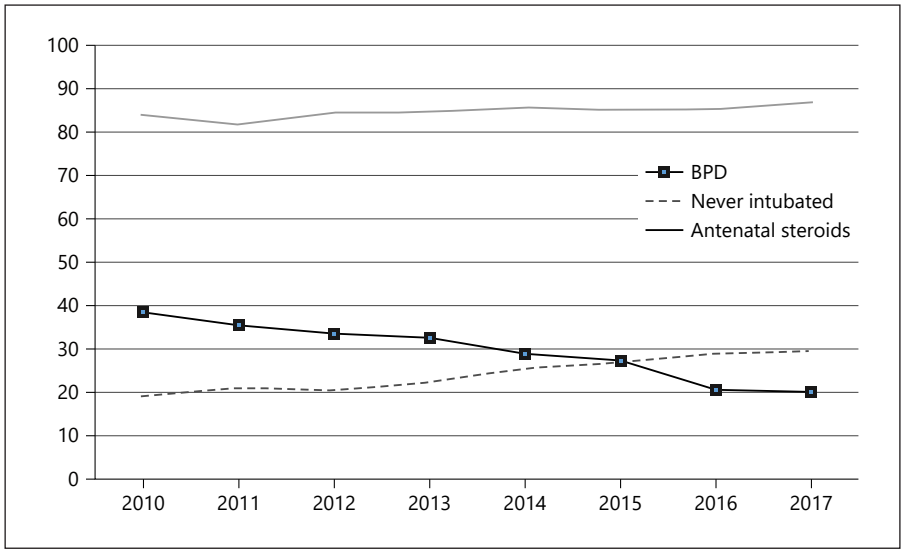

Fig. 2. Percentages of moderate/severe BPD, infants who were never endotracheally intubated, and infants who had received antenatal steroids during 2010–2017.

Discussion

These population-based data of almost 20,000 preterm infants with a gestational age of 24 weeks 0 days to 27 weeks 6 days born in Germany between 2010 and 2017 demonstrate a moderate and significant decline in mortality, absolute risk difference (ARD) −2.4%, and a small increase in the rate of severe ROP per survivor (ARD +0.9%) of borderline significance. There was no change in rates of severe IVH or NEC, while BPD rates declined continuously throughout the 8-year observation period.

Interpretation of these findings must proceed with caution, as the data were collected case-wise, entailing a risk of inaccurate calculations for ongoing conditions such as NEC or ROP possibly present both before and after transfer between two hospitals. Furthermore, their use for benchmarking purposes may have led to some underreporting, e.g., of BPD or sepsis. In addition, some infants may have reached the maximum ROP stage after discharge. Data collection was not subject to monitoring, in contrast to that in most RCTs. We could only analyze aggregate data as published and therefore were unable to use combined outcome variables such as "death or BPD" or "death or severe ROP." These systematic errors are inherent to the surveillance system throughout the years but are unlikely to have changed much during the observation period.

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The quality surveillance system is focusing on results but not procedures. Recommendations to standardize oxygen saturation targets are not widely adopted [29]. In 19 hospitals of the National Institute of Child Health and Human Development Neonatal Research Network studied in 2006–2014 (10 with, 9 without a change of the policy for oxygen saturation alarm settings), changing alarm policies were not associated with reduced mortality or increased rates of severe ROP among infants born very preterm [30]. In 984 surviving infants of 24–27 weeks' gestational age born in 2005–2009 in the same network, there were complex interactions between the duration of oxygen saturation and the percentage of time spent in high or very saturation ranges [31]. Compliance with oxygen saturation targeting appears to be low, with substantial variations among units, among infants cared for in the same unit, and for individual infants over time [32, 33]. While it is already difficult to ascertain oxygenation policies and practices on a unit level, it is impossible to do so on a population level. In contrast, endotracheal intubation had been an item of the nationwide surveillance, allowing for the provision of quantitative data as to the percentage of infants never intubated.

The meta-analysis of individual participant data of the five RCTs on oxygen saturation targets enrolling infants born before 28 weeks' gestation found an ARD of death before the discharge of −2.6% which is comparable to the data presented here (−2.4%). We observed reduced mortality only in SGA infants. This matches a secondary analysis of SUPPORT that found that higher versus lower oxygen saturation targets reduced mortality by more than 50% in SGA infants, while there was no effect in appropriate for gestational age infants [34]. In contrast, the significant increase of severe ROP associated with higher oxygenation targets (ARD +4.0%) was not mirrored in this cohort, displaying only small and inconsistent changes. Furthermore, we did not observe a risk reduction for NEC, whereas rates of both early and late sepsis declined significantly.

The decline in both early and late-onset sepsis might have contributed to the reduced mortality observed. However, while a similar downward trend in rates of late-onset sepsis over time has been found in a retrospective analysis among extremely preterm infants cared for at 12 hospitals participating in the National Institute of Child Health and Human Development Neonatal Research Network over 12 years period, this decline in late-onset sepsis was not accompanied by a decrease in mortality [35].

The individual participant data meta-analysis of the five RCTs on oxygen saturation targets reported a significant risk increase for BPD, as defined by oxygen treatment at a postmenstrual age of 36 weeks (ARD +5.6%) [13]. In contrast, we found a substantial and sustained decline in BPD rates (ARD −10.7%) between 2010 and 2017, with BPD being defined as a requirement for supplemental oxygen to maintain arterial oxygenation of 90% or more at 36 weeks [25]. Employing a similar physiological definition of BPD, the recent multinational OPTIMIST-A trial demonstrated that surfactant administration without intubation was associated with a significantly reduced incidence of BPD in survivors [21]. The observed ARD (−7.8%) was very similar to that obtained by a previous meta-analysis comparing RCTs that randomized surfactant administration with or without endotracheal intubation (ARD −7.6%) [20]. We noted a large increase of infants managed without endotracheal intubation (ARD +7.1%) in the 2010–2017 cohort, together with a small increase of infants with antenatal steroids (ARD +2.0%). It is tempting to speculate that the decline of BPD in infants of 24–27 weeks' gestation might be related in part to the concomitant increase in the fraction of infants managed without endotracheal intubation. Less invasive ventilation may have further contributed to the decline of mortality observed, as suggested by the LISA meta-analysis [20], although LISA did not reduce the rate of death in the most recent OPTIMIST-A trial [21].

Conclusions

Observed trends in mortality (moderate decline), rates of severe ROP (insignificant increase), and BPD (substantial decline) from 2010 to 2017 are only partly in line with the assumption that expected changes made in response to results of large RCTs on oxygen saturation targets and LISA influenced outcome on a population level. Data collection of national surveillance programs should contain data on procedures and types of treatment in addition to outcome variables.

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Statement of Ethics

As only de-identified aggregate data were used for the analysis that had been collected and published according to federal regulation, informed consent was not possible. Anonymized secondary data research does not require approval by an ethical review board in Germany.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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Author Contributions

Christoph Bührer and Ulrich H. Thome framed the research question and conceptualized the study. Günther Heller procured data collection and analysis. All authors contributed to data interpretation and literature search. Christoph Bührer drafted the initial and edited the final manuscript. All authors reviewed and revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Data Availability Statement

The manuscript is based on published aggregate data which can be provided upon request. There are no individual patient data to be shared.

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