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ORIGINAL ARTICLE

# Treatment for retinopathy of prematurity in Sweden 2008–2021: Reduced gestational age of treated infants and remaining differences in treatment type and recurrence rates between hospitals

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**Abstract**

**Purpose:** This study aimed to investigate various aspects of treatment for retinopathy of prematurity (ROP) in Sweden over the past 14 years, nationally and at a hospital level.

**Methods:** Data on screening and treatment for ROP in infants born in Sweden from 2008 to 2021 were extracted from the national ROP register, SWEDROP. During this period, Swedish screening guidelines were reduced from gestational age (GA) < 32 weeks to <31 weeks in 2012 and to <30 weeks in 2020.

**Results:** Altogether, 10 959 infants were screened and 600 infants treated for ROP during the study period. Parallel to changed guidelines, the number of screened infants decreased ($p < 0.000$) and the incidence of ROP and frequency of treatment increased ($p < 0.001$), while both remained similar in infants with a GA below 30 weeks. Among treated infants, GA and BW were reduced over the years ($p < 0.001$). Laser treatment (85.2% of primary treatments) became less common and anti-VEGF injections (13.6%) became more common over time ($p < 0.001$). Altogether 16 eyes were treated with the encircling band and 13 with vitrectomy. The total frequency of retreatment (32.7% of treated eyes) remained similar over time but was more common after primary anti-VEGF injection (67.7%) than laser treatment (27.2%). There were differences between the seven university hospitals regarding type of treatment and number of retreatments ($p < 0.001$).

**Conclusion:** The frequency of treatment and retreatment for ROP remained similar over time, but the type of treatment changed and anti-VEGF injections became more common. Differences between treating hospitals emphasize the importance of centralizing the most severe cases.

**KEYWORDS**
anti-VEGF injection, laser treatment, retinopathy of prematurity, retreatment, screening, treatment

## 1 | INTRODUCTION

During the past decade, neonatal care has continuously improved, resulting in more and more immature babies born and surviving (Norman, Hallberg, et al., 2019). This development has led to an increased proportion of extremely preterm children with a high risk of severe retinopathy of prematurity (ROP) requiring treatment. Further, during the past decade, new modes of treatment have been introduced internationally, particularly intravitreal injections of anti-vascular growth factor (anti-VEGF) (Mintz-Hittner et al., 2011; Stahl et al., 2019).

There are few population-based studies, including information on screening and treatment for ROP and development over time. Based on a Swedish register for ROP

(SWEDROP), we have previously reported on various aspects of infants treated for ROP for 5 years (2008–2012) (Holmstrom et al., 2016). That study revealed a significant variation in the number of treatments per doctor and a high frequency of re-treatments compared with other international studies. Recently, a high-retreatment rate was also shown in extremely preterm Swedish babies (gestational age (GA) < 24 weeks) and born between 2007 and 2018 (Lundgren et al., 2021). Further, that study found that treatment centers highly influenced the retreatment rate.

The quality of treatment is crucial for the outcome, both anatomically and functionally, which was recently shown by Spandau et al. (2020) and by Norman, Hellstrom, et al. (2019), revealing deficiencies in screening, diagnosis and treatment in Swedish children visually impaired by severe ROP.

The present study analysed various treatment trends for ROP in Sweden over the past 14 years. It also aimed to investigate hospital treatment aspects, including treatment type and re-treatment rate. The overall goal of our study was to optimize the quality of treatment for ROP in the whole country.

## 2 | MATERIAL

This population study, based on SWEDROP, includes prematurely born children screened and treated for ROP in Sweden from 2008 to 2021. Initial national criteria for ROP screening during this period were infants born in Sweden with GA of less than 32 weeks. Criteria were modified twice to less than 31 weeks in 2012 and to less than 30 weeks in 2020 (Holmstrom et al., 2012, 2020). Furthermore, neonatologists are recommended to refer also severely diseased infants at risk of ROP and above this gestational age.

The coverage rate of the register was calculated by comparison with the Swedish neonatal quality register (SNQ). The mean coverage rate during the total study period was 97.9% (range 95.8%–100%), and after the first 2 years, the yearly coverage rate varied between 98% and 100%.

The international classification of ROP was used (Chiang et al., 2021; International Committee for the Classification of Retinopathy of Prematurity, 2005) and treatment criteria were based on the ETROP recommendations (Early Treatment For Retinopathy Of Prematurity Cooperative Group, 2003). Treatment was performed in seven university hospitals (A–G) in Sweden.

The following variables were extracted from the SWEDROP register:

Gestational age (GA) (weeks), birth weight (BW) (g), sex, incidence of ROP, various characteristics of ROP, such as stage, zone, plus and Type of ROP, frequency, type and number of treatments, postnatal age (PNA), and postmenstrual age (PMA) at treatment.

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

This study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration. The study was approved by the Regional Ethical Review Board in Uppsala (Dnr 2010-117) and the Swedish Ethics Review Board (Dnr 2021-05134).

### 2.1 | Statistical analyses

Data were primarily analysed using descriptive statistics, where numerical variables were presented as median and range and categorical variables as number and percent. Changes over the years were analysed using linear regression for numerical variables and chi-square test for trends in proportions for categorical variables. Comparison of retreatment between laser and anti-VEGF was performed using T-test and Fisher exact test depending on data. Comparison between hospitals was performed using one-way ANOVA and Fisher exact test. To explore factors related to the risk of retreatment, logistic regression models were used. In the first step, pre-defined variables were analysed univariably, followed by a multivariable analysis where factors with a $p$-value < 0.05 were included. The Akaike Information Criteria (AIC) determined the optimal model using a stepwise approach. No multiplicity adjustment has been performed; thus, the $p$-values are all nominal. All the statistical analyses were performed in R version 4.2.2.

## 3 | RESULTS

During the study period from 1 January 2008 to 31 December 2021, 10 959 infants (45.8% girls) were fully screened for ROP and registered in SWEDROP. Median GA was 28.9 weeks (range 21.9–40.4) and median BW was 1150 g (range 307–3540).

Parallel to changed screening guidelines from GA less than 32 weeks to less than 31 weeks in 2012 and to less than 30 weeks in 2020, the number of screened infants per year was reduced ($p < 0.001$); see Table 1, and GA and BW declined over time ($p < 0.001$). Further, the incidence of ROP (total 29.2%, 3197/10959 infants) increased over the years ($p < 0.001$), as did the frequency of treatment (5.5%, 600/10959 infants) ($p < 0.000$), Table 1.

For comparison over time, a separate cohort of 7618 infants born with GA less than 30 weeks, i.e. the criteria for screening since January 2020, was created, Table 1. In this cohort, linear regression analyses revealed that the yearly number of infants screened for ROP remained similar over time (range 486–597), as did GA (median 27.7 weeks, range 21.9–29.9 weeks) and BW (median 994 g, range 307–2913 g). The proportion of girls (43.6%) and boys (56.5%) was also constant. Furthermore, in this group of infants, ROP developed in 39.8% (range 34.4%–44.7% over the years), and treatment was performed in 7.9% (range 5.6%–10.1%). Both incidence of ROP and frequency of treatment remained similar over the years. The relation to GA (weeks) at birth is illustrated in Figure 1.

Altogether, 600 infants were treated for ROP during the study period. The proportion of girls (43.6%) and boys (56.5%) remained similar over time. Their GA (weeks) and BW (g) were reduced over the years ($p = 0.001$; $p < 0.001$), Table 1. The median GA was 24.4 weeks (range 21.9–31.4) and the median BW was 640 g (range 340–1700).

**TABLE 1** Gestational age (weeks), birth weight (g), incidence of ROP and frequency of treatment in the total group of infants screened for ROP ($n=10\,959$ infants) and in infants with a gestational age of <30 weeks ($n=7618$ infants), as well as gestational age and birth weight in infants treated for ROP during the study period 2008–2021.

| | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total group | | | | | | | | | | | | | | | |
| *N* | 906 | 941 | 874 | 948 | 840 | 754 | 802 | 805 | 825 | 767 | 695 | 711 | 551 | 540 | 10959 |
| GA (weeks), median | 29.4 | 29.4 | 29.3 | 29.4 | 29.1 | 28.4 | 28.6 | 28.6 | 28.6 | 28.9 | 28.9 | 28.7 | 27.7 | 28.0 | 28.9 |
| Range | 22.4–36.1 | 22.6–35.1 | 22.7–38.0 | 22.3–35.9 | 22.0–39.4 | 22.1–35.7 | 22.6–35.0 | 21.9–40.4 | 21.9–34.6 | 22.4–35.1 | 22.1–35.4 | 22.6–34.9 | 22.1–35.9 | 22.0–35.4 | 21.9–40.4 |
| BW (g), median | 1250 | 1260 | 1224 | 1228 | 1189 | 1094 | 1100 | 1100 | 1130 | 1152 | 1134 | 1115 | 993 | 1020 | 1150 |
| Range | 307–2695 | 400–2400 | 420–2520 | 382–2615 | 340–3230 | 415–2525 | 387–2364 | 415–2445 | 348–3245 | 390–2405 | 410–2380 | 340–2913 | 384–3540 | 385–2090 | 307–3540 |
| ROP, yes | 194 (21.4) | 247 (26.2) | 215 (24.6) | 213 (22.5) | 224 (26.7) | 236 (31.3) | 255 (31.8) | 286 (35.5) | 272 (33.0) | 211 (27.5) | 221 (31.8) | 229 (32.2) | 199 (36.1) | 195 (36.1) | 3197 (29.2) |
| ROP, treated | 36 (4.0) | 43 (4.6) | 47 (5.4) | 31 (3.3) | 30 (3.6) | 41 (5.4) | 45 (5.6) | 60 (7.5) | 60 (7.3) | 50 (6.5) | 40 (5.8) | 43 (6.0) | 44 (8.0) | 30 (5.6) | 600 (5.5) |
| GA<30 | | | | | | | | | | | | | | | |
| *N* | 521 | 532 | 517 | 545 | 531 | 572 | 589 | 597 | 593 | 563 | 486 | 545 | 522 | 505 | 7618 |
| GA (weeks), median | 27.7 | 27.6 | 27.6 | 27.9 | 27.6 | 27.6 | 27.6 | 27.6 | 27.4 | 27.9 | 27.6 | 27.7 | 27.6 | 27.7 | 27.7 |
| Range | 22.4–29.9 | 22.6–29.9 | 22.7–29.9 | 22.3–29.9 | 22.0–29.9 | 22.1–29.9 | 22.6–29.9 | 21.9–29.9 | 21.9–29.9 | 22.4–29.9 | 22.1–29.9 | 22.6–29.9 | 22.1–29.9 | 22.0–29.9 | 21.9–29.9 |
| BW (g), median | 1014 | 982 | 1004 | 1026 | 990 | 980 | 982 | 977 | 961 | 1000 | 988 | 1012 | 976 | 1008 | 994 |
| Range | 307–2356 | 400–2220 | 420–1896 | 382–2070 | 340–2280 | 415–1798 | 387–2080 | 415–1730 | 348–2122 | 390–1955 | 410–2045 | 340–2913 | 384–1870 | 385–1955 | 307–2913 |
| ROP, yes | 179 (34.4) | 229 (43.0) | 201 (38.9) | 201 (36.9) | 207 (39.0) | 226 (39.5) | 243 (41.3) | 267 (44.7) | 262 (44.2) | 201 (35.7) | 209 (43.0) | 219 (40.2) | 198 (37.9) | 192 (38.0) | 3034 (39.8) |
| ROP, treated | 36 (6.9) | 43 (8.1) | 47 (9.1) | 31 (5.7) | 30 (5.6) | 41 (7.2) | 45 (7.6) | 59 (9.9) | 60 (10.1) | 50 (8.9) | 40 (8.2) | 43 (7.9) | 44 (8.4) | 30 (5.9) | 599 (7.9) |
| Treated group | | | | | | | | | | | | | | | |
| *N* | 36 | 43 | 47 | 31 | 30 | 41 | 45 | 60 | 60 | 50 | 40 | 43 | 44 | 30 | 600 |
| GA (weeks), median | 24.5 | 24.7 | 24.9 | 24.6 | 24.5 | 24.4 | 24.6 | 24.3 | 24.4 | 24.1 | 24.2 | 24.6 | 23.9 | 24.6 | 24.4 |
| Range | 22.6–28.9 | 22.6–28.6 | 22.7–29.7 | 22.9–28.9 | 22.0–29.6 | 22.1–27.4 | 22.7–27.9 | 21.9–31.4 | 21.9–28.6 | 22.4–29.1 | 22.6–27.9 | 22.6–28.3 | 22.1–27.7 | 22.0–28.9 | 21.9–31.4 |
| BW (g), median | 689 | 614 | 722 | 685 | 633 | 597 | 650 | 658 | 630 | 620 | 632 | 610 | 578 | 650 | 640 |
| Range | 480–1230 | 400–1700 | 448–1140 | 410–1029 | 385–1200 | 415–914 | 437–1158 | 420–1225 | 380–1129 | 424–1150 | 425–975 | 340–1286 | 384–990 | 385–1172 | 340–1700 |

Abbreviations: BW, birth weight; GA, gestational age; *N*, number; ROP, retinopathy of prematurity.

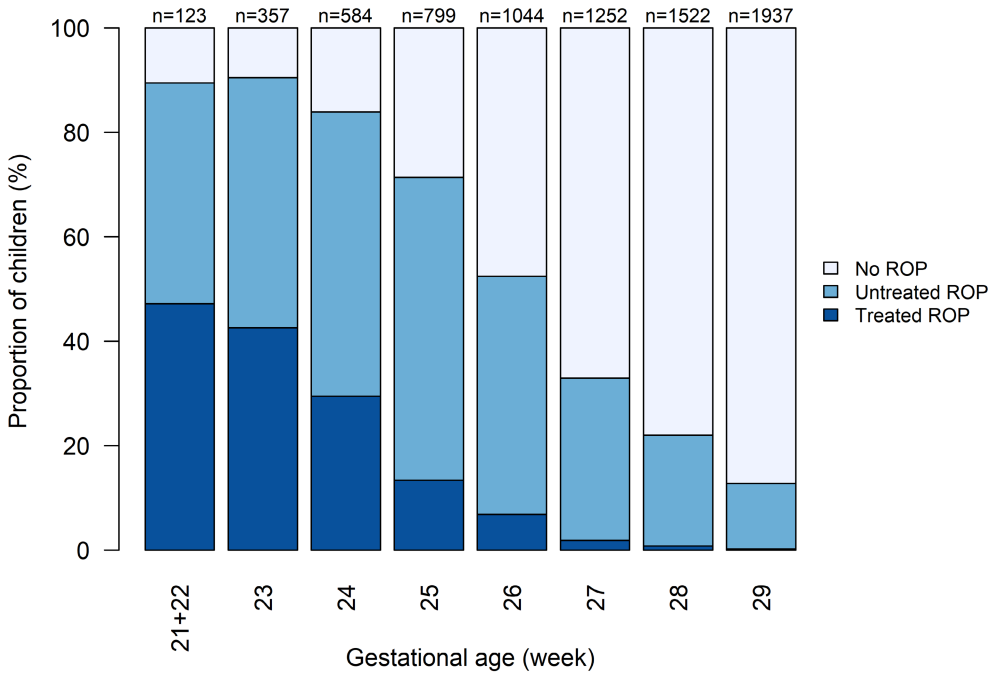


**FIGURE 1** Percentage of Retinopathy of prematurity by gestational age (weeks) at birth in 7618 infants with a gestational age of less than 30 weeks. ROP, retinopathy of prematurity.

Of the 600 infants treated for ROP, 560 infants had a GA of less than 27 weeks and 595 infants had a GA of less than 29 weeks. One treated infant born in 2015 had been referred for screening despite a GA of 31+4 weeks because of extreme sickness (Holmstrom et al., 2020). Four infants with a GA of 29 weeks were treated during the study period, but none with a GA of 30 weeks.

Of the 600 infants, treatment had been performed in both eyes in 586 infants, while seven infants were treated in the right eye only and seven in the left eye only. Altogether, treatment had been undertaken in 593 right and 593 left eyes.

The stage of ROP, zone of ROP, plus disease, and Type of ROP among the treated eyes are presented in Table 2. Type 1 ROP had developed in at least one eye in 529 (88.2%) infants (502 right, 500 left eyes). Aggressive ROP (A-ROP) had developed in at least one eye of 54 (9.0%) infants (54 right, 54 left eyes).

Regarding type of primary treatment, laser only was given to 85.8% (509 eyes) of the right eyes and 84.7% (502 eyes) of the left eyes, while anti-VEGF injections only were given to 13.7% (81 eyes; 8 Bevacizumab, 72 Ranibizumab, 1 Aflibercept) of the right eyes and 13.5% (80 eyes; 5 Bevacizumab, 74 Ranibizumab, 1 Aflibercept) of the left eyes. Seven eyes (two right, five left) had a combination of laser and anti-VEGF, three left eyes had cryo-treatment and one left eye had laser and cryo-treatment, one right eye had vitrectomy, anti-VEGF and lensectomy and one left eye had vitrectomy, laser and lensectomy, and one left eye had an encircling band. The initial eye examination as well as the screening intervals, had been strongly delayed in the infant with the vitrectomies (both eyes) and the infant with encircling band (one eye).

Over the years, the frequency of primary laser treatment was reduced ($p<0.001$) and the frequency of primary anti-VEGF injections was increased ($p<0.001$), Figure 2.

**TABLE 2** Various characteristics of the treated eyes of the 600 infants.

| | Right eyes (*N*=593) | Left eyes (*N*=593) | Any eye (*N*=600) |
|---|---|---|---|
| Max stage ROP | | | |
| Stage 2 | 16 (2.7%) | 22 (3.7%) | 7 (1.2%) |
| Stage 3 | 549 (92.6%) | 543 (91.5%) | 553 (92.2%) |
| Stage 4A | 13 (2.2%) | 8 (1.4%) | 15 (2.5%) |
| Stage 4B | 5 (0.8%) | 8 (1.4%) | 8 (1.3%) |
| Stage 5 | 10 (1.7%) | 12 (2.0%) | 17 (2.8%) |
| Plus disease | | | |
| Yes | 485 (81.8%) | 486 (82.0%) | 516 (86.0%) |
| No | 101 (17.0) | 100 (16.8%) | 80 (13.3%) |
| Unknown | 7 (1.2%) | 7(1.2%) | 4 (0.7%) |
| Zone of ROP | | | |
| Zone 1 | 79 (13.3%) | 80 (13.5%) | 85 (14.2%) |
| Zone 2 | 494 (83.3%) | 495 (83.5%) | 499 (83.2%) |
| Zone 3 | 10 (1.7%) | 8 (1.3%) | 7 (1.1%) |
| Unknown | 10 (1.7%) | 10 (1.7%) | 9 (1.5%) |
| Type of ROP | | | |
| Type 1 | 501 (84.5%) | 500 (84.3%) | 529 (88.2%) |
| Type 2 | 84 (14.2%) | 85 (14.3%) | 68 (11.3%) |
| None | 5 (0.8%) | 4 (0.7%) | 0 (0%) |
| Unknown | 3 (0.5%) | 4 (0.7%) | 3 (0.5%) |
| A-ROP | | | |
| Yes | 54 (9.1%) | 54 (9.1%) | 54 (9.0%) |
| No | 539 (90.9%) | 539 (90.9%) | 546 (91.0%) |

Abbreviations: A-ROP, aggressive retinopathy of prematurity; *N*, number; ROP, retinopathy of prematurity.

During the total study period, 136 (22.7%) of the infants had any anti-VEGF injection (126 right eyes, 118 left eyes). The number of infants treated with anti-VEGF at any time increased over the study period ($p<0.001$).

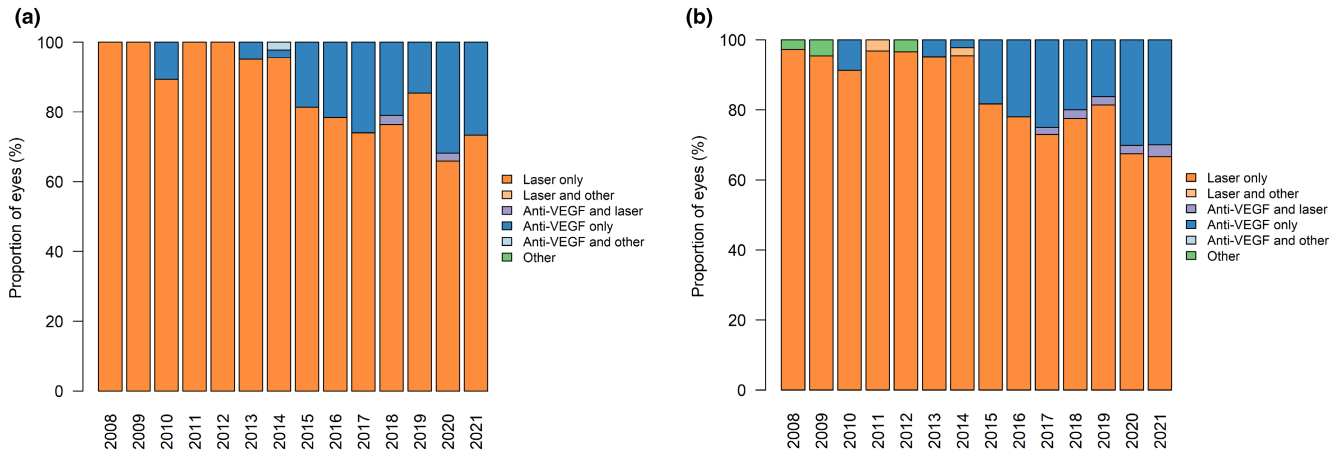


**FIGURE 2** Type of primary treatment in the 593 right (a) and 593 left eyes (b). "Other" includes lensectomy, encircling band, and cryo treatment. VEGF, vascular endothelial growth factor.

Further, eight right eyes and eight left eyes had been treated with encircling band, five right and eight left eyes had vitrectomy and one right eye had been eviscerated. No surgery with encircling band had been performed since 2017, and only one vitrectomy had been performed since 2016.

Number of treatments per eye varied between 1 and 5. Retreatment was performed in 32.7% (194/593) of the right eyes and in 32.2% (191/593) left eyes. Altogether 197 infants (32.8%) were retreated in one of their eyes.

The frequency of re-treatment remained similar over the years.

Furthermore, retreatment was more common in eyes primarily treated with anti-VEGF injections (67.9%, 55/81 right eyes, 67.5%, 54/80 left eyes) than in eyes primarily treated with laser (27.7%, 141/509 of the right eyes, 26.7%, 134/502 of the left eyes) ($p<0.001$).

The median PNA at the first treatment of any of the eyes in the 600 infants was 12.6 weeks (range 6.3–29.3 weeks) and the median PMA at the first treatment was 37.0 weeks (range 32.1–52.9 weeks). The age (PNA/PMA) at the first treatment remained similar over the years.

The median PNA at the second treatment of any of the eyes (194 right/191 left eyes) was 15.9 weeks (range 9.4–86.9 weeks). The median PMA at the second treatment of any of the eyes was 40.3 weeks (range 34.6–109.7 weeks). The PNA and the PMA at the second treatment increased over time ($p<0.001$ and $p=0.003$, respectively). The median time between first and second treatment was 3 weeks (range 0.3–73.4 weeks) and increased over time ($p<0.001$).

Comparisons between eyes primarily treated with laser versus anti-VEGF injections revealed no differences between right and left eyes. Thus, regarding the right eyes primarily treated with anti-VEGF (81 eyes), the infants had lower GA (median 23.6 vs. 24.6 weeks) and lower BW (median 555 vs. 650 g) than in infants with eyes primarily treated with laser (509 eyes) ($p=0.001$). They had also more severe ROP at the first treatment, i.e., higher frequencies of Type 1 ROP (97.5% vs. 82.5%) ($p=0.003$), Zone 1 ROP (55.6% vs. 6.7%) ($p=0.001$) and A-ROP (42% vs. 3.9%) ($p=0.001$) than the eyes treated with laser.

The eyes treated primarily with anti-VEGF, were treated at an earlier PNA (median 11 weeks, range 7.7–24.3 weeks, vs. 12.7 weeks, range 6.3–27.7 weeks) and PMA (median 34.9 weeks, range 32.1–47.1 weeks vs. 37.4 weeks, range 32.4–52.1 weeks), as compared with the eyes primarily treated with laser ($p<0.001$). Further, the frequency of re-treatment was higher in eyes primarily treated with anti-VEGF (67.9%) than in eyes primarily treated with laser (27.7%), and treatment was performed at a higher PNA (median 19.4 weeks, range 12.3–86.9 weeks) and PMA (median 42.6 weeks, range 36.3–109.7 weeks) than in eyes primarily treated with laser (PNA median 15 weeks, range 9.4–30.4 weeks; PMA median 39.9 weeks, range 34.6–56.7 weeks) ($p<0.001$). Consequently, the time between the first and second treatments was longer in the infants treated primarily with anti-VEGF ($p<0.001$), Figure 3.

## 3.1 | Treatment hospitals (A–G)

Primary treatment was performed in seven university hospitals (range 21–186 infants), Table 3. The median GA of the treated infants differed between 23.6 and 25.4 weeks and the median BW differed between 581 and 690 g in the various hospitals ($p<0.001$; $p=0.003$).

Primary treatment with laser was the major type of treatment in all hospitals, but the frequency differed between the hospitals ($p<0.001$). Primary treatment with anti-VEGF was significantly more used in two of the hospitals ($p<0.001$). Vitrectomies (4 right eyes/7 left eyes) had been performed in three of the hospitals, while encircling bands had been performed in mainly one hospital (15 eyes in one hospital and one eye in another hospital).

The overall frequency of retreatment varied between the seven hospitals (11.3%–58.0%, $p<0.001$). The frequency of retreatment after primary laser also varied between hospitals ($p<0.001$), while there was no significant difference regarding re-treatment after primary anti-VEGF treatment in the different hospitals.

In univariate regression analyses of risk factors for retreatment after primary laser, including GA, BW, sex, zone, A-ROP, and treating hospital, only Zone of ROP ($p=0.001$), A-ROP ($p=0,0312$) and treating hospital ($p<0.001$) were significant risk factors.

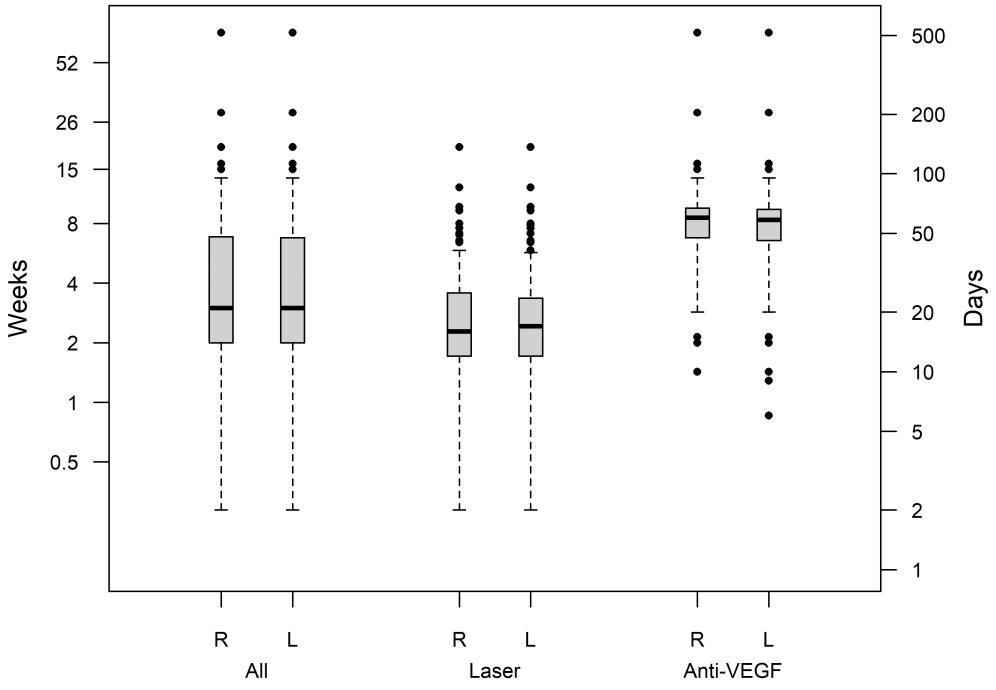


**FIGURE 3** Time (weeks and days, respectively) between first and second treatment in all eyes, eyes treated primarily with laser and eyes treated primarily with anti-VEGF. Due to the skewed distribution the y-axis is on a log-scale. L, left; R, right; VEGF, vascular endothelial growth factor.

**TABLE 3** Characteristics of infants treated in the seven university hospitals (A–G), including gestational age (weeks), birth weight (g), type of first treatment and frequency of retreatment.

| | A | B | C | D | E | F | G | Total |
|---|---|---|---|---|---|---|---|---|
| Treated group | | | | | | | | |
| *N* | 84 | 186 | 25 | 71 | 169 | 44 | 21 | 600 |
| GA (weeks), median | 23.6 | 24.5 | 24.7 | 24.4 | 24.6 | 24.1 | 25.4 | 24.4 |
| Range | 21.9–28.6 | 22.4–28.0 | 22.4–29.6 | 22.1–31.4 | 22.0–29.7 | 22.3–27.7 | 22.9–29.4 | 21.9–31.4 |
| BW (g), median | 581 | 650 | 655 | 644 | 654 | 622 | 690 | 640 |
| Range | 380–1286 | 340–1130 | 385–1200 | 424–1230 | 384–1700 | 385–990 | 440–1175 | 340–1700 |
| Type of first treatment, right | | | | | | | | |
| Laser only | 55 (67.1) | 174 (94.6) | 25 (100.0) | 71 (100.0) | 123 (73.7) | 43 (97.7) | 18 (90.0) | 509 (85.8) |
| Anti-VEGF only | 26 (31.7) | 9 (4.9) | 0 (0.0) | 0 (0.0) | 44 (26.3) | 1 (2.3) | 1 (5.0) | 81 (13.7) |
| Other | 1 (1.2) | 1 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.0) | 3 (0.5) |
| Type of first treatment, left | | | | | | | | |
| Laser only | 52 (62.7) | 174 (94.1) | 23 (95.8) | 69 (97.2) | 125 (74.4) | 41 (97.6) | 18 (90.0) | 502 (84.7) |
| Anti-VEGF only | 28 (33.7) | 9 (4.9) | 0 (0.0) | 0 (0.0) | 42 (25.0) | 0 (0.0) | 1 (5.0) | 80 (13.5) |
| Other | 3 (3.6) | 2 (1.1) | 1 (4.2) | 2 (2.8) | 1 (0.6) | 1 (2.4) | 1 (5.0) | 11 (1.9) |
| Any retreatment | 28 (33.3) | 21 (11.3) | 8 (32.0) | 23 (32.4) | 98 (58.0) | 11 (25.0) | 8 (38.1) | 197 (32.8) |
| Retreatment after laser only | 14 (26.4) | 13 (7.6) | 8 (33.3) | 23 (32.4) | 66 (54.1) | 11 (26.8) | 7 (41.2) | 142 (28.4) |
| Retreatment after Anti-VEGF only | 14 (53.8) | 8 (88.9) | 0 (0) | 0 (0) | 32 (76.2) | 0 (0) | 1 (100.0) | 55 (70.5) |

Abbreviations: BW, birth weight; GA, gestational age; *N*, number; VEGF, vascular endothelial growth factor.

In a multiple regression analysis (right and left eyes had similar values), only Zone of ROP (Right eyes: OR 4.53, 95% confidence interval 2.03–10.13, $p<0.001$) and hospital (Right eyes: Hospital B vs. Hospital A: OR 0.26, 95% confidence interval 0.11–0.60, $p=0.002$, and Hospital E vs. Hospital A: OR 3.64, 95% confidence interval 1.76–7.52, $p<0.001$) remained significant risk factors for retreatment of both eyes after primary laser treatment.

## 4 | DISCUSSION

This Swedish population study, based on the SWEDROP register, reported details on 600 infants treated for ROP during a 14-year period. The type of treatment changed over time, while the number of retreatments remained similar but high. There were obvious differences between the seven hospitals, both regarding type of treatment and frequency of retreatment.

The number of yearly screened infants was reduced over the years parallel to changed screening guidelines (Holmstrom et al., 2012, 2020), while the number of treated infants remained similar. Among infants born before GA < 30 weeks, the yearly number of screened infants remained similar, as well as their GA, BW, incidence of ROP and frequency of treatment. Regarding the 600 infants treated for ROP, however, GA and BW were reduced, probably reflecting improved neonatal care over the years. Furthermore, all the infants treated for ROP had a GA at birth below the actual screening guidelines, except one infant, previously described, with a GA of 31 weeks, born in 2015 and referred because of high risk for ROP because of severe illness (Holmstrom et al., 2020).

There are few national population-based studies on treatment for ROP. Apart from this study, Adams et al. (2017) have reported on treatment for ROP in Great Britain and Trzcionkowska et al. in the Netherlands (Trzcionkowska et al., 2021). In the present study, 88.2% of the treated infants fulfilled the ETROP criteria for treatment (Early Treatment For Retinopathy Of Prematurity Cooperative Group, 2003) with Type 1 ROP in at least one of their eyes. This was a higher frequency than in the studies from Great Britain (62% of right eyes) and the Netherlands (76.5%). Altogether, 6.6% of the treated infants in our study progressed to stages 4 and 5 in at least one of the eyes. Despite the lower criteria for screening in Sweden with lower GA and BW, the frequency of late stages of ROP was lower than in the study from the Netherlands (10.3%), while our frequency of A-ROP (9%) was similar to the British study (8.3% in right eyes) (Adams et al., 2017; Trzcionkowska et al., 2021). Reassuringly, no infant progressed to stage 5 during the past 4 years, possibly mirroring a more accurate diagnosis and treatment due to increased use of wide-angle photography in screening and treatment for ROP in Sweden.

During the 14-year study period, the type of treatment changed. The frequency of primary laser treatment declined, while there was an increasing use of anti-VEGF injections as first treatment. This is in line with national reports from Britain (Adams et al., 2017), the United States and Germany (Dammann et al., 2023; Khan et al., 2022). Reassuringly, infants who had been primarily treated with anti-VEGF were more immature and had more severe ROP, i.e., higher frequencies of Zone 1 and A-ROP, than infants primarily treated with laser. Within our country, however, there were obvious differences between hospitals regarding use of anti-VEGF. Finally, during the 14-year study period, 16 of the 1186 treated eyes had been treated with encircling band and 13 with vitrectomy.

The frequency of retreatment remained high during the study period. Comparison with other studies is difficult since the frequency of Type 1 ROP may differ and not all studies include early retreatment of skip lesions as a retreatment (Adams et al., 2017; Stahl et al., 2019; Trzcionkowska et al., 2021). Like other studies (Adams et al., 2018; Chang et al., 2022; Mintz-Hittner et al., 2016), however, we found a higher recurrence rate and a higher age (PNA and PMA) at retreatment after primary anti-VEGF treatment than after primarily laser treatment, underlining the importance of long-term follow-up after anti-VEGF injections. In accordance with a previous Swedish study of infants born before GA of 24 weeks (Lundgren et al., 2021), our study reveals significant differences in retreatment frequency in the seven treating hospitals, also after adjusting for other risk factors.

Visual and ophthalmological deficiencies are well-known sequels of severe and treated ROP (Hellgren et al., 2016; Holmstrom & Larsson, 2008; Larsson et al., 2023). Furthermore, in a study of 6.5-year-old children, we recently showed that retreatment is a significant risk factor for visual dysfunction (Larsson et al., 2023). Despite national screening and treatment guidelines, there are still inequities in ROP treatment in our country, as shown in the present study reporting differences between hospitals. The cause of the variations in retreatment rate between the different hospitals is not fully known, but may be explained by inadequate laser treatment, as previously pointed out by Norman, Hellstrom, et al. (2019) and Spandau et al. (2020).

## 4.1 | Strengths and limitations

The present study is based on prospectively collected and registered data in the Swedish registry for ROP, SWEDROP. The register has a high coverage rate of around 98% of all prematurely born infants in Sweden, fulfilling the criteria for ROP screening. Furthermore, the register also includes data on infants with higher gestational ages and who have been referred for ROP screening. A limitation of our study might be the use of register data only, thus, not including data acquired from medical records.

## 4.2 | Conclusion

This Swedish population-based 14-year study showed more immature infants treated for ROP over time, a similar frequency of treatment, a persistent high frequency of retreatment, and an increasing use of anti-VEGF injections over the years, although in the minority. Furthermore, there were differences in treatment choice and rate of retreatments between hospitals. A recently started centralization of treatment of severe cases of ROP to three university hospitals and of cases needing vitrectomies to only one of these, will hopefully improve the quality of treatment and lead to more equal care in the country.

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## REFERENCES


Adams, G.G., Bunce, C., Xing, W., Butler, L., Long, V., Reddy, A. et al. (2017) Treatment trends for retinopathy of prematurity in the UK: active surveillance study of infants at risk. *BMJ Open*, 7(3), e013366.

Adams, G.G., Bunce, C., Xing, W., Butler, L., Long, V., Reddy, A. et al. (2018) Retinopathy of prematurity in the United Kingdom: retreatment rates, visual and structural 1-year outcomes. *Eye (London, England)*, 32(11), 1752–1759.

Chang, E., Josan, A.S., Purohit, R., Patel, C.K. & Xue, K. (2022) A network meta-analysis of retreatment rates following bevacizumab, Ranibizumab, Aflibercept, and laser for retinopathy of prematurity. *Ophthalmology*, 129(12), 1389–1401.

Chiang, M.F., Quinn, G.E., Fielder, A.R., Ostmo, S.R., Paul Chan, R.V., Berrocal, A. et al. (2021) International classification of retinopathy of prematurity, third edition. *Ophthalmology*, 128(10), e51–e68.

Dammann, O., Hartnett, M.E. & Stahl, A. (2023) Retinopathy of prematurity. *Developmental Medicine and Child Neurology*, 65(5), 625–631.

Early Treatment For Retinopathy Of Prematurity Cooperative G. (2003) Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Archives of Ophthalmology*, 121(12), 1684–1694.

Hellgren, K.M., Tornqvist, K., Jakobsson, P.G., Lundgren, P., Carlsson, B., Kallen, K. et al. (2016) Ophthalmologic outcome of extremely preterm infants at 6.5 years of age: extremely preterm infants in Sweden study (EXPRESS). *JAMA Ophthalmology*, 134(5), 555–562.

Holmstrom, G., Hellstrom, A., Granse, L., Saric, M., Sunnqvist, B., Wallin, A. et al. (2020) New modifications of Swedish ROP guidelines based on 10-year data from the SWEDROP register. *The British Journal of Ophthalmology*, 104(7), 943–949.

Holmstrom, G., Hellstrom, A., Jakobsson, P., Lundgren, P., Tornqvist, K. & Wallin, A. (2016) Five years of treatment for retinopathy of prematurity in Sweden: results from SWEDROP, a national quality register. *The British Journal of Ophthalmology*, 100(12), 1656–1661.

Holmstrom, G. & Larsson, E. (2008) Long-term follow-up of visual functions in prematurely born children—a prospective population-based study up to 10 years of age. *Journal of AAPOS*, 12(2), 157–162.

Holmstrom, G.E., Hellstrom, A., Jakobsson, P.G., Lundgren, P., Tornqvist, K. & Wallin, A. (2012) Swedish national register for retinopathy of prematurity (SWEDROP) and the evaluation of screening in Sweden. *Archives of Ophthalmology*, 130(11), 1418–1424.

International Committee for the Classification of Retinopathy of P. (2005) The international classification of retinopathy of prematurity revisited. *Archives of Ophthalmology*, 123(7), 991–999.

Khan, S.I., Ryu, W.Y., Wood, E.H., Moshfeghi, D.M., Shah, J.K. & Lambert, S.R. (2022) Retinopathy of prematurity treatment trends from 2003 to 2020 in the United States. *Ophthalmology*, 129(10), 1216–1218.

Larsson, E., Hellstrom, A., Tornqvist, K., Wallin, A., Sunnqvist, B., Sandgren Hochhard, K. et al. (2023) Ophthalmological outcome of 6.5 years children treated for retinopathy of prematurity: a Swedish register study. *Br J Ophthalmol*, bjo-2022-322022. Available from: https://doi.org/10.1136/bjo-2022-322022. Online ahead of print.

Lundgren, P., Jacobson, L., Hard, A.L., Al-Hawasi, A., Larsson, E., Granse, L. et al. (2021) High rate and large intercentre variability in retreatment of retinopathy of prematurity in infants born <24 gestational weeks. *BMJ Open Ophthalmology*, 6(1), e000695.

Mintz-Hittner, H.A., Geloneck, M.M. & Chuang, A.Z. (2016) Clinical Management of Recurrent Retinopathy of prematurity after Intravitreal bevacizumab monotherapy. *Ophthalmology*, 123(9), 1845–1855.

Mintz-Hittner, H.A., Kennedy, K.A., Chuang, A.Z. & Group B-RC. (2011) Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *The New England Journal of Medicine*, 364(7), 603–615.

Norman, M., Hallberg, B., Abrahamsson, T., Bjorklund, L.J., Domellof, M., Farooqi, A. et al. (2019) Association between year of birth and 1-year survival among extremely preterm infants in Sweden during 2004-2007 and 2014-2016. *Journal of the American Medical Association*, 321(12), 1188–1199.

Norman, M., Hellstrom, A., Hallberg, B., Wallin, A., Gustafson, P., Tornqvist, K. et al. (2019) Prevalence of severe visual disability among preterm children with retinopathy of prematurity and association with adherence to best practice guidelines. *JAMA Network Open*, 2(1), e186801.

Spandau, U., Larsson, E. & Holmstrom, G. (2020) Inadequate laser coagulation is an important cause of treatment failure in type 1 retinopathy of prematurity. *Acta Ophthalmologica*, 98(8), 795–799.

Stahl, A., Lepore, D., Fielder, A., Fleck, B., Reynolds, J.D., Chiang, M.F. et al. (2019) Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. *Lancet*, 394(10208), 1551–1559.

Trzcionkowska, K., Vehmeijer, W., Kerkhoff, F.T., Bauer, N.J.C., Bennebroek, C.A.M., Dijk, P.H. et al. (2021) Increase in treatment of retinopathy of prematurity in The Netherlands from 2010 to 2017. *Acta Ophthalmologica*, 99(1), 97–103.



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