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KEY WORDS
necrotizing enterocolitis, premature infants, perinatal mortality, perinatal care, epidemiology, trends, seasonal variation

ABBREVIATIONS
CI — confidence interval
ICD-9 — International Classification of Diseases, Ninth Revision
ICD-10 — International Classification of Diseases, Tenth Revision
IRR — incidence rate ratio
NCD — National Cause of Death Register
NEC — necrotizing enterocolitis
NPR — National Patient Register
SMB — Swedish Medical Birth Register

Dr Ahle initiated the study, participated in the design of the study and the request of the database extract, processed and analyzed the data, drafted the initial manuscript, and approved the final manuscript as submitted. Dr Drott suggested the field of study, took part in the discussion of study design, definition of terms, and interpretation of results, reviewed and revised the manuscript; and approved the final manuscript as submitted. Dr Andersson suggested the method, participated in the design of the study and the request of the database extract, carried out some of the analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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WHAT’S KNOWN ON THIS SUBJECT: The incidence of necrotizing enterocolitis (NEC), a devastating condition in neonates, varies geographically and with time. Although the most consistent risk factors are prematurity and low birth weight, it has not been convincingly shown to increase in the post-surfactant era.

WHAT THIS STUDY ADDS: The incidence of NEC, especially among the highly premature but also in more mature groups, has increased in recent decades, concurrent with dramatically improved early infant survival. Seasonal variation of NEC suggests environmental etiological factors.

abstract

OBJECTIVE: To investigate temporal, seasonal, and geographic variations in the incidence of necrotizing enterocolitis (NEC) and its relation to early infant survival in the Swedish population and in subgroups based on gestational age, birth weight, and gender.

METHODS: In the Swedish birth cohort of 1987 through 2009 all children with a diagnosis of NEC were identified in the National Patient Register, the Swedish Medical Birth Register, and the National Cause of Death Register. NEC incidence, early mortality, and seasonality were analyzed with descriptive statistics, Poisson regression, and auto regression.

RESULTS: The overall incidence of NEC was 3.4 in 10 000 live births, higher in boys than in girls (incidence rate ratio 1.22, 95% confidence interval 1.06–1.40, P = .005), with a peak in November and a trough in May, and increased with an average of ∼5% a year during the study period. In most subgroups, except the most immature, an initial decrease was followed by a steady increase. Seven-day mortality decreased strongly in all subgroups over the entire study period (annual incidence rate ratio 0.96, 95% confidence interval 0.95–0.96, P < .001). This was especially marked in the most premature and low birth weight infants.

CONCLUSIONS: After an initial decrease, the incidence of NEC has increased in Sweden during the last decades. An association with the concurrent dramatically improved early survival seems likely. Pediatrics 2013;132:1–9
Survival of preterm infants has increased dramatically over the past decades due to improved perinatal and neonatal care. There are concerns that this may lead to increased incidence rates of morbidities specific to the premature, for example, necrotizing enterocolitis (NEC). Reports of trends in the incidence of NEC are, however, contradictory, showing both decreasing and increasing rates (Table 1).

NEC incidence is known to vary geographically with frequencies thought to be especially low in Japan, Switzerland, and some Scandinavian countries. Most studies are from the United States and report incidence rates between 0.7 and 1 in 1000 live births with significantly higher incidence rates in infants of African American descent (1.6–2.2 per 1000 live births) than whites (0.5–0.6 per 1000 live births). In the United Kingdom and Ireland, 0.3 cases of proven NEC in 1000 live births were estimated (0.5 when including suspected cases). Among infants with birth weights of 1500 g or less, NEC was reported in 6% in the Netherlands in 1983, 2% in Italy from 1994 through 2005, and 7% in Spain from 2002 through 2005.

To our knowledge, there is no truly population based study from Europe, and most studies are based only on selected infants with low birth weights and premature gestational ages. In the databases held by the Swedish National Board of Health and Welfare, the National Patient Register (NPR), the Swedish Medical Birth Register (SMB), and the National Cause of Death Register (NCD), all children born in 1987 through 2009 with a diagnosis of NEC (ICD-9 or the 10th revision of the ICD [ICD-10] code 777F or P77, respectively), in the NPR, NCD, or SMB were identified. Gestational age, weight at birth, and other perinatal data were obtained by linkage with the SMB based on the children’s unique national Personal Identity Number (ICD-9 or the 10th revision of the World Health Organization’s International Classification of Diseases (ICD-9). This allows for a survey of a long period of time in which major changes in neonatal care have taken place.

The current study is a population-based study of the incidence of NEC in Sweden from 1987 through 2009. We describe temporal, seasonal, and geographic variations, as well as associations with gestational age, birth weight, and gender. To address the question of potentially increasing NEC incidence in relation to improvement in ante- and perinatal care, we also analyze the development of early mortality.

METHODS

Data were obtained from the following registers held by the Swedish National Board of Health and Welfare: the National Patient Register (NPR), the Swedish Medical Birth Register (SMB), and the National Cause of Death Register (NCD). All children born in 1987 through 2009 with a diagnosis of NEC (ICD-9 or the 10th revision of the ICD [ICD-10] code 777F or P77, respectively), in the NPR, NCD, or SMB were identified. Gestational age, weight at birth, and other perinatal data were obtained by linkage with the SMB based on the children’s unique national Personal Identity Number assigned to >99.9% of all Swedish residents at birth or immigration.

Because of a few weeks’ delay in receiving the identity number after birth, this number was missing for some registrations in the NPR and NCD, which impeded linkage with the SMB. Some of these discharges represent a chain of consecutive admissions of the same child because of referrals between hospitals of different levels of care and repeated admissions because of complications. On the basis of registry data on gender, date of birth, dates of discharge and admission, place of residency, diagnoses other than NEC, as well as knowledge of the referral system between hospitals, we were able to trace and link most of the admissions to unique individuals. Special care was taken with multiple births as marked in the SMB variable and/or detected by ICD codes in the NPR. The study was approved by the Regional Ethical Review Board of Linköping.

The background population consists of all children born in Sweden from 1987 through 2009. A deidentified extract was obtained from the SMB Register containing demographic data and perinatal information including date of birth, gender, gestational age, and birth weight. Subgroups were defined by gender, gestational age, and birth weight. Limits were chosen to fit definitions of ICD-10. The number of children belonging to the lowest weight classes specified by specialist codes (<500 g and 500–749 g), however, were too small to allow for meaningful statistical analysis and were therefore brought together in the subgroup with a birth weight <750 g. Among children with a birth weight >4500 g or a gestational age >42 weeks, NEC is extremely rare, which justified merging

### TABLE 1 Development of NEC Incidence Over Time According to Earlier Studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>Study Periods</th>
<th>NEC Frequency during study periods</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>Nonselected</td>
<td>1986–1992</td>
<td>Signs of increasing rates</td>
<td>2,3</td>
</tr>
<tr>
<td>Sweden</td>
<td>Birth wt &lt;1000 g</td>
<td>1990–1992</td>
<td>2%</td>
<td>5</td>
</tr>
<tr>
<td>United States</td>
<td>Nonselected</td>
<td>1981–1984</td>
<td>Relative risk 1.8 for the second period compared with the first</td>
<td>1</td>
</tr>
<tr>
<td>Sweden</td>
<td>&lt;32 wk gestation</td>
<td>1985–1999</td>
<td>1.2%</td>
<td>6</td>
</tr>
<tr>
<td>Sweden</td>
<td>&lt;27 wk gestation</td>
<td>2004–2007</td>
<td>6%</td>
<td>7</td>
</tr>
</tbody>
</table>

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these groups with the groups of full term and normal weight births, respectively. The study period was divided into 4 subperiods of 6, 6, 6, and 5 years, respectively. The incidence of NEC per 10 000 live births, including trends over time as well as geographic and seasonal variation, was analyzed for the entire population and for subgroups. Trends of early mortality, defined as death within 7 days of birth per 1000 live births, were also analyzed in the population as a whole and in the subgroups.

**Statistical Methods**

Data were analyzed with descriptive statistics. To obtain robust estimates and confidence intervals (CIs) of the count data, Poisson regression was used for trends and covariations and results presented as incidence rate ratio (IRR). To describe the strength of trends over time, the term “annual IRR” is used as a measure of average annual change in incidence rates. Seasonal variation was analyzed by investigating the presence of harmonic cyclicity with auto correlation. The eventual peak and trough were identified graphically by a seasonal subseries plot. The complete monthly time series was used for these analyses.

**Missing Data**

Individuals with NEC for whom the perinatal data of the SMB could not be traced because of incomplete identity information in the NPR and NPD, as described earlier, were excluded. To evaluate the influence of the these cases on the epidemiologic results, the distribution of the diagnosis “highly premature” or “very low birth weight” (765A according to ICD-9 or P070 or P072 according to ICD-10), “other” premature or low birth weight (ICD-9 765B; ICD-10 P071 or P073), and “small for gestational age” (ICD-9 764A, 764B, 764D, 764E or 764X; ICD-10 P05.0 or P051) as well as in-hospital deaths was compared for the children with and without traceable perinatal data in the SMB.

**RESULTS**

**Patients**

During the studied period, 2 381 318 live births were registered in SMB, 1 223 501 (51%) boys and 1 157 387 (49%) girls. In 430 infants, information on gender was missing.

Nine hundred twenty cases of NEC, 521 (57%) boys and 399 (43%) girls, were found in the NPR, NCD, and/or SMB. For 112 cases, 66 (59%) boys and 46 (41%) girls, the perinatal information in the SMB could not be traced. A diagnosis of prematurity was less frequent among these cases compared with the 808 cases for whom the perinatal information could be traced (64% vs 80%, P < .001), but the proportion diagnosed as highly premature was similar (38% vs 42%, P = .36). The group with missing perinatal information make up 11% of all NEC cases diagnosed as “highly premature” (765A, P070, or P072) and 9% of those diagnosed as “other premature” (765B, P071, or P073; P = .31).

**Incidence of NEC**

The overall incidence of NEC during the study period was 3.4 in 10 000 live births (3.8 in 10 000 including the cases with incomplete identity information; Table 2). There were strong associations with prematurity and low birth weights, but 18% of all the NEC patients were full term and 19% had a birth weight of ≥2500 g. The incidence was higher in boys than in girls (3.7 vs 3.0/10 000, P = .02 or IRR 1.22, 95% CI 1.06–1.40, P = .005). This difference remained after adjustment for birth weight, gestational age, and birth year (IRR 1.25, 95% CI 1.08–1.43, P = .002). It was especially marked in children with birth weights 1000 to 1499 g (183 vs 119.3/10 000, P = .006) and 1500 to 2499 g (22.7 vs 14.7/10 000, P = .006) but not seen among the children with gestational age <28 weeks or birth weight <1000 g.

Except for a higher frequency of NEC in the county of Stockholm, the capital of Sweden and its largest city, there were no differences in incidence rates according to region or population density. The increased incidence rates of Stockholm County compared with the rest of the country were seen in all subgroups with minor fluctuations over time. However, the incidence of NEC in children that died within 28 days was the same in Stockholm as in the rest of the country.

A certain seasonal variation in NEC incidence rates was seen with a peak in November and a trough in May, which persisted after adjustment for prematurity and was confirmed by auto regression.

**Trends**

The incidence curve of NEC showed a j-shaped pattern with an initial decrease between the first and the second subperiod (1987–1992 and 1993–1998), followed by a steady increase (Table 3, Figs 1 and 2). This pattern was seen for all subgroups of gestational age and birth weight, except in gestational ages <28 full weeks and birth weights <1000 g, in which NEC incidence rates increased over the entire period. The proportion of term infants among NEC cases decreased from 30% in the first subperiod to 14% in the last (P < .001). From the first to the last subperiod, the proportions of infants with gestational ages <28 weeks and birth weights <750 g increased in the background population from 24.4 to 30.4 per 10 000 live births (IRR 1.25, 95% CI 1.16–1.34, P < .001) and from 9.0 to 14.4 per 10 000 live births (IRR 1.61, 95% CI 1.45–1.79, P < .001), respectively. For the other subgroups, there were only small changes over time.

During the study period, 7-day mortality decreased strongly (annual IRR 0.96, 95% CI 0.85–0.96, P < .001; Table 4, Figs 3 and 4). The trend was similar in all subgroups of birth weight, and gestational age, with
the strongest decrease in the groups with birth weights of 750 to 999 g (annual IRR 0.93, 95% CI 0.92–0.95, P < .001) and gestational ages 28 to 31 weeks (annual IRR = 0.94, 95% CI 0.92–0.95, P < .001), corresponding to reductions of 66% and 63% respectively from the first subperiod to the last.

**DISCUSSION**

This study shows a considerable increase in NEC incidence together with strongly decreasing infant mortality in Sweden during 1987 through 2009, a period of major changes in perinatal care. The first case reports of NEC were published in the first half of the 19th century, but it was with the development of neonatal intensive care in the 1960s that the condition became more common and was described as a clinical, radiographic, and pathologic entity. In Sweden, the routine use of antenatal steroids and surfactant was gradually introduced during the 1990s. Since 2001, national guidelines for management of extremely preterm births, apart from centralization of perinatal services, encourage individualized evaluation rather than a fixed gestational age limit for intervention, and from an international perspective, perinatal and neonatal care in Sweden is comparatively proactive. The national Extremely Preterm Infants Study reports 70% 1-year survival among infants with 27 full weeks’ gestation during 2004 through 2007, compared with a survival rate of 48% in a historical cohort of extremely low birth weight infants born in Sweden in April 1990 through March 1992.

Our results, in contrast to others, reveal that concerns about a possible rise in incidence rates of NEC are justified, but the mechanisms behind this observation seem to be complex, with improved survival of the most premature as 1 of many contributing factors. Whereas early mortality has been steadily decreasing in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Background Population, n</th>
<th>Incidence Per 10 000 Live Births</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2 381 318</td>
<td>808</td>
<td>3.4</td>
</tr>
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</table>

**TABLE 2** Distribution of the Background Population of All Live Births in Sweden and the 808 NEC Patients With Available Perinatal Data

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<td>808</td>
<td>3.4</td>
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</table>

**TABLE 3** Incidence of NEC per 10 000 Live Births for the 4 Subperiods Studied and the Trend Expressed as Annual IRR

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<tbody>
<tr>
<td>All</td>
<td>2.6</td>
<td>2.2</td>
<td>3.5</td>
<td>5.7</td>
<td>1.05 (1.04–1.06)</td>
</tr>
</tbody>
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<td>All</td>
<td>2.6</td>
<td>2.2</td>
<td>3.5</td>
<td>5.7</td>
<td>1.05 (1.04–1.06)</td>
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</table>
all subgroups for the entire study period, the NEC incidence curve is j-shaped in all groups but those with gestational ages <28 full weeks and birth weights <1000 g, where an increasing trend is seen throughout the period. Holman suggested that improved perinatal care initially helped reduce NEC incidence before the continuously increasing survival of the most vulnerable individuals caused a subsequent rise. Preventive measures that may have helped reduce

FIGURE 1
NEC incidence in subgroups according to gestational age. Note that the scale of the y-axis differs between the subgroups.

FIGURE 2
NEC incidence in subgroups according to birth weight. Note that the scale of the y-axis differs between the subgroups.
NEC incidence when introduced during the first subperiod include scheduled feedings and the use of human milk.26–28 There are also data to suggest that surfactant, at least in repeated doses, may prevent NEC.29 It is generally accepted that 90% of all patients with NEC are premature.13 The proportion of term infants reported from various studies, however, varies from 7% to 25%.1,14,30–34 Possibly reflecting a relatively low frequency of prematurity in Sweden, 30% of NEC cases were full term during our first subperiod. The decrease to 14% during the last period can be explained by a combination of an increasing proportion of premature infants and a more rapidly rising incidence rate in the extremely premature and low birth weight infants. The latter supports the role of early survival in these groups. Nevertheless, NEC incidence tends to rise in all groups. Starting from the subperiod with the lowest incidence rate (1993–1998), the annual IRR is 1.05 (95% CI 1.00–1.09, P = .04) in full-term infants. Only in birth weights ≥2500 g does the trend not reach statistical significance. It could be that, also in the mature groups, an improved initial survival of individuals with conditions making them susceptible to NEC plays a role in the rising incidence rate, but the impact of specific risk factors needs additional investigation and will be addressed in a forthcoming case-control study of the same population. The incidence rate in the population as a whole is lower than that reported from the United States,1,11–13 but, especially in the last subperiod, similar to United Kingdom and Ireland14 and the Caucasian population in the United States.1,13 The overall incidence among infants of our population with birth weights <2500 g (268.6/10 000) is higher than in the Italian study,15 especially during the last subperiod (507.3/10 000) but lower than in the Dutch and Spanish populations.16,17 Why NEC incidence varies between countries is not fully understood, but

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<tbody>
<tr>
<td>All</td>
<td>2.82</td>
<td>2.16</td>
<td>1.74</td>
<td>1.27</td>
<td>0.96 (0.95–0.96)</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full term</td>
<td>0.96</td>
<td>0.72</td>
<td>0.61</td>
<td>0.40</td>
<td>0.96 (0.95–0.96)</td>
</tr>
<tr>
<td>32–36 wk</td>
<td>11.34</td>
<td>8.81</td>
<td>7.1</td>
<td>5.08</td>
<td>0.96 (0.95–0.97)</td>
</tr>
<tr>
<td>28–31 wk</td>
<td>70.47</td>
<td>47.41</td>
<td>32.91</td>
<td>25.78</td>
<td>0.94 (0.93–0.95)</td>
</tr>
<tr>
<td>&lt;28 wk</td>
<td>348.29</td>
<td>256.27</td>
<td>180.65</td>
<td>153.75</td>
<td>0.95 (0.94–0.96)</td>
</tr>
<tr>
<td>Birth wt, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2500 g</td>
<td>0.90</td>
<td>7.16</td>
<td>0.57</td>
<td>0.39</td>
<td>0.95 (0.95–0.96)</td>
</tr>
<tr>
<td>1500–2499 g</td>
<td>15.42</td>
<td>10.37</td>
<td>8.75</td>
<td>6.24</td>
<td>0.95 (0.94–0.96)</td>
</tr>
<tr>
<td>1000–1499 g</td>
<td>87.58</td>
<td>58.21</td>
<td>42.38</td>
<td>32.36</td>
<td>0.94 (0.93–0.96)</td>
</tr>
<tr>
<td>750–899 g</td>
<td>229.82</td>
<td>142.41</td>
<td>75.49</td>
<td>78.79</td>
<td>0.93 (0.92–0.95)</td>
</tr>
<tr>
<td>&lt;750 g</td>
<td>502.40</td>
<td>395.83</td>
<td>275.36</td>
<td>251.58</td>
<td>0.96 (0.95–0.97)</td>
</tr>
</tbody>
</table>

FIGURE 3
Early mortality in subgroups according to gestational age. Note that the scale of the y-axis differs between the subgroups.
differences in ethnicity may play a role alongside great differences in the proportion of premature births.\textsuperscript{35} Seasonal variation in NEC incidence has seldom been studied. Snyder found a periodicity of 6 months with peaks in June and December.\textsuperscript{36} In contrast, our data suggest a periodicity of 12 months with a peak in November and a trough in May. This may indicate that there are environmental factors with seasonal variation influencing the incidence of NEC but that these factors do not occur in the same patterns in different populations.

Our study is comparatively large, truly population based, and stretches over a considerable period of time, including the years before the gradual introduction of antenatal steroids and surfactant in routine perinatal care during the 1990s.\textsuperscript{7} The registers, held by the Swedish National Board of Health and Welfare, provide high-quality information on all hospital discharges in Sweden, which entail good conditions for comprehensive population-based epidemiologic studies.\textsuperscript{21,22} However, certain difficulties, some of which are especially obvious in the newborn, arise from the use of passive rather than active case ascertainment methodology.

During the study period, newborn infants received their identification numbers with some weeks delay, and there are 112 cases of NEC, representing 12\% of all cases, for whom the perinatal data could not be obtained from the SMB. A discharge diagnosis indicating prematurity was less common among the cases with missing perinatal information, but there was no difference in the proportion of highly premature or in-hospital deaths. Therefore, it seems reasonable to assume that these missing cases do not induce any substantial selection bias in the analyses based on perinatal data. Missing identification numbers are less frequent during the last subperiod than before, especially in boys. The overall positive incidence trend for the whole population, as well as for boys and girls separately, is, however, not significantly affected if the cases with missing perinatal information are included or not.

The limitations of hospital discharge data, registered as part of an administrative routine rather than according to a research protocol with strict diagnostic criteria to fit the issue of a specific study, must also be taken into consideration when interpreting the major results of the study. The regional differences, with similar incidence throughout the country among the children that died within 28 days but higher incidence rate in Stockholm among the survivors, indicate that less severe cases have been diagnosed and may illustrate a possible influence from differences in registration praxis. In cases with long hospitalizations and many conditions, a minor episode of NEC, healed long before discharge, may be forgotten when diagnoses are reported. Conversely, because no information is available on the criteria used for diagnosing NEC, suspected

\textbf{FIGURE 4} Early mortality in subgroups according to birth weight. Note that the scale of the y-axis differs between the subgroups.
cases will have been included along with certain ones. On the other hand, criteria requiring a positive radiograph may miss a substantial proportion of real cases. The recent discussion on differential diagnosis in NEC could influence the incidence rates over time because some cases might get other diagnoses toward the end of the study period. This, however, should cause decreasing incidence rates rather than increasing. With an augmented awareness of NEC, the readiness to suspect the diagnosis may increase over time. In that case, however, less serious cases would be included and NEC incidence would rise faster in those who survived 28 days than in those who did not, but the trend did not differ significantly between the groups: annual IRR, adjusted for birth weight and gestational age, 1.04 (95% CI 1.03–1.05, \( P < .01 \)) for survivors and 1.06 (95% CI 1.04–1.09, \( P < .01 \)) for nonsurvivors, and a positive trend in the proportion of live born dying from NEC as main or contributing cause parallels the incidence trend: annual IRR 1.05 (1.02–1.08, \( P = 0001 \)).

CONCLUSIONS

We have shown an important increase in the incidence rate of NEC in Sweden from 1987 through 2009 alongside a dramatically improved survival, especially for the premature and low birth weight infants. Because early survival of the most vulnerable infants continues to improve, the incidence rates of NEC most probably will continue to rise. Differentiated epidemiologic knowledge and improved understanding of the pathogenesis and pathophysiology of NEC are needed to achieve effective prevention strategies and early detection of individuals at risk.

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REFERENCES

Margareta Ahle, Peder Drott and Roland E. Andersson

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/early/2013/06/26/peds.2012-3847