

## REGULAR ARTICLE

# Population-based study showed that necrotising enterocolitis occurred in space–time clusters with a decreasing secular trend in Sweden

Amanda Magnusson (amanda.magnusson@vgregion.se)<sup>1</sup>, Margareta Ahle<sup>2,3</sup>, Diana Swolin-Eide<sup>1</sup>, Anders Elfvin<sup>1</sup>, Roland E. Andersson<sup>4</sup>

1.Department of Pediatrics, Institution of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

2.Division of Radiology, Department of Medical and Health Sciences, Faculty of Health Sciences, Linköping University, Linköping, Sweden

3.Department of Radiology in Linköping, County Council of Östergötland, Linköping, Sweden

4.Department of Surgery, County Hospital Ryhov, Jönköping, Sweden

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## Correspondence

A Magnusson, Department of Pediatrics, Institution of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Tel: +46 31 342 10 00 |

Fax: +46317863399 |

Email: amanda.magnusson@vgregion.se

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## INTRODUCTION

Necrotising enterocolitis (NEC) is the most common gastrointestinal emergency among neonates, and it mainly affects preterm infants, with mortality rates ranging from 10% to 50%. The highest mortality rate is found among infants requiring surgery (1–5). The overall incidence of NEC varies between studies, from 0.3 to 1.0 per 1000 live births (1,6,7). However, in extremely preterm and very low birth weight infants, the incidence is approximately 7% (5,8). The pathogenesis of NEC is multifactorial, and there are some factors that remain unknown (4,5).

Most cases of NEC occur sporadically. Nevertheless, reports of clusters or outbreaks suggest that an infectious element could be a causal factor in NEC (3,9–13). This hypothesis is supported by the fact that improvements in infection-control procedures have stopped outbreaks of NEC (11,14). Seasonal variations in the incidence of NEC have been described, which also indicate that an infectious agent may contribute to the clustering of the disease

## Abbreviations

NEC, Necrotising enterocolitis; NICU, Neonatal intensive care unit.

## ABSTRACT

**Aim:** This study investigated space–time clustering of neonatal necrotising enterocolitis over three decades.

**Methods:** Space–time clustering analyses objects that are grouped by a specific place and time. The Knox test and Kulldorff's scan statistic were used to analyse space–time clusters in 808 children diagnosed with necrotising enterocolitis in a national cohort of 2 389 681 children born between 1987 and 2009 in Sweden. The municipality the mother lived in and the delivery hospital defined closeness in space and the time between when the cases were born – seven, 14 and 21 days – defined closeness in time.

**Results:** The Knox test showed no indication of space–time clustering at the residential level, but clear indications at the hospital level in all the time windows: seven days ( $p = 0.026$ ), 14 days ( $p = 0.010$ ) and 21 days ( $p = 0.004$ ). Significant clustering at the hospital level was found during 1987–1997, but not during 1998–2009. Kulldorff's scan statistic found seven significant clusters at the hospital level.

**Conclusion:** Space–time clustering was found at the hospital but not residential level, suggesting a contagious environmental effect after delivery, but not in the prenatal period. The decrease in clustering over time may reflect improved routines to minimise the risk of contagion between patients receiving neonatal care.

(6,12,15). Several microbial organisms have been proposed as possible causes of NEC, for example *Klebsiella pneumoniae*, *Staphylococcus Aureus*, *Escherichia coli*, *Clostridium difficile*, norovirus and rotavirus, but no specific causative organism was identified in some outbreaks (9,11,14,16,17). It has also been suggested that overcrowding in neonatal intensive care units (NICUs) has contributed to clusters of NEC (14). Nevertheless, the majority of reports describing outbreaks of NEC are retrospective and based on observed suspected outbreaks that could just be random.

## Key notes

- This study investigated space–time clustering of necrotising enterocolitis from 1987 to 2009 using national Swedish data on nearly 2.4 million births.
- Clustering was found at the hospital level during 1987–1997, but not during 1998–2009, and not at the residential level.
- The decrease in clustering over time could be related to enhanced routines to minimise the spread of any potential necrotising enterocolitis inducing contagion between patients in the neonatal intensive care unit.

Furthermore, most of the described outbreaks have been on a hospital level, while clustering based on the mother's residential municipality has not been addressed (9,11–13). In reports on NEC outbreaks, the cluster concept tends to be used subjectively without a standard definition (18).

Our group previously presented a national, population-based study on NEC epidemiology and trends in Sweden, which described an increase in the incidence of NEC between 1987 and 2009 (6). The same cohort was used in the present study to investigate space–time clusters of NEC on two levels for closeness in space: the mother's residential municipality and the delivery hospital. Furthermore, the present study was designed to examine whether there had been any change in the occurrence of space–time clusters over time, by studying two subperiods: 1987–1997 and 1998–2009.

## PATIENTS AND METHODS

### Study design and population

A cohort of newborn infants with a diagnosis of NEC was identified from the following registers held by the Swedish National Board of Health and Welfare: the National Patient Register, the Swedish Medical Birth Register and the National Cause of Death Register. All children born between 1987 and 2009 in Sweden with a discharge diagnosis of NEC according to the 9th or 10th revision of the International Classification of Diseases – ICD-9 code 777F or ICD-10 code P77 – were identified. The NEC diagnosis was introduced to ICD-9 in 1987 and is based on the modified Bell NEC staging criteria (19,20). As it was not possible to identify the exact date for the NEC diagnosis, the date of birth of the study subjects was used for time comparisons in the cluster analysis. Further details about the identification process were previously described (6).

An anonymised extract covering the background population of all children born in Sweden during the same time period as the NEC cases was also obtained from the Birth Register. This extract contained perinatal information and demographic data, including the municipality the mother lived in and the delivery hospital.

Sweden has a highly centralised care policy for very preterm and extremely preterm infants, based on intention to transfer mothers with a high risk of preterm delivery to a regional level three hospital before they give birth. As a result, most of the infants diagnosed with NEC are admitted to the NICU at the hospital in which they were born.

### Statistical methods

Two methods were used to analyse for space–time interactions between NEC cases: the Knox space–time cluster analysis and Kulldorff's space–time permutation scan statistic (21,22). The Knox test is based on an analysis of the proximity in space and time of all possible  $n(n - 1)/2$  distinct pairs of cases (23). Each individual pair is classified into one of four cells in a  $2 \times 2$  table, with distance (close/not close) and time (close/not close) on the two axes, according to whether the two parts are close

or not close to each other in terms of geographical distance and time. A pair of cases is regarded as being in close proximity if their dates of birth are close and if their geographical locations at the time of birth are close. Closeness in the date of birth was divided into time windows of seven, 14 and 21 days apart. Two geographical levels were used to define closeness in space: the mother's residential municipality and the delivery hospital. The number of pairs of cases observed in close proximity was compared with the expected number of pairs, which was obtained from the cross-products of the column and row totals. If the observed number of pairs of cases exceeded the expected number of pairs, there was evidence of space–time clustering. The magnitude of the excess, or deficit, was estimated by calculating the strength of clustering using the equation  $S = [(O-E)/E] \times 100$ , where  $S$  was the strength,  $O$  was the number of pairs of cases observed and  $E$  was the expected number of pairs.

To study any changes over time in NEC clustering, the population was divided into two cohorts according to the subjects' year of birth: 1987–1997 and 1998–2009. The Knox test was used to compare the two time periods, and the binomial test was used to compare the change in incidence of NEC in the two time periods.

In addition, Kulldorff's scan statistic, based on a space–time permutation model, was used to identify the presence of space–time and purely temporal clusters of cases (21). Kulldorff's scan statistic is based on the number of observed cases among all births that have taken place within a circle of varying radius in space in one dimension and in a time window with a varying duration in the other dimension. The statistic is centred at all geographical locations to look for possible clusters. Thus, the circular window is flexible in location, size and time. For the analyses of clustering on the residential level, we used the geographical coordinates of the centre of the mothers' residential municipality. For the analyses of clustering at each delivery hospital, we used a purely temporal scan statistic, with a time window of varying duration. The number of observed cases in a cluster was compared to what would have been expected if the spatial and temporal locations of all cases were independent of each other, so that there was no space–time interaction. As described by Kulldorff et al., the scan statistic makes minimal assumptions about the time, geographical location or size of the cluster and can be adjusted for both purely spatial and purely temporal variations (21).

The Poisson distribution was used for testing the statistical significance of the difference between the observed and expected number of pairs in the Knox test. Kulldorff's scan statistic was assessed by Monte Carlo hypothesis testing in 999 simulations, which meant that the smallest  $p$  value we could get was 0.001 (24). Statistical significance was set at  $p < 0.05$ .

The study used Stata Statistical Software, version 13 (StataCorp LP, College Station, TX, USA) and SaTScan, version 9.4.2 (Kulldorff M. and Information Management Services Inc., MA, USA) for the statistical analyses (25).

The study was approved by the Regional Ethical Review Board of Linköping (Dnr 2010/405-32).

## RESULTS

The study was based on a total of 2 389 681 births from 1987 to 2009, and the patient characteristics are described in Table 1. Information about the delivery hospital and the mothers' residential municipality was missing for 5,621 and 19,130 children, respectively. We identified 808 cases of NEC, including 27 pairs of twins. Each twin pair with NEC was counted as one instance of NEC for the cluster analyses. Information about the mother's residential municipality and delivery hospital was missing for 12 and seven of the 808 cases, respectively. After we excluded the 27 second twins and the births with missing information on municipality or delivery hospital, there were 769 cases for the analyses based on municipality and 774 cases for the analyses based on delivery hospital. Due to the centralised care of preterm infants in Sweden, 422 of the 774 NEC cases (54%) occurred at a hospital that did not match the residential municipality of the mother. To be specific, 58% of all the NEC cases among extremely preterm births, with a gestational age under 28 weeks, and 22% of all the NEC cases among term births, with a gestational age over 36 weeks, occurred at a hospital that was not the closest to the mother's municipality.

**Table 1** Characteristics of patients with NEC and the background population of all live births in Sweden between 1987 and 2009

Characteristics	NEC, n	Background population, n	NEC Incidence per 1000 live births	p-value
Total	808	2 381 318	0.34	
Gestational age*				
Full term	145	2 232 308	0.06	
32–36 weeks	138	124 307	1.11	<0.001 <sup>†</sup>
28–31 weeks	220	14 822	14.84	<0.001 <sup>†</sup>
<28 weeks	304	6595	46.10	<0.001 <sup>†</sup>
Birth weight, G*				
≥2500	157	2 271 751	0.07	
1500–2499	158	85 419	1.85	<0.001 <sup>‡</sup>
1000–1499	168	11 047	15.21	<0.001 <sup>‡</sup>
750–999	158	3793	41.66	<0.001 <sup>‡</sup>
<750	147	2768	53.11	<0.001 <sup>‡</sup>
Sex				
Girls	353	1 157 387	0.30	
Boys	455	1 223 501	0.37	=0.006 <sup>§</sup>
Period				
1987–1997	289	1 113 946	0.26	
1998–2009	519	1 275 735	0.41	<0.001 <sup>¶</sup>

\*Information is missing in some registrations, which explains why the sum of the numbers will not always match the total number.

<sup>†</sup>p-value compared to full term.

<sup>‡</sup>p-value compared to BW >2500 g.

<sup>§</sup>p-value compared to girls.

<sup>¶</sup>p-value compared to 1987–1997.

The cohort in the first time period, 1987–1997, consisted of 1 113 946 infants and 289 cases of NEC, resulting in an NEC incidence of 0.26 per 1000 live births. During the second time period, 1998–2009, the cohort consisted of 1 275 735 infants and 519 cases of NEC, giving an NEC incidence of 0.41 per 1000 live births. There was a significant increase in the incidence of NEC in the second time period compared to the first time period ( $p < 0.001$ ) (Table 1).

## The Knox test

The Knox test did not indicate any space–time clustering at a residential level in any of the studied time windows of seven, 14 or 21 days. There was a significant space–time clustering at a hospital level, with the strongest clustering at a time window of seven days ( $S = 36.3$ ,  $p = 0.026$ ) (Table 2). The Knox test is sensitive to time-related shifts in the background population, which can give biased results. We therefore performed separate analyses for each of the two time periods. The first time period showed significant space–time clustering of NEC in the time windows of seven and 14 days, with the strongest clustering at seven days ( $S = 122.2$ ,  $p = 0.003$ ) (Table 2). During the second time

**Table 2** Knox space–time cluster analysis

Time period	Number of pairs of observations					
	Close in space	Close in time	Close in time and space			Strength*
			Observed	Expected	p-value	
<b>1987–2009</b>						
Time window <sup>†</sup>	Residential municipality (769 cases, total number of pairs = 295 296)					
7 days	11 859	641	27	25.7	0.775	5.1
14 days	11 859	1172	45	47.1	0.777	–4.5
21 days	11 859	1767	67	71.0	0.647	–5.6
Time window	Delivery hospital (774 cases, total number of pairs = 299 151)					
7 days	18 956	649	56	41.1	0.026	36.3
14 days	18 956	1238	102	78.4	0.010	30.1
21 days	18 956	1798	146	113.9	0.004	28.2
<b>Subperiod 1987–1997</b>						
Time window	Delivery hospital (283 cases, total number of pairs = 39 903)					
7 days	2307	140	18	8.1	0.003	122.2
14 days	2307	297	28	17.2	0.016	62.8
21 days	2307	436	35	25.2	0.062	38.9
<b>Subperiod 1998–2009</b>						
Time window	Delivery hospital (491 cases, total number of pairs = 120 295)					
7 days	8516	509	38	36.0	0.721	5.6
14 days	8516	941	74	66.6	0.363	11.1
21 days	8516	1362	111	96.4	0.143	15.13

The results are analysed at two geographical levels for defining closeness in space: residential municipality and delivery hospital.

\*S = strength, calculated as  $[(Observed - Expected)/Expected] \times 100$ .

<sup>†</sup>Closeness of date of birth was divided into time windows of seven, 14 and 21 days apart.

period, there was no significant clustering at a hospital level in any of the studied time windows.

### Kulldorff's scan statistic

At a residential level, Kulldorff's scan statistic only identified one single space-time cluster of four cases during 17 days in January 1990. The four cases came from four different municipalities within a radius of 34 kilometres.

At a hospital level, the purely temporal cluster analysis identified seven instances of temporal clusters at seven different hospitals (Table 3). In four of the seven clusters identified by Kulldorff's scan statistic, the cluster only consisted of two patients. However, several of these clusters occurred in hospitals with a low number of deliveries and few expected cases of NEC in the given time interval. Of the seven statistically significant clusters, five occurred during November to April and only two clusters occurred during May to October.

### DISCUSSION

The present study showed that NEC occurred in clusters at a hospital level, as found with both the Knox test and Kulldorff's scan statistic. When we compared two different time periods – 1987–1997 and 1998–2009, using the Knox test, significant clustering was only found in the early time period and the strongest significance was found using seven days as the time window. Our results showed no signs of space-time clustering related to the mother's residential municipality with the Knox test and only one single cluster with Kulldorff's scan statistic.

Several possible explanations for clustering on a hospital level have previously been described. One explanation is that NEC is associated with a nosocomial infection spread from one child to another in a NICU. Hill et al. described an outbreak of NEC associated with *Klebsiella pneumoniae* in all cases at one NICU (26). Han et al. and Alfa et al. described outbreaks of NEC associated with the *Clostridium* species (27,28).

A second possible mechanism for clustering on a hospital level could be transmission from the healthcare

workers to the infants, as suggested by Harbarth et al., who described an outbreak of *Enterobacter cloacae* during a period of overcrowding and understaffing in the NICU (29). As the present study was a retrospective register study, no investigations could be carried out into whether the bacteria in the infants and among the staff contributed to the clusters.

Contamination of human milk fortifier or formula is a third possibility for clustering on a hospital level. Van Acker et al. described an outbreak of NEC where the same bacteria were isolated from both the neonates with NEC and the powdered milk formula (10). In Sweden, most infants receive human breast milk in NICUs, either from their mother or from a milk bank, but this milk is frequently enriched with human milk fortifier.

A fourth possible explanation for clustering on a hospital level may be an accumulation of preterm births at referral hospitals due to referrals of at-risk pregnancies. This could theoretically lead to an overestimation of the number of clusters. The results from the Knox test showed significant clustering during 1987–1997, but not during 1998–2009, which did not support an overestimation of clusters due to centralised care, as the centralisation of neonatal intensive care in Sweden has increased over the last few decades. The finding of a decrease in clustering over time could be related to improvements in the neonatal intensive care of preterm infants. In this study, it was not possible to analyse whether the decrease in clusters was related to improved control of infection in the NICU, less overcrowding, better routines in the NICU or other reasons for reduced transmission of NEC between patients. Even though the Knox test showed no significant clustering of NEC during the last decade, Kulldorff's scan statistic indicated that clusters of NEC do still occur.

Clustering on a residential level would, as described above, indicate that NEC is associated with causative agents, such as infections in the community. Stuart et al. described a strong association with the norovirus in an outbreak of NEC (11). Chany et al. showed a significant association between coronavirus infections and NEC (30). These findings could indicate that the virus had its origin

**Table 3** Kulldorff's space-time permutation scan statistic

No. of births at the hospital (1987–2009)	No. of NEC cases at the hospital (1987–2009)	Year of the cluster	Time frame for the cluster	Time interval for the cluster (days)	Observed no. of NEC cases in the cluster	Expected no. of NEC cases in the time interval	Observed/Expected	p-value
19 105	5	1990	9 Jan–26 Jan	18	2	0.015	131.8	0.042
43 670	13	1991	7 Aug–7 Aug	1	2	0.0015	1343.7	0.001
70 857	63	1993	29 Sep–29 sep	1	3	0.0071	421.8	0.002
31 045	8	2002	29 Apr–2 May	4	2	0.0054	369.6	0.031
57 011	19	2003	9 Nov–11 Nov	3	2	0.0043	461.6	0.035
105 428	67	2007	14 Nov–7 Dec	24	5	0.24	20.5	0.037
108 255	137	2009	10 Apr–15 Apr	6	4	0.1	39.5	0.029

Characteristics of the seven temporal clusters at the hospital level, identified by the purely temporal cluster method using Kulldorff's space-time permutation scan statistic.

in the community and was then transmitted to the infants. The findings in the present study, in which the Knox test found no clustering on a residential level and Kulldorff's scan statistic found only one cluster, are strong indications against the theory that there is a connection between NEC and infections spread in the community. However, when studying the clusters on a hospital level with the Kulldorff's scan statistic, it was noticed that the majority of the clusters at a hospital level occurred during November to April, which is also the season when most infections in the community occur. Our group has previously described this seasonal variation, with a peak in incidence of all cases of NEC in November and a decrease in May (6).

## CONCLUSION

The present study showed indications of space-time clustering of NEC on a hospital level in Sweden, but not at the level of the mother's residential municipality, suggesting a contagious environmental effect after delivery.

The decrease in clustering on a hospital level over the last few decades may indicate that improved routines in modern neonatal care are effective in minimising the transfer of agents involved in the development of NEC between patients in the NICU. However, continued awareness of signs of clusters is still warranted to further minimise the risk of environmental factors for NEC being transferred from one patient to another.

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## CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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