Contemporary Outcomes for Infants with Necrotising Enterocolitis – A Systematic Review

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Author Contribution

The search strategy was developed by both authors. Both authors screened abstracts and full papers for inclusion in the review. Mr Jones performed the statistical analysis, produced the figures and wrote the first draft of the manuscript. Both authors approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Abbreviations:

Bell (1-3) – Bell stage for Necrotising enterocolitis

BSID: Bayley scales of infant development;

ELBW – Extremely low birth weight (<1000g)

IF – Intestinal failure

MDI: Mental Developmental Index

NEC – Necrotising enterocolitis

NDD – Neurodevelopmental disability

PDI: Psychomotor developmental index

OECD: Organisation for Economic Co-operation and Development

Abstract

Objective

We aimed to develop an accurate understand of outcomes for necrotising enterocolitis (NEC), in order to inform parental counselling, clinical care and research agendas.

Study Design

A Systematic review of recent (January 2010 – January 2018) large cohort studies reporting outcomes of infants who developed NEC. Only studies reporting national, regional or multicentre outcomes of NEC in high income countries were included. Outcomes assessed were mortality, neurodevelopmental outcome and intestinal failure (IF). Meta-analyses were used to generate summary statistics for these outcomes.

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Results

Of 1,375 abstracts, 38 articles were included. Overall mortality was 23.5% in all neonates with confirmed (Bell 2a+) NEC (95% C.I. 18.5–28.8%), 34.5% (30.1–39.2%) for neonates that underwent surgery for NEC, 40.5% (37.2–43.8%) for extremely low birthweight infants (ELBW; <1000g) and 50.9% (38.1-63.5%) for ELBW infants with surgical NEC. Studies examining cause of neonatal mortality showed NEC is responsible for around 1 in 10 of all neonatal deaths. Neurodevelopmental disability was reported in four studies at between 24.8% and 61.1% (1209 total NEC cases). Three studies reported IF with incidence of 15.2-35.0% (n=1370). The main limitation of this review is the lack of agreed definition for diagnosing NEC and the differences in the way that outcomes are reported.

Conclusions

Mortality following NEC remains high. These contemporary data inform clinical care and justify ongoing research efforts. All infants with NEC should have long-term neurodevelopmental assessment. Data on the long-term risk of intestinal failure are limited.

Introduction

Necrotising enterocolitis (NEC) remains a great scourge of neonatal intensive care units. Despite decades of research and significant improvements in neonatal care, studies that specifically compare different time periods show that outcomes for NEC are essentially unchanged[1]. Whilst real advances in neonatal care have led to improved outcomes overall for premature babies, NEC still conveys a significant mortality and morbidity. [2, 3] Moreover, the increased survival of very premature babies means an increase in the size of the at-risk population, which is reflected in some studies reporting a long term increase in the incidence of NEC[4].

Understanding the true burden of the disease is vital for assessing any potential future treatments, for clinical decision-making and counselling parents of affected neonates, and for justifying research funding. We aimed to understand the current burden of NEC in terms of mortality, as well as assessing the morbidity for survivors, by including the outcomes of neurodevelopmental disability (NDD) and intestinal failure (IF) as these two encompass the majority of post-NEC morbidity.

Methods

We performed a systematic review in accordance with the PRISMA Statement[5] and registered the protocol in advance with PROSPERO (CRD42018094791). A search strategy was developed to identify studies of infants that reported outcomes of NEC, including mortality, neurodevelopmental disability and intestinal failure in high-income countries. The Medline database was interrogated using Pubmed in January 2018 using a search that included the terms “NEC”, “outcomes”, “mortality”, “morbidity”, “neurodevelopmental

outcome", and "intestinal failure". Full detail of the search strategy is summarised in table 1 (online only). References of included studies were checked for additional eligible studies.

Studies were included in this review if satisfying all of the following criteria: 1.Full text in English; 2. Reported NEC outcomes of interest; 3. Published since 1st January 2010; 4. Reported international, national, regional or multicentre data; 5. Data reported was from high income countries, defined as members of the Organisation for Economic Co-operation and Development (OECD).

Excluded studies: 1. Review articles rather than primary data, 2. Outcomes of NEC not retrievable from published data. Studies that report NEC outcomes were included for qualitative assessment, even if the data reported could not be included in quantitative analysis. This includes papers that reported odds ratios but not the primary data and studies that examined the causes of neonatal mortality. Studies were also excluded if they combined outcomes for spontaneous intestinal perforation (SIP) and NEC.

After duplicates had been removed, the abstracts were assessed against both inclusion and exclusion criteria. Articles identified as potentially eligible underwent a full text review. Articles that satisfied the inclusion/exclusion criteria were included and the data extracted. All stages of this process were performed independently by both authors and any disagreements resolved by discussion. Where papers reported outcomes from the same (or largely overlapping) datasets, only the most recent papers were included for quantitative analysis. If papers were published in the same year, the larger dataset was used. In each paper, the source of the data, the definition of NEC used, a description of the population and the definition(s) of mortality, NDD and IF used were extracted and reported.

Statistical analysis was performed using *metaphor*[6] and *meta*[7] in *R*(version 3.5.1)[8]. Meta-analyses of the proportions (using a random effects model) were used to combine the outcome data from the included studies. Double Arcsine transformation was used to normalise the datasets and heterogeneity was estimated by means of tau, Q and I^2 statistics.

Since the relationship between birthweight and NEC outcome, particularly mortality, is well-established (infants with birthweight of less than 750g have a mortality rate that is three times higher than those weighing between 1250 and 1500g at birth[2]), we determined *a priori* to perform subgroup analysis stratified by birthweight. Similarly, some studies only report outcomes for patients who underwent surgery for NEC, a subset known to have worse outcomes. Hence, it would be inappropriate to combine data from studies only examining a surgical population with data from those examining infants who did not have surgery. The following subgroups were therefore used for meta-analyses: all neonates with NEC, all neonates with surgical NEC, neonates with BW <1500g (Bell 2a+), neonates with BW <1000g (Bell 2a+), neonates with BW <1500g and surgical NEC, and neonates with BW<1000g and surgical NEC. These subgroups were defined on the basis of the data available since it was not possible to determine which subgroups would be usable prior to completing the search.

Table 1(online only): Summary of Search Strategy: Combining NEC with each of the outcomes of interest.

Results

The initial search returned 1371 articles after duplicates were excluded . After screening of the abstracts, the full text of 89 articles was obtained for assessment. Four further papers that met the inclusion criteria were identified from the reference list of included papers. In total,

38 articles reported at least one of the outcomes of interest (Figure 1, online only). Table 2 (online only) shows the papers included in this analysis and the data sources.

Table 2 (online only): All papers included in this review: numbers indicate total number of patients with a diagnosis of NEC.

Mortality

Of these 38 articles, 31 reported mortality from NEC in a format that allowed a series of meta-analyses to be performed. Table 3 shows the reported NEC mortality rates in each included study, the timepoint at which mortality was assessed and the definition of NEC used (i.e. Bell 1 to 3 or Bell 2a+)

Zhang *et al.* (2011)[46] and Choo *et al.* (2011)[17] are related studies and used the same databases (*Nationwide Inpatient Sample* 1988 – 96, 98, 2001, 02 and *Kids' Inpatient Database* 1997, 2000, 03). For this reason, only Zhang *et al.* (2011) was used in the meta-analysis of neonates with surgical NEC. Similarly, in the subgroup of infants with a birthweight of less than 1500g and requiring surgery, Fisher *et al.* (2014), Fullerton *et al.* (2016) and Hull *et al.* (2014) all drew their datasets from the Vermont-Oxford Network. Hence only the Fullerton *et al.* (2016) data was used for the meta-analysis.

From these datasets, the overall mortality from confirmed NEC (Bell 2a+) is estimated at 23.5% (95% C.I. - 18.5 - 28.8%) with, as-expected, higher rates for infants of lower birth-weights and for those that underwent surgery. Meta-analysis of each of these main sub-groups provides estimates for the mortality rates of each group (Table 4, Figures 2-3, (figure 3, online-only). The highest mortality was seen in infants with a birthweight of less than

1000g who required surgery for NEC in whom mortality was 50.9% (95% C.I. - 38.1 - 63.5%).

Just one study reported mortality for neonates with a birth weight greater than 2500g with overall mortality of 11.0% (8.0% for medical NEC, 22.1% for surgical NEC, n=1629)[43]. Similarly just one study reported outcome of NEC in infants with congenital cardiac disease. Mukerjee *et al.*(2010)[30] reported that NEC mortality in the context of CHD was 19.6%. This is similar to the mortality for CHD alone of 16.1%.[30]

Three articles (Seeman *et al.* (2016)[35], Patel *et al.* (2015)[32] and Berrington *et al.* (2012)[15]) report NEC as a cause of death. These data sets, based primarily on death certification, do not allow a mortality rate for NEC to be derived as the denominator of the number of cases of NEC is not recorded. However, they do report neonatal mortality and thus the NEC-related infant mortality rate (IMR). These datasets give an NEC-IMR of 12.5 per 100,000 live births for all neonates,[35] and much higher for premature babies; 2,800 per 100,000 live births between 22 and 29 weeks completed gestation[32] and 1,100 per 100,000 live births between 24 and 31 weeks completed gestation[15]. Overall NEC is responsible for between 10 and 21% of infant mortality in premature babies[15, 32].

Table 3: Reported NEC Mortality

Table 4: Meta-analyses of NEC mortality as a % of total cases.

Neurodevelopmental Disability

Five studies reported data on neurodevelopmental outcomes following NEC (Table 5). Overall, severe NDD ranges from 24.8%[23] to 59.3%[24] in these series. The exact definition of NDD used varied between studies, as indicated in the table. The differences in population, definition of NEC and definition of NDD between these studies meant that assimilation with

a meta analysis was not possible. Synnes *et al.*[40] reported an increased risk of NDD associated with NEC in infants born before 29 weeks gestation with an odds ratio of 1.88. However, the actual number of patients with NEC and NDD were not reported.

Table 5: NEC Morbidity: Rates of Severe neurodevelopmental disability following NEC and Rates of Intestinal Failure following NEC.

Intestinal failure

Three studies report IF rates following NEC (Table 5). IF rates vary from 15.2% in all neonates with NEC (n=394) to 35.4% in neonates with NEC requiring surgery (n=147). Whilst the definition of IF used was relatively consistent, the populations and definition of NEC is variable thus making assimilation into a meta-analysis difficult.

Discussion

In recent years, several large, multicentre studies have reported outcomes of NEC. The purpose of this review is to collate these studies' results in order to report contemporary outcomes for NEC. Due to limited availability of specialist neonatal care and consequential poorer outcomes outside of high-income countries[52] we excluded data from developing countries. The main outcomes in this review are mortality, neurodevelopmental disability and intestinal failure. The choice of NDD and IF reflects that these two outcomes encapsulate the majority of the longer term morbidity associated with and specifically related to NEC [53].

In this review, based on large cohorts (at least 3000 infants) we have been able to estimate contemporary mortality in clinically relevant sub-groups of infants with acceptable precision (Table 4, Figures 2-3). We have also reported the incidence of NDD and the risk of IF, although the differences in definitions and populations meant it was not possible to combine these in summary statistics. The key findings of our review are that NEC confers a mortality

of 23.5% for confirmed cases (Bell stage 2+) rising to over 50% for ELBW infants who undergo surgery for NEC. For survivors, there is significant morbidity with rates of severe NDD of between 25% and 61% and intestinal failure reported at between 15 and 35%. Overall our results confirm that NEC continues to confer a very significant disease burden. In an era when mortality for preterms in high-income countries is actually relatively low (approaching 95% survival for those born between 28 and 32 weeks (90% without impairment)[52]), contracting NEC clearly has a large detrimental effect on the mortality and morbidity of these infants.

Mortality

One of the challenges in providing meaningful estimates of mortality in the context of NEC is variation in the definition of both the population at risk and the timing of death reported. To account for differences in definition or severity of NEC, we have conducted as series of subgroup analyses, aiming to achieve a largely homogenous population within each subgroup and therefore more useful data. Without such stratification the range of mortality is between 12.8 % and 58.9% [33, 41]. The time at which mortality is reported also varied between studies. Where clearly stated we have used all-cause mortality for analysis. Of the 21 studies used in the quantitative analysis of mortality, 17 reported only in-hospital mortality rates. Four studies Allin *et al.* (2018)[12], Heida (2017)[25] Fullerton (2017)[22] and Tashiro *et al.* (2017)[41] report both in-hospital and a later mortality. These data show a minority, between 5% and 30.5% of the deaths that occur do so after initial discharge and hence any estimate based on in-hospital mortality is likely to underestimate the true mortality of NEC. This is summarised in table 6.

Table 6 (online only): Mortality from NEC following initial discharge

Neurodevelopmental disability

The rates of NDD follow the same pattern as mortality with much higher rates in smaller infants and those who underwent surgery. Whilst the mechanisms remain unclear, NEC has a detrimental effect on the developing brain conferring a worse neurodevelopmental outcome comparable to pre-term infants who do not contract NEC. Foetal brain development is driven by both genetic and environmental factors. Accordingly, the preterm brain is susceptible to damage due to a multitude of environmental factors introduced by premature ex-utero life[54]. This multifactorial encephalopathy is seen in the absence of NEC but rates of severe NDD are not as high. Fullerton *et al.* (2017)[22] followed a cohort of over 10,000 ELBW infants, reporting severe NDD in 17% of these very premature infants in the absence of NEC. Those that contract NEC have much higher rates; 31% overall and 24% and 38% for medical and surgical NEC respectively. A consensus based definition of severe NDD is lacking. The presence of features such as cerebral palsy, sight loss or hearing loss would constitute severe NDD. Similarly, the widely-used Bayley Scales of Infant Development with an appropriate threshold such as a Mental Development Index (MDI) score <70 can be used to define severe NDD. Each of the studies included in this review used similar combinations of these features to define NDD. The variation in the estimates of NDD reported are likely related to differences in definitions used within individual studies but also an overall sparsity of data in this area. However, it is clear that NEC confers a significant risk of severe NDD and all neonates who have had a diagnosis of NEC should therefore undergo long-term neurodevelopmental follow-up.

Intestinal Failure

IF in children is broadly defined as the inability to absorb sufficient nutrition via the gut for normal growth[55]. In the context of NEC, extensive surgical resection may lead to

anatomically short-gut but moreover, babies with ostensibly sufficient bowel, can have persistent reduced gut function that precludes adequate nutrition absorption. It is well recognised that NEC is a major cause of intestinal-failure in children.[56] However, the specific risk of IF to an individual baby diagnosed with NEC is much less clear. The commonly used measure of p*arenteral nutrition (PN) dependence at 90 days* is relatively easy to measure but arguably incomplete. Requiring PN at 90 days is a clear indicator of disease burden in the medium term but a proportion of these children will still go on to achieve enteral autonomy[56]. Using this measure we have been able to estimate the overall risk for an infant with surgical NEC of between 22 and 35% but given the limited number of reports identified further characterisation of the burden of IF related to NEC would be useful. Since conducting this search, Bexelius *et al.* (2019)[57] have published a series on IF. These data show IF rates of 6% for infants with NEC. The definition of IF used was based on clinical coding between 14 days of age and two years. This shows a fifteen-fold increase compared to a cohort matched for gestational age (0.4% prevalence). However, these data whilst capturing re-admission for IF will still include patients who are PN-dependent immediately after contracting NEC. A cohort study of IF suggests that over 60% of children whose IF is secondary to NEC will achieve enteral autonomy by 72 months follow-up[56].

There are several strengths to this review: as far as we are aware, this is the first systematic review of NEC outcomes to be reported. It is based on large, population based datasets with each sub-population estimate of NEC mortality based on large numbers. The main limitations of this review lie in the variety of definitions used for both the exposure and outcomes as already discussed. If agreed definitions of NEC and measures of mortality, severe NDD and IF can be reached and used this would facilitate better assessment of potential treatment interventions as well as enhance comparison between studies. We therefore welcome initiatives such as Core Outcomes In Neonatology that aim to address some of these issues [58].

Due to the level of heterogeneity between studies we used random effects models for meta-analysis. The accuracy of estimates of heterogeneity is known to be limited when the number of studies available for inclusion is small and should be interpreted with caution[59]. Moreover, as the analysis here is of mortality (i.e. a proportion) rather than effect size, the importance of this high level of heterogeneity should not be overstated. In essence, it means that the point estimates for each group are less precise than one might wish but still provide a meaningful answer within the limitations of the published data.

Conclusion

In this review, we report contemporary outcomes for NEC in specific groups of neonates. We estimate overall mortality from confirmed NEC at 23.5%, rising to 50.9% in ELBW infants who require surgery. For survivors, the risk of significant NDD is high (25-61% of survivors). Intestinal failure is common after NEC with 15-35% requiring prolonged intravenous nutrition. Standardised outcome reporting would facilitate comparison between studies.

Figure 1 (online only) Prisma Flow diagram.

Figure 2 Meta analyses of mortality of all neonates with a diagnosis of NEC

(**2a:** NEC defined as Bell stages 1-3; **2b:** NEC defined as Bell stage 2a+ and; **2c:** Meta analysis of mortality of all neonates who underwent surgery for NEC).

Figure 3 (online only) Meta analyses of mortality in subgroups with NEC

(**3a**: Mortality of neonates with a birthweight of less than 1500g and NEC (Bell 2a+); **3b**: Mortality of neonates with a birthweight of less than 1500g who underwent surgery for NEC; **3c**: Mortality of neonates with a birthweight of less than 1000g and NEC (Bell 2a+); **3d**: Mortality of neonates with a birthweight of less than 1000g who underwent surgery for NEC)

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Table 1

(“Necrotising enterocolitis” or “necrotising enterocolitis” or “NEC”)[All Fields] OR [MeSH terms])	AND	“Outcomes” [All Fields] OR [MeSH terms]	AND	(English[Language]) AND ("2010/01/01"[PDAT] : "3000"[PDAT]) NOT review[Publication Type])
	AND	“Mortality” [All Fields] OR [MeSH terms]	AND	
	AND	“Morbidity” [All Fields] OR [MeSH terms]	AND	
	AND	“Neurodevelopmental outcomes” [All Fields] OR [MeSH terms]	AND	
	AND	“Disability” [All Fields] OR [MeSH terms]	AND	
	AND	“Intestinal Failure” [All Fields] OR [MeSH terms]	AND	
	AND	(“Parenteral nutrition dependence” OR “Parenteral nutrition” OR total parenteral nutrition”) [All Fields] OR [MeSH terms]	AND	
	AND	Epidemiology[All Fields] OR [MeSH terms]	AND	

Table 2

Paper	Reports NEC Mortality (n)	Reports NDD associated with NEC (n)	Reports IF associated with NEC (n)	Location: data source*	Data collections (years)
Abdullah 2010 [9]	20822			USA: NIS & KID	88, 96, 02,
Adams-Chapman 2013 [10]	✓			USA	06-08
Allin 2017 [11]	189			UK	13-14
Allin 2018 [12]	159			UK	13-14
Autmizguine 2014 [13]	2780			USA: PMG	97-02
Battersby 2017 [14]	531			UK	12-13
Berrington 2012 [15]	✓			UK	88-08
Bhatt 2017 [16]	223		223	USA: CHCA	09-15
Choo 2011 [17]	4657			USA: NIS & KID	88-05
Clark 2012 [18]	7099			USA: PM7	97-09
Duro 2010 [19]			394	USA	04-07
Fisher 2014 [20]	4072			USA: VON	06-10
Fullerton 2016 [21]	4328			USA:VON	09-13
Fullerton 2017 [22]	2881	866		USA:VON	99-12
Ganapathy 2013 [23]	316	103		USA: Texas	02-03
Hayakawa 2015 [24]	44	18		Japan	03-12
Heida 2017 [25]	441			Netherlands	05-13
Hull 2014 [26]	17156			USA: VON	06-10
Kastenberg 2015 [27]	1879			USA: California	05-11
Kelley-Quon 2012[28]	1272			USA: California	99-07
Martin 2010 [29]	✓			USA	02-04
Mukherjee 2010 [30]	194			USA: NIS & KID	88-03
Murthy 2014 [31]	753			USA	10-13
Patel 2015 [32]	✓			USA	00-11
Rees 2010 [33]	211			UK	05, 06
Sayari 2016 [34]	1542			USA: KID	03, 06, 09
Seeman 2016 [35]	✓			USA	10-13
Shah 2012 [36]	208			USA	98-09
Shah 2015 [37]	784			Canada	10-13
Steurer 2015 [38]	✓			Switzerland	02-11
Stey 2015 [39]	1375			USA: California	99-07
Synnes 2016 [40]		✓		Canada	09-11
Tashiro 2017 [41]	886			USA: KID	03-09
Thome 2017 [42]	✓			Germany	08-12
Velazco 2017 [43]	1629			USA & Canada	09-15
Wadhawan 2014 [44]	472	220		USA: NRN	00-05
Youn 2015 [45]	149			Korea	13-14
Zhang 2011 [46]	5374			USA: NIS & KID	88-03

Table 2 – All papers included in this review: The numbers shown (n) indicate the total number of infants included in each study with a diagnosis of NEC and for whom the outcome is reported.
**Abbreviations: NIS: National (Nationwide) Inpatient Sample[47] KID: Kid's Inpatient Database [48]PMG: Pediatrix Medical Group[49]. VON: Vermont Oxford Network[50] (In most cases only N.American VON centres contributed to dataset). NRN: Neonatal Research Network[51]*

Table 3

Paper	Population	Definition of NEC	Definition of mortality	NEC deaths	Total number with NEC	Mortality %
Rees 2010[33]	All neonates	Bell 1 to 3	In-hospital	27	211	12.8%
Abdullah 2010[9]	All neonates	ICD-9	In-hospital	2718	20822	13.1%
Clark 2012[18]	All neonates	Bell 2+	In-hospital	1505	7099	21.2%
Ganapathy 2013[23]	All neonates	ICD-9	6 months	66	316	20.9%
Heida 2017[25]	All neonates	Bell 2+	30 day	117	441	26.5%
Zhang 2011[46]	All neonates	Surgical NEC	In-hospital	1660	5374	30.9%
Choo 2011[17]	All neonates	Surgical NEC	In-hospital	1115	4657	23.9%
Murthy 2014[31]	All neonates	Surgical NEC	In-hospital	259	753	34.4%
Stey 2015[39]	All neonates	Surgical NEC	In-hospital	473	1375	34.4%
Battersby 2017[14]	All neonates	Surgical NEC	In-hospital	247	531	46.5%
Allin 2017[11]	All neonates	Surgical NEC	28 days	29	189	15.3%
Allin 2018[12]	All neonates	Surgical NEC	1 year	41	159	25.8%
Ganapathy 2013*[23]	All neonates	Surgical NEC	6 months	38	111	34.2%
Hull 2014[26]	<1500g BW	Bell 2+	In-hospital	4804	17156	28.0%
Autmizguine 2015[13]	<1500g BW	All NEC	In-hospital	645	2780	23.2%
Youn 2015[45]	<1500g BW	Bell 2+	In-hospital	63	149	42.3%
Kastenberg 2015[27]	<1500g BW	Bell 2+	unclear	411	1879	21.9%
Hayakawa 2015[24]	<1500g BW	Bell 2+	In-hospital	17	44	38.6%
Shah 2012[36]	<1000g BW	Bell 2+	In-hospital	105	208	50.5%
Fullerton 2017[22]	<1000g BW	Bell 2+	2 years	952	2881	33.0%
Kelley-Quon 2012[28]	<1500g BW	Surgical NEC	In-hospital	496	1272	39.0%
Fisher 2014[20]	<1500g BW	Surgical NEC	In-hospital	1547	4072	38.0%
Fullerton 2016[21]	<1500g BW	Surgical NEC	In-hospital	1742	4328	40.2%
Hull 2014*[26]	<1500g BW	Surgical NEC	In-hospital	3127	8935	35.0%
Autmizguine 2015*[13]	<1500g BW	Surgical NEC	In-hospital	322	706	45.6%
Youn 2015*[45]	<1500g BW	Surgical NEC	In-hospital	23	77	29.9%
Wadhawan 2014[44]	<1000g BW	Surgical NEC	In-hospital	252	472	53.4%
Tashiro 2017[41]	<1000g BW	Surgical NEC	2 years	522	886	58.9%
Fisher 2014*[27]	<1000g BW	Surgical NEC	In-hospital	1127	2782	40.5%
Fullerton 2017*[22]	<1000g BW	Surgical NEC	2 years	637	1668	38.2%
Mukherjee 2010[30]	CHD	ICD-9	In-hospital	38	194	19.6%
Shah 2015[37]	<32/40	Bell 2+	*2 years*	225	784	28.7%
Sayari 2016[34]	<37/40	ICD-9	In-hospital	528	1542	34.2%
Bhatt 2017[16]	<37/40	Surgical NEC	In-hospital	83	223	37.2%
Velazco 2017[43]	>2500g BW	Bell 2+	In-hospital	179	1629	11.0%
Seeman 2016[35]	All neonates	NEC as cause of death	NEC mortality: 12.5/100 000 live births			
Patel 2015[32]	<29/40	NEC as cause of death	10% of infant deaths due to NEC			
Berrington 2012[15]	<32/40	NEC as cause of death	11-21% of infant deaths due to NEC			

**Data derived from a sub-group outcome reported in paper*

BW: Birth weight. <32/40: less than 32 weeks gestation, <29/40: less than 29 weeks gestation. CHD: Congenital heart disease

Table 4

Group	**n**	**Mortality % (95% C.I.)**	***Figure***
All neonates with NEC (Bell 1 to 3)	21349	15.3 (10.8 - 20.4)	*2*
All neonates with NEC (Bell 2a+)	7540	23.5 (18.5 - 28.8)	*2*
All neonates with surgical NEC	8303	34.5 (30.1 - 39.2)	*2*
Neonates with BW <1500g (Bell 2a+)	22008	30.1 (24.3 - 36.2)	*3*
Neonates with BW <1000g (Bell 2a+)	3089	41.3 (25.0 - 58.7)	*3*
Neonates with BW <1500g & Surgical NEC	6383	40.5 (37.2 - 43.8)	*3*
Neonates with BW <1000g & Surgical NEC	5808	50.9 (38.1 - 63.5)	*3*

Table 5

NEC Morbidity						
Paper	**Population**	**Definition of NEC**	**Definition of NDD**	**Number with NDD**	**n**	**NDD %**
Ganapathy 2013[23]	All neonates	ICD-9	@24-36m - definition unclear	26	105	24.8%
Hayakawa 2015[24]	<1500g BW	Bell 2a+	18m corrected age: developmental quotient <70, or the presence of neurological sequelae	11	18	61.1%
Fullerton 2017[22]	<1000g BW	Bell 2a+	Any severe disability (incl BSID: MDI or PDI <70)	267	866	30.8%
Fullerton 2017*[22]	<1000g BW + Surgery	Surgical NEC	Any severe disability (incl BSID: MDI or PDI <70)	169	449	37.6%
Wadhawan 2014[44]	<1000g BW + Surgery	Surgical NEC	1 or more of: mod/severe CP, bilateral blindness, bilateral hearing loss needing amplification, MDI or PDI < 70.	125	220	56.8%
Paper	**Population**	**Definition of NEC**	**Definition of Intestinal Failure**	**Number with IF**	**n**	**IF rates %**
Duro 2010[19]	All neonates	Bell 1 -3	Failure to achieve full enteral feeds @90d	60	394	15.2%
Murthy 2014[31]	Surgical NEC	Surgical NEC	>90d PN	171	753	22.7%
Bhatt 2017[16]	Surgical NEC (<37/40)	Surgical NEC	Failure to achieve full enteral feeds @90d	78	223	35.0%

**sub-group outcome data reported in paper*
BSID: Bayley scales of infant development; MDI: Mental Developmental Index
PDI: psychomotor developmental index
90d: 90 days
PN: Parenteral Nutrition

Table 6

Paper	In-hospital Mortality deaths	n	%	Total Mortality deaths	n	%	Proportion of Mortality that is 'late' %
Allin 2018[12]	29	189*	15.3%	41	159*	25.8%	29.3%
Heida 2017[25]	117	441	26.5%	147	441	33.3%	20.4%
Tashiro 2017[41]	363	886	41.0%	522	886	58.9%	30.5%
Fullerton 2017[22]	904	2881	31.4%	952	2881	33.0%	5.0%

*Allin *et al.* 2018 reports outcomes at 28 days and 1 year. The paper states that the status of 30 infants from the original cohort is 'unknown' hence the discrepancy in these numbers.

Figure 1

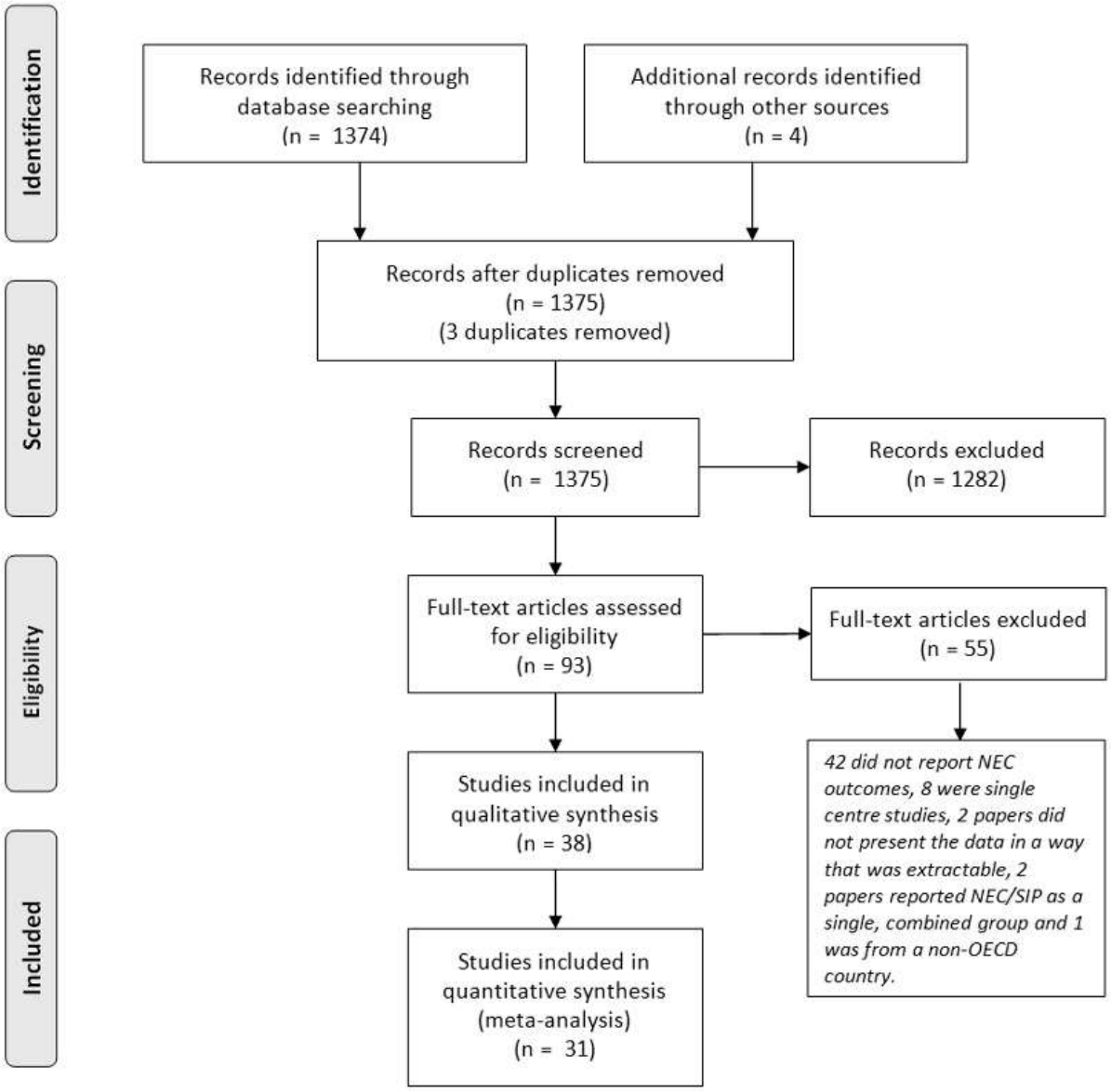
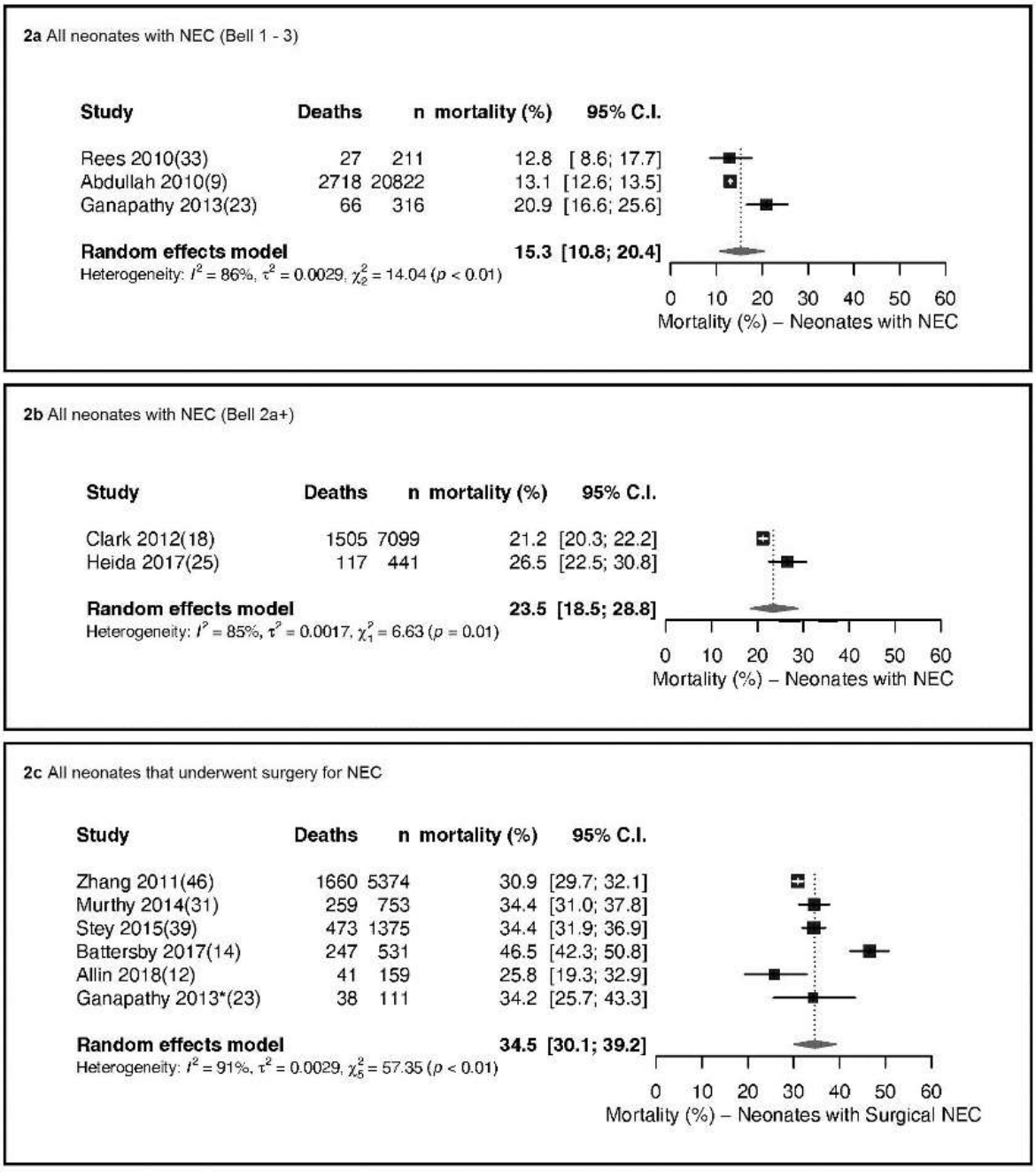

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 1374)
Additional records identified through other sources (n = 4)
Records after duplicates removed (n = 1375) (3 duplicates removed)
Records screened (n = 1375)
Records excluded (n = 1282)
Full-text articles assessed for eligibility (n = 93)
Full-text articles excluded (n = 55)
42 did not report NEC outcomes, 8 were single centre studies, 2 papers did not present the data in a way that was extractable, 2 papers reported NEC/SIP as a single, combined group and 1 was from a non-OECD country.
Studies included in qualitative synthesis (n = 38)
Studies included in quantitative synthesis (meta-analysis) (n = 31)

Figure 2


2a All neonates with NEC (Bell 1 - 3)
Study Deaths n mortality (%) 95% C.I.
Rees 2010(33) 27 211 12.8 [8.6; 17.7]
Abdullah 2010(9) 2718 20822 13.1 [12.6; 13.5]
Ganapathy 2013(23) 66 316 20.9 [16.6; 25.6]
Random effects model 15.3 [10.8; 20.4]
Heterogeneity: I^2 = 86%, τ^2 = 0.0029, χ^2_2 = 14.04 (p < 0.01)
0 10 20 30 40 50 60
Mortality (%) – Neonates with NEC
2b All neonates with NEC (Bell 2a+)
Study Deaths n mortality (%) 95% C.I.
Clark 2012(18) 1505 7099 21.2 [20.3; 22.2]
Heida 2017(25) 117 441 26.5 [22.5; 30.8]
Random effects model 23.5 [18.5; 28.8]
Heterogeneity: I^2 = 85%, τ^2 = 0.0017, χ^2_1 = 6.63 (p = 0.01)
0 10 20 30 40 50 60
Mortality (%) – Neonates with NEC
2c All neonates that underwent surgery for NEC
Study Deaths n mortality (%) 95% C.I.
Zhang 2011(46) 1660 5374 30.9 [29.7; 32.1]
Murthy 2014(31) 259 753 34.4 [31.0; 37.8]
Stey 2015(39) 473 1375 34.4 [31.9; 36.9]
Battersby 2017(14) 247 531 46.5 [42.3; 50.8]
Allin 2018(12) 41 159 25.8 [19.3; 32.9]
Ganapathy 2013*(23) 38 111 34.2 [25.7; 43.3]
Random effects model 34.5 [30.1; 39.2]
Heterogeneity: I^2 = 91%, τ^2 = 0.0029, χ^2_5 = 57.35 (p < 0.01)
0 10 20 30 40 50 60
Mortality (%) – Neonates with Surgical NEC

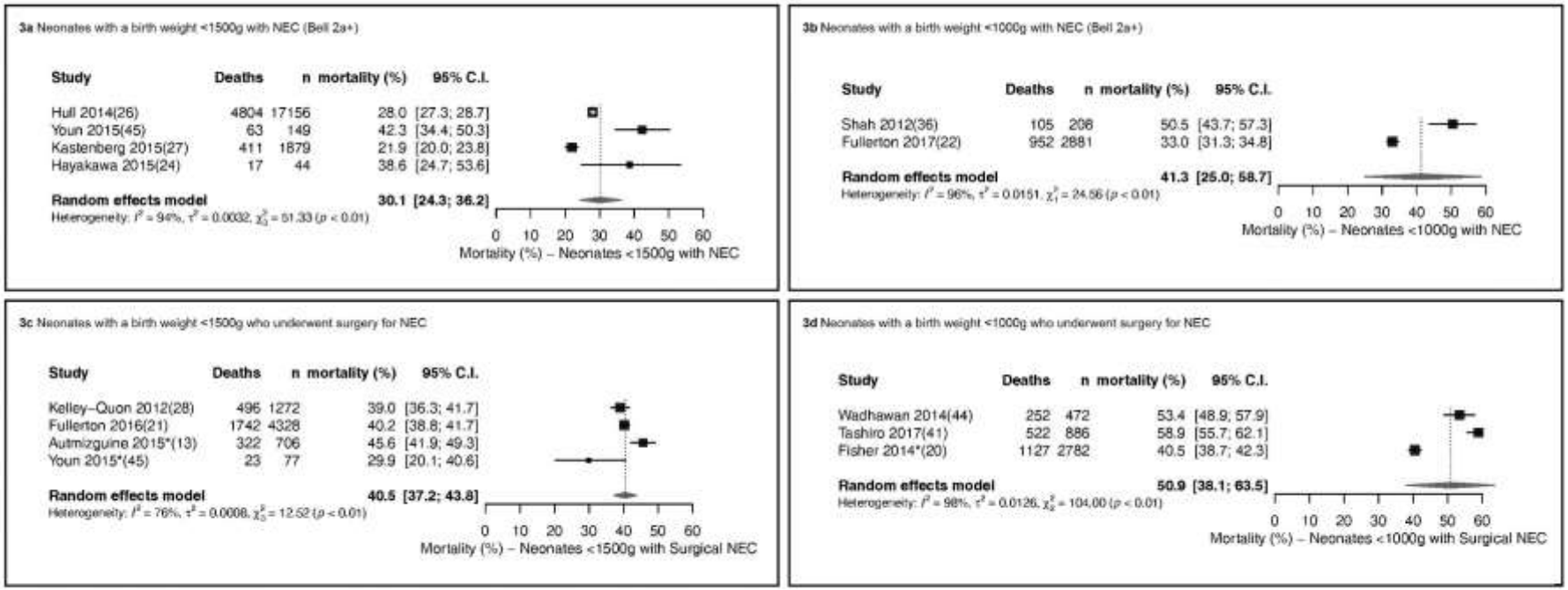

3a Neonates with a birth weight <1500g with NEC (Bell 2a+)
Study Deaths n mortality (%) 95% C.I.
Hull 2014(26) 4804 17156 28.0 [27.3; 28.7]
Youn 2015(45) 63 149 42.3 [34.4; 50.3]
Kastenberg 2015(27) 411 1879 21.9 [20.0; 23.8]
Hayakawa 2015(24) 17 44 38.6 [24.7; 53.6]
Random effects model 30.1 [24.3; 36.2]
Heterogeneity: I^2 = 94%, τ^2 = 0.0032, χ^2_3 = 51.33 (p < 0.01)
0 10 20 30 40 50 60
Mortality (%) – Neonates <1500g with NEC
3b Neonates with a birth weight <1000g with NEC (Bell 2a+)
Study Deaths n mortality (%) 95% C.I.
Shah 2012(36) 105 208 50.5 [43.7; 57.3]
Fullerton 2017(22) 952 2881 33.0 [31.3; 34.8]
Random effects model 41.3 [25.0; 58.7]
Heterogeneity: I^2 = 96%, τ^2 = 0.0151, χ^2_1 = 24.56 (p < 0.01)
0 10 20 30 40 50 60
Mortality (%) – Neonates <1000g with NEC
3c Neonates with a birth weight <1500g who underwent surgery for NEC
Study Deaths n mortality (%) 95% C.I.
Kelley–Quon 2012(28) 496 1272 39.0 [36.3; 41.7]
Fullerton 2016(21) 1742 4328 40.2 [38.8; 41.7]
Autmizguine 2015*(13) 322 706 45.6 [41.9; 49.3]
Youn 2015*(45) 23 77 29.9 [20.1; 40.6]
Random effects model 40.5 [37.2; 43.8]
Heterogeneity: I^2 = 76%, τ^2 = 0.0008, χ^2_3 = 12.52 (p < 0.01)
0 10 20 30 40 50 60
Mortality (%) – Neonates <1500g with Surgical NEC
3d Neonates with a birth weight <1000g who underwent surgery for NEC
Study Deaths n mortality (%) 95% C.I.
Wadhawan 2014(44) 252 472 53.4 [48.9; 57.9]
Tashiro 2017(41) 522 886 58.9 [55.7; 62.1]
Fisher 2014*(20) 1127 2782 40.5 [38.7; 42.3]
Random effects model 50.9 [38.1; 63.5]
Heterogeneity: I^2 = 98%, τ^2 = 0.0126, χ^2_2 = 104.00 (p < 0.01)
0 10 20 30 40 50 60
Mortality (%) – Neonates <1000g with Surgical NEC

Figure 3