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The development of a gestational age-specific case-definition for neonatal Necrotising Enterocolitis

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Abstract (353/350 words)

Importance: Necrotising Enterocolitis (NEC) is a major cause of neonatal morbidity and mortality. Preventive and therapeutic research, surveillance and quality improvement initiatives, are hindered by variations in case-definitions.

Objective: To develop a gestational age (GA) specific case-definition for NEC.

Design, Setting, and Participants: We conducted a prospective 34 month population study using clinician-recorded findings between December 2011 and September 2014 across all 163 neonatal units in England.

Exposure: Abdominal X-ray (AXR) performed to investigate clinical concerns.

Main outcomes and measures: Ordinal NEC likelihood score, dichotomous case-definition, and GA-specific probability plots. We secured clinician commitment to record data prospectively into each infant's Electronic Patient Record (EPR). We obtained study data from the UK National Neonatal Research Database that holds information extracted regularly from the neonatal EPR. We split study data into test and validation datasets. We entered GA, birth-weight z score, clinical and AXR findings as candidate variables in a logistic regression model, performed model fitting 1000 times, averaged the predictions, and used estimates from the fitted model to develop an ordinal NEC score, and cut-points to develop a dichotomous case-definition based upon the highest area under the receiver operating characteristic curves and positive predictive values.

Results: We included data from 3866 infants (2978 without and 888 with NEC). Less mature infants were less likely to present with pneumatosis, blood or mucus in stools, and were more likely to have a gasless AXR. In the ordinal NEC score analysis we allocated three points to pneumatosis, two points to blood in stools. One

point each was allocated to: abdominal tenderness;abdominal discolouration; the composite of increased and/or bilious aspirates AND abdominal distension;one or more of pneumoperitoneum, fixed loop and portal venous gas. The cut-off scores for the dichotomous gestational age-specific case-definition were ≥2 (<30 weeks GA); ≥3 (30 to <37 weeks); ≥4 (≥37 weeks). The ordinal NEC score and dichotomous case-definition discriminated well between infants with and without NEC (AUC 87% and 80% respectively).

Conclusions and relevance: NEC risk and clinical presentation are related to GA. Adoption of a consistent GA- specific case-definition would strengthen global efforts to reduce the population burden of this devastating neonatal disease.

Manuscript text 2525/3000 words

INTRODUCTION

Necrotising Enterocolitis (NEC) is a serious gastrointestinal inflammatory disease predominantly but not exclusively affecting the preterm neonate. Presenting signs are often non-specific and the diagnosis of disease of lesser degrees of severity can be difficult. The lack of a consistent case-definition adds to the difficulties of determining true disease burden, synthesising the results of clinical trials, progressing preventive and therapeutic research, and evaluating the effectiveness of quality improvement interventions. Commonly used definitions include that of the Vermont Oxford Network [1] and Bell's staging criteria [2,3] ; of note is that the latter was developed as a criterion for staging *after* the diagnosis was made as not as a case-definition. Other definitions include those from the Centers for Disease Control and Prevention in the United States [4] and varying groupings of clinical and radiological findings used by individual study authors. [5-8] None of these definitions are evidence-based, validated, or incorporate gestational age (GA), although this influences the risk of NEC. [9] Our aim was to develop a GA-specific case-definition for NEC to facilitate research, surveillance and quality improvement.

METHODS

Study design, data source and regulatory approvals

This study has been reported according to STARD guidelines.[10] Daily clinical information on infants admitted to neonatal units in England is recorded in a point-of-care, clinician-entered Electronic Patient Record (EPR). A defined data extract, the Neonatal Dataset (NHS Information Standard ISB1595) is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London and Chelsea and

Westminster NHS Foundation Trust where patient episodes across different hospitals are merged, data are cleaned, and entered into the National Neonatal Research Database (NNRD). [11] Over 400 data items are held on the NNRD and comprise static *'once-only'* basic demographic details (e.g. month and year of birth, birth-weight, gestational age) applicable to all infants; episodic *'only-if'* (e.g. blood culture, clinical outcomes and diagnoses) and '*daily data'* (e.g. respiratory support, feeding, surgical procedures, drugs received). Each data item is clearly defined in an accompanying meta-data set, and mapped to existing national standards as well as ICD codes. Diagnoses include fixed choice and free-text items with the pseudo-anonymised NHS number as principal identifier.

Neonatal units contributing to the NNRD are known as the UK Neonatal Collaborative (UKNC). The NNRD is approved by the National Research Ethics Service (10/H0803/151), Confidentiality Advisory Group of the Health Research Authority (8-05(f)/2010) and the Caldicott Guardians and Lead Clinicians of contributing hospitals. This investigation is a component of the UKNC-NEC study (UK Clinical Research Network Portfolio ID 11853; National Research Ethics Service ref 11/LO/1430). We invited clinical leads from all neonatal units in England to participate. Clinical staff prospectively recorded a predefined list of clinical and X-ray findings in the Electronic Patient Record (EPR) of any infant who had an abdominal X-ray (AXR) to investigate gastrointestinal concerns.

Data extraction

From the NNRD, we extracted data on all infants who had clinical and AXR findings recorded between November 2011 and September 2014. These comprised demographic data (gestational age, birth weight), diagnoses, procedures, clinical opinion on the certainty of NEC diagnosis, whether NEC was confirmed by visual

inspection of bowel, histology and/or autopsy, and daily NEC treatment (medical or surgical). Diagnoses of NEC were made by clinical and surgical teams locally across 163 neonatal units and 21 surgical centres. Spontaneous Intestinal Perforation (SIP) was considered a distinct entity, and not included in the NEC analyses. We identified infants that received surgery and in whom the diagnosis of NEC was either confirmed or refuted, and infants without surgery for whom the final diagnosis was considered unequivocally “yes” or “no” by the attending clinician; data were excluded if the diagnosis of NEC was considered “uncertain”. For infants that received surgery, we included information from the first AXR indicating that surgery had been performed. For infants without surgery with multiple AXR, we used computer-generated code to select one at random for each infant. We performed internal cross-validation for the outcomes of ‘NEC’ or ‘no NEC’ by comparing these with other data held on the infant (diagnoses, daily NEC diagnosis and procedures) and excluded infants for whom data were inconsistent. For the infants retained in the analysis, we noted the following variables: GA, birth-weight, clinical findings (increased and/or bilious aspirates, blood in stool, mucous in stool, abdominal discolouration, abdominal distension, abdominal mass, abdominal tenderness) and radiological findings (gasless, portal venous gas, fixed loop, pneumatosis, pneumoperitoneum). We categorised GA into groups (<26w Group 1; 26w to <30w Group 2; 30w to <37w Group 3; ≥37w Group 4). We calculated birth-weight z score and categorised these into tertiles. We collated variables with very low (defined as <10%) or high prevalence (defined as >30%) among infants with and without NEC into a single composite variable.

Statistical methods

We investigated whether presentation of NEC varied with GA by comparing clinical and radiological findings among infants with and without NEC using the Chi-square and Fisher's exact tests as appropriate. For each clinical and radiological sign, we determined the odds ratio for NEC, sensitivity, specificity, Positive Predictive Value (PPV) and area under the receiver operating characteristic curve (AUC). We split the dataset at random using a computer-generated code into 'model development' and 'validation' datasets of equal size.On the 'model development' dataset, we used stepwise logistic regression to determine the model which best predicted the probability of NEC. We assessed the quality of this prediction model using the 'validation' dataset. We replicated this procedure 1000 times. All available covariates (clinical and radiological findings, birth-weight and GA) were entered into the model and the covariate with the lowest absolute *T ratio* was removed at each step. Model fitting and validation were performed 1000 times and the resulting predictions averaged. We calculated the absolute deviation,[12] defined as the difference between the probability of NEC based on the model (in the range from 0 to 1 for every infant) and the diagnosis of NEC (1 for NEC and 0 for no NEC).Infants with an absolute deviation greater than 0.5 were considered to have an incorrect prediction. We selected the model with the lowest rate of incorrect predictions. To determine the points allocated for the clinical and/or radiological signs in an ordinal NEC score, we rounded the coefficients from the model up or down to an integer and assessed the corresponding AUC and PPV. For each GA group, we found the 'cut-point' which minimised misclassification[13] by applying two conditions: i) positive predictive value exceeding 60%, and ii) highest area under the AUC. We conducted a sensitivity analysis by applying the definition to only infants who had their diagnoses confirmed by surgery. Finally, we compared the performance of the case-definition with that

from the Vermont Oxford Network [1], defined as at least one clinical sign (bilious aspirate or vomiting, abdominal distension or blood in the stool) and at least one radiological finding (pneumatosis, hepatobiliary gas, pneumoperitoneum). All analyses were performed in R (2013) and Stata (version 11.0).

RESULTS

We secured the participation of all 163 neonatal units (43 Special Care; 76 High Dependency; 44 Intensive Care) in England across 23 clinical networks. We included 3866 AXR from 3866 infants; 2978 without NEC and 888 with NEC, of which 204 cases were confirmed at surgery and the rest by clinician ascertainment (Figure 1). Infants with NEC tended to be more preterm (median (IQR) NEC 28 (25-30) weeks; no NEC 35 (29-39) weeks). Among infants with NEC, the most frequent findings were abdominal distension, pneumatosis, increased and/or bilious aspirates and abdominal tenderness (Table 1). Among infants without NEC, the most frequent clinical findings were abdominal distension and increased and/or bilious aspirates (Table 1). In the whole cohort, a gasless abdomen, portal venous gas, abdominal mass, fixed loop, pneumoperitoneum and mucous in the stool were rare findings with prevalences below 10%. Except for gasless abdomen and abdominal mass, all other findings were significantly different between infants with and without NEC (Table 1). No single clinical or radiological finding discriminated infants with and without NEC, as evidenced by the relatively low AUC. Even pneumatosis, which on its own increased the odds of NEC 76-fold, had an AUC of only 71%. In subsequent analyses we found that the prediction of NEC was improved using combinations of clinical signs and AXR findings. Comparing the clinical presentation of NEC by GA group, infants with NEC born at lower gestational ages were less likely to present

with pneumatosis (p=0.011), blood in stool (p<0.001) or mucous in tools (p=0.048), and more likely to present with a gasless AXR (p=0.009) (Figure 2).

Predictive model for NEC and ordinal NEC score

We grouped three radiological findings (pneumoperitoneum, fixed loop, portal venous gas), each with very low frequency to create a new variable PFP assigning '1' if one or more of these variables were present and '0' if none waspresent. We grouped two clinical findings (increased and/or bilious aspirates and abdominal distension), each with relatively high frequencies into another variable 'AA*'* ('1' if *both* findings were present). The model with the lowest rate of *incorrect predictions* included six variables (blood in stools, abdominal discolouration, abdominal tenderness, pneumatosis, PFP, AA) and GA group. The coefficients were roughly in the proportion 3:2:1 for pneumatosis (3.855), blood in stool (2.760), and the other signs (1.46 for abdominal discolouration; 1.46 for abdominal tenderness; 1.65 for one or more of pneumoperitoneum, fixed loop and portal venous gas (PFP); 0.83 for increased and/or bilious aspirates AND abdominal distension (AA). Therefore, to create an ordinal NEC score, we allocated three points to pneumatosis and two points to blood in stools. One point each was allocated to: abdominal tenderness discolouration; abdominal tenderness; PFP; AA. The sum of points provided the ordinal NEC score. This had an AUC of 0.88 (0.86-0.89), indicating that it discriminated well between infants with and without NEC.

GA-specific NEC score cut-points

The NEC scores were perfectly aligned with the corresponding PPV i.e. the higher the score, the higher the PPV (Table 2) but not with the AUC. Applying the two conditions of highest AUC and PPV yielded the same cut-point of two for GA groups

1 and 2, but different cut-points for GA groups 3 and 4. Cut-point 2 provided the highest AUC for GA group 3, but the PPV was only 41.0%; therefore we selected a cut-point of 3 (PPV 70.7%), with the trade-off of a slightly lower AUC (80% vs 84%). Similarly, for GA group 4, we selected cut-point 4 even though cut-point 2 provided the highest AUC because the PPV was only 8.3%, again accepting a slightly lower AUC (75% versus 84%). The final cut-points for the NEC score were 2 for GA group 1 and 2; 3 for GA group 3; 4 for GA group 4 is. Applying this to the entire dataset yielded a sensitivity (95% CI) of 66.2% (63.0-69.4), specificity 94.4% (93.2-95.4), AUC 80.0% (79-82%) and PPV 85.5 (82.6-88.1). Figure 3 provides a schematic summary of the NEC score, its use in a dichotomous case-definition with GA-specific cut-points, and GA-specific probability plots.

Sensitivity analysis for the subset of infants who received surgery

Applying the cut-points to the 431 infants that had surgery yielded a sensitivity of 76.5% (70.0-82.1), specificity 74.4% (68.3-80.0), AUC 75.0% (71.0- 80.0) and PPV 72.9% (66.4-78.7).

Comparison with Vermont Oxford Network definition

The estimated misclassification rates were 10.5% and 13.7% respectively for applying our NEC score and the VON definition. The difference between the estimated error rates was 3.1%, which was statistically significant ($p < 0.001$). The Vermont Oxford Network definition applied to the entire dataset yielded ~~a~~ sensitivity of 49.7% (46.3-53.0), specificity 97.2% (97.6-97.8), AUC 73.0% (72.0-75.0) and PPV 84.2% (80.7-87.2), and to the subset of infants who had surgery sensitivity 68.1% (61.3-74.5); specificity 71.8% (65.5-77.6); AUC 70.0% (66.0-74.0) and PPV 68.5% (61.6-74.8) (eTable)

DISCUSSION

Using a large population sample we confirm previous observations that risk and clinical presentation of NEC are related to gestational age. [9] We show that a combination rather than a single clinical or AXR finding provides the highest diagnostic accuracy. We developed an ordinal NEC score corresponding to the GA-specific probability of NEC, a dichotomous case-definition with GA-specific cut-offs, and show that these perform favourably when compared with the widely used Vermont Oxford case-definition. As our aim was to develop a simple and pragmatic case-definition suitable for widespread clinical application we concluded that it was worth sacrificing some precision in order to develop a case-definition that would be easy to use. Therefore the coefficients in the model were rounded up or down to an integer to create an ordinal NEC score.

The strength of our study is that it is based on a large population dataset using information captured as part of each infant's clinical care. In contrast to widely used criteria such as the Vermont Oxford case-definition and Bell's staging, we incorporated GA into our case-definition. We recognise that the use of clinical ascertainment in addition to visual inspection at surgery and/or histological evidence, to identify unequivocal NEC may be considered a limitation, hence of note is that our conclusions remained robust to the sensitivity analysis performed on the subset of infants that received surgery in whom the diagnosis was secure. We also note that restricting analysis to infants with NEC confirmed at surgery would not represent the population for which the case-definition is intended. Until there is a reliable non-invasive diagnostic test or biomarker for the disease in infants who do not receive surgery, this challenge cannot be overcome. This study was based on a pragmatic design using a comprehensive national dataset. The decision as to whether an infant

had NEC or SIP was determined by the attending medical and surgical teams, although we acknowledge the difficulty of reliably separating SIP from NEC.

The two conditions used to select the cut-point for the dichotomous case-definition were selected a priori. The highest AUC (maximum sensitivity and specificity) was applied to avoid over and under-reporting, as false negatives and false positives are viewed as equally important when developing a case-definition for which the primary purpose is use in clinical research, surveillance, and quality improvement, as opposed to clinical treatment decisions. The AUC is a trade-off between sensitivity and specificity and therefore we applied the second condition requiring the PPV to exceed 60%. PPV is influenced by prevalence, but sensitivity, specificity and AUC are not. We accept that a more stringent definition with a lower sensitivity and higher specificity may also be appropriate. Our case-definition was not developed for use to guide clinical decision making but nonetheless does provide an objective measure that in part reflects pooled clinician judgment. Additionally, the GA specific probability plots may provide clinical utility in illustrating the likelihood of “true” NEC for any given score.

NEC is a disease feared by parents and clinicians because it can strike suddenly and with little warning, has a high mortality and morbidity, with preventive and therapeutic options that remain limited. Basic and applied research, complemented by quality improvement initiatives underpinned by rigorous surveillance are essential to tackle this devastating disease, but meta-analysis and interpretation of studies requires consistency and hence comparability of case-definitions. We suggest that the ordinal score and dichotomous case-definition we provide offer opportunity to strengthen global efforts to reduce the burden of neonatal NEC.

Contributors

CB, KC and NM were involved in the study inception and protocol development; CB extracted and prepared the dataset; CB and NL (Imperial College London) analysed the data. CB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. CB wrote the first draft of the paper; CB, NM and NL contributed to subsequent drafts. All authors reviewed the paper, and approved the final version submitted; NM is the guarantor.

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References

1. VON. Vermont Oxford Network Database Manual of Operations: Part 2: Data definitions and data forms for infants born in 2013. *Vermont Oxford Network.* 2012;17 ed(R Release).

2. Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of illness. *Curr Probl Pediatr.* Apr 1987;17(4):213-288.

3. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg.* Jan 1978;187(1):1-7.

4. Leistner R, Piening B, Gastmeier P, Geffers C, Schwab F. Nosocomial infections in very low birthweight infants in Germany: current data from the National Surveillance System NEO-KISS. *Klin Padiatr.* 2013;225(2):75-80.

5. Guthrie SO, Gordon PV, Thomas V, Thorp JA, Peabody J, Clark RH. Necrotizing enterocolitis among neonates in the United States. *J Perinatol.* Jun 2003;23(4):278-285.

6. Cust AE, Darlow BA, Donoghue DA. Outcomes for high risk New Zealand newborn infants in 1998-1999: a population based, national study. *Arch Dis Child Fetal Neonatal Ed.* 2003;88(1):F15-22.

7. Luig M, Lui K. Epidemiology of necrotizing enterocolitis--Part II: Risks and susceptibility of premature infants during the surfactant era: a regional study. *J Paediatr Child Health.* Apr 2005;41(4):174-179.

8. Kastenberg ZJ, Lee HC, Profit J, Gould JB, Sylvester KG. Effect of deregionalized care on mortality in very low-birth-weight infants with necrotizing enterocolitis. *Jama, Pediatr.* 2015;169(1):26-32.

9. Sharma R, Hudak ML, Tepas JJ, III, et al. Impact of gestational age on the clinical presentation and surgical outcome of necrotizing enterocolitis. *J Perinatol.* 2006;26(6):342-347.

10. Equator network. STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies 2015; http://www.equator-network.org/reporting-guidelines/stard/.

11. Spencer A, Modi N. National neonatal data to support specialist care and improve infant outcomes. *Archives of Disease in Childhood - Fetal and Neonatal Edition.* January 3, 2012 2012.

12. Shaughnessy J, Garfield J, Greer B. Data Handling. In: Bishop A, Clements K, Keitel C, Kilpatrick J, Laborde C, eds. New York: Springer-Verlag; 1997:205-237.

13. George N, Lu T-P, Chang C-W. Cost-sensitive performance metric for comparing multiple ordinal classifiers *Artifical Intelligence Research* 2016;5:135-143.

Figure legends

Figure 1 Derivation of study dataset

Figure 2 Clinical and AXR findings among infants with NEC (cases of NEC) and without NEC (negatives); bold lines are findings included in the final model

GA group 1 (<26 weeks), group 2 (26 to <30), group 3 (30 to <37), group 4 (≥37 weeks)

Figure 3 Schematic summary: ordinal NEC score, GA-specific case-definition and corresponding probabilities for NEC by GA group

Table 1 Univariate analysis: diagnostic characteristics for clinical and radiological signs of NEC

Clinical and radiological findings	**No NEC n=2978**	**NEC n=888**	**Odds ratio for NEC (95% CI)**	**p- value**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**AUC (%)**
Clinical signs	N (%)	N (%)						
Abdominal distension	1444 (48.5)	740 (83.3)	5.3 (4.4 to 5.4)	<0.001	83.3	51.3	33.9	67.0
Abdominal tenderness	175 (5.9)	369 (41.6)	11.4 (9.3 to 14.0)	<0.001	41.6	94.1	67.8	68.0
Increased and/or bilious naso-gastric aspirates	1060 (35.6)	370 (41.7)	1.3 (1.1 to 1.5)	<0.001	41.7	64.4	25.9	53.0
Abdominal discolouration	71 (2.4)	182 (20.5)	10.6 (8.0 to 14.1)	<0.001	20.5	97.6	71.9	59.0

Abdominal mass	32 (1.1)	12 (1.4)	1.3 (0.6 to 2.4)	0.496	1.4	98.9	27.3	50.0
Blood in stool	72 (2.4)	187 (21.1)	10.8 (8.1 to 14.4)	<0.001	21.1	97.6	72.2	59.0
Mucus in stool	20 (0.7)	44 (5.0)	7.7 (4.6 to 13.4)	<0.001	5.0	99.3	68.8	52.0
Radiological signs								
Pneumatosis	30 (1.0)	387 (43.6)	75.9 (52.6 to 113.6)	<0.001	43.6	99.0	92.8	71.0
Portal venous gas	4 (0.1)	22 (2.5)	18.9 (6.5 to 55.0)	<0.001	2.5	1.6	84.6	51.0
Pneumoperitoneum	57 (1.9)	70 (7.9)	4.4 (3.1 to 6.3)	<0.001	7.9	98.1	55.1	53.0
Fixed loop	79 (2.7)	62 (7.0)	2.8 (2.0 to 3.9)	<0.001	7.0	97.3	44.0	52.0
Gasless abdomen	95 (3.2)	40 (4.5)	1.3 (1.0-2.1)	0.062	4.5	96.8	29.6	51.0

PPV Positive predictive value; AUC area under the ROC curve; N (%) Number of infants (%)

Table 2 NEC score and corresponding PPV and AUC by Gestational age group

	<26 weeks (GA group 1) n=450		26 to <30 weeks (GA group 2) n=941		30 to <37 weeks (GA group 3) n=1168		≥37 weeks (GA group 4) n=1307	
NEC score	**PPV**	**AUC ≥ score (95% CI)**	**PPV**	**AUC ≥ score (95% CI)**	**PPV**	**AUC ≥ score (95% CI)**	**PPV**	**AUC ≥ score (95% CI)**
1	52.0	73.0 (69.0-77.0)	31.2	78.0 (75.0-80.0)	16.9	82.0 (80.0-84.0)	2.5	84.0 (79.0-90.0)
2	63.3	74.0 (70.0-78.0)	67.0	82.0 (79.0-84.0)	41.0	84.0 (81.0-87.0	8.3	84.0 (77.0-92.0)
3	89.1	73.0 (69.0-76.0)	88.8	77 (74.0-79.0)	70.7	80.0 (77.0-83.0)	15.4	76.0 (67.0-85.0)
4	95.1	65.0 (62.0-68.0)	96.8	68.0 (66.0-71.0)	82.4	74.0 (71.0-77.0)	75.0	75.0 (66.0-84.0)
5	94.1	57.0 (54.0-59.0)	95.5	60.0 (58.0-62.0)	92.7	68.0 (65.0-72.0)	100.0	66.0 (57.0-74.0)
6	100.0	53.0 (52.0-55.0)	100.0	55.0 (54.0-57.0)	100.0	58.0 (56.0-60.0)	100.0	58.0 (51.0-64.0)
7	100.0	51.0 (50.0-52.0)	83.3	51.0 (50.0-52.0)	100.0	52.0 (51.0-53.0)	100.0	55.0 (50.0-60.0)

8	100.0	50.0 (50.0-51.0)	100.0	50.0 (50.0-51.0)	100.0	51.0 (50.0-52.0)	100.0	52.0 (49.0-55.0)
9	NA	—	100.0	50.0 (50.0)	—	—	—	—

Shaded grey areas correspond to the NEC score cut-point

95% CI (confidence intervals)

Data from the following UK Neonatal Collaborative neonatal networks (neonatal units and UKNC-NEC Study leads) were included in this study:

Cheshire & Merseyside (Arrowe Park Hospital: Dr O Rackham; Countess of Chester Hospital: Dr S Brearey; Leighton Hospital: Dr A Thirumurugan; Liverpool Women's: Dr N Subhedar; Macclesfield District General Hospital: Dr G Whitehead; Ormskirk District General Hospital: Dr T McBride; Warrington Hospital: Dr C Zipitis, Dr D Webb, Dr H Satish; Whiston Hospital: Dr L Chilukuri)

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Midlands North Staffordshire, Shropshire and Black Country (Manor Hospital: Dr AK Bhaduri; New Cross Hospital: Dr A Skinner; Royal Shrewsbury Hospital: Dr S Deshpande; Russells Hall Hospital: Dr T Pillay; Staffordshire General Hospital: Dr KK Tewary; University Hospital of North Staffordshire: Dr K Palmer)

Midlands South West (Alexandra Hospital: Dr A Short; Worcestershire Royal Hospital: Dr A Gallagher; Birmingham City Hospital: Dr J Nycyk; Birmingham Heartlands Hospital: Dr R Mupanemunda; Good Hope Hospital: Dr J Meran; Birmingham Women's Hospital: Dr I Morgan, Dr A Bedford-Russell; Hereford County Hospital: Dr HC Underhill)

North Central London (Barnet Hospital, Chase Farm Hospital: Dr T Wickham; The Royal Free Hospital: Dr V van Someren; University College Hospital: Dr S Watkin; Whittington Hospital: Dr R Blumberg)

North East London (Homerton Hospital: Dr N Aladangady; King George Hospital, Queen's Hospital: Dr B Sharma; Newham General Hospital, North Middlesex University Hospital: Dr L Alsford; The Royal London Hospital, Whipps Cross University Hospital: Dr C Sullivan)

North Trent (Barnsley District General Hospital: Dr S Hamdan; Bassetlaw District General Hospital: Dr H Mulenga; Diana Princess of Wales Hospital: Dr P Adiotomre; Scunthorpe General Hospital: Miss A Jackson; Doncaster Royal Infirmary: Dr JS Ahmed; Chesterfield & North Derbyshire Royal Hospital: Dr A Foo; Rotherham District General Hospital: Dr C Harrison; The Jessop Wing, Sheffield: Dr E Pilling)

North West London (Chelsea & Westminster Hospital: Dr S Uthaya; Ealing Hospital: Dr R Mathur; Hillingdon Hospital: Dr M Cruwys; Northwick Park Hospital: Dr C Philipp, Dr R Nicholl; West Middlesex University Hospital: Dr E Eyre)

Northern (Cumberland Infirmary, West Cumberland Infirmary; Dr P Whitehead and M Ben-Hamida; Darlington Memorial Hospital, University Hospital of North Durham: D A Bowes; James Cook University Hospital, Friarage : Dr N Sabrine; Queen Elizabeth Hospital, Gateshead: Dr D Bosman; Royal Victoria Infirmary: Dr N Embleton; South Tyneside District Hospital: Dr R Bolton; Sunderland Royal Hospital: Dr M Abu-Harb; University Hospital of North Tees: Dr C Harikumar ; Wansbeck General Hospital: Dr J Olivier)

Peninsula (Derriford Hospital: Dr N Maxwell; North Devon District Hospital: Dr Y Cherinet; Royal Cornwall Hospital: Dr P Munyard; Royal Devon & Exeter Hospital: Dr N Osbourne; Torbay Hospital: Dr M Raman)

South East London (Guy's & St Thomas' Hospital: Dr K Turnock; King's College Hospital: Dr A Hickey; Princess Royal University Hospital, Queen Elizabeth Hospital: Dr O Banjoko; University Hospital Lewisham: Dr J Kuna)

South West London (Croydon University Hospital: Dr A Kumar; Epsom General Hospital: Dr K Watts; St Helier Hospital: Dr R Shephard; Kingston Hospital: Dr D Lindo; St George's Hospital: Dr L De Rooy)

South Central South Coast (North & South) (Basingstoke & North Hampshire Hospital: Dr R Wigfield; Dorset County Hospital: Dr P Wylie; Milton Keynes Foundation Trust Hospital: Dr I Misra; Oxford University Hospitals, Horton Hospital: Dr N Shettihalli; John Radcliffe Hospital: Dr E Adams; Poole Hospital NHS Foundation Trust: Dr M Khashu; Princess Anne Hospital: Dr F Pearson; Queen Alexandra Hospital: Dr C Groves; Royal Berkshire Hospital: Dr P de Halpert; Royal Hampshire County Hospital: Dr D Schapira; Salisbury District Hospital: Dr N Brown; St Mary's Hospital Isle of Wight: Dr C Burtwell; St Richard's Hospital: Dr N Brennan; Stoke Mandeville Hospital: Dr S Salgia; Wexham Park Hospital: Dr R Sanghavi)

Surrey and Sussex (Conquest Hospital: Dr G Whincup; East Surrey Hospital: Dr K Khader; Frimley Park Hospital: Dr A Mallik; Princess Royal Hospital, Royal Sussex County Hospital: Dr P Amess; Royal Surrey County Hospital: Dr M Hardo; St Peter's Hospital: Dr P Reynolds; Worthing Hospital: Dr E Vamvakiti)

Trent (King’s Mill Hospital: Dr V Noble; Lincoln County Hospital and Pilgrim Hospital: Dr AS Rao; Nottingham City Hospital, Nottingham University Hospital (QMC): Dr S Wardle, Dr J Dorling; Royal Derby Hospital: Dr M Ratnayaka)

Western (Gloucestershire Royal Hospital: Dr J Holman; Great Western Hospital: Dr S Zengeya; Royal United Hospital: Dr S Jones; Southmead Hospital: Dr P Mannix; St Michael’s Hospital: Dr P Cairns; Taunton & Somerset Hospital: Dr RJ Mann; Yeovil District Hospital: Dr M Eaton)

Yorkshire (Airedale General Hospital: Dr M Babirecki; Bradford Royal Infirmary: Dr S Oddie; Calderdale Royal Hospital: Dr K Schwarz; Dewsbury & District Hospital, Pontefract General Infirmary (Pinderfields): Dr D Gibson; Harrogate District Hospital: Dr C Jampala; Hull Royal Infirmary: Dr K Green, Dr J Preece; Leeds Neonatal Service: Dr K Johnson; Scarborough General Hospital: Dr A Hawkridge; York District Hospital: Dr G Millman)

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