**Supplementary File Table S3.** The association between the cumulative incidence of NEC, epoch and other predictors, estimated using three separate regression models. The first is a proportional hazards regression with a single parameter for the association between NEC and epoch. The second allows the association between NEC and epoch to vary with time since birth. The third is as the second but with the addition of a factor representing calendar year, thereby estimating and controlling for a linear trend with time.

| Factor                        | Level                     | Single predictor | Time-varying effect | Regression Discontinuity |
|-------------------------------|---------------------------|------------------|---------------------|--------------------------|
|                               |                           | Sub Hazard Ratio | p-value             | Sub Hazard Ratio        | p-value              | Sub Hazard Ratio | p-value |
| Epoch                         | Routine vs pre-probiotics | 0.44 (0.23–0.85) | 0.014               | -                       | -                    | -                | -       |
| Epoch: first week after birth | Routine vs pre-probiotics | -                | -                   | 0.08 (0.01–0.59)        | 0.014               | 0.04 (0.00–0.63) | 0.023   |
| Epoch: second week after birth| Routine vs pre-probiotics | -                | -                   | 0.43 (0.13–1.42)        | 0.166               | 0.68 (0.07–6.74) | 0.740   |
| Epoch: beyond second week     | Routine vs pre-probiotics | -                | -                   | 0.85 (0.36–2.01)        | 0.716               | 1.01 (0.18–5.67) | 0.992   |
| Calendar year: first week after birth | Per year                 | -                | -                   | -                       | -                    | 1.16 (0.77–1.75) | 0.479   |
| Calendar year: second week after birth | Per year                 | -                | -                   | -                       | -                    | 0.91 (0.62–1.36) | 0.656   |
| Calendar year: beyond second week | Per year                 | -                | -                   | -                       | -                    | 0.97 (0.72–1.30) | 0.838   |
| Gestational age at birth      | <25 weeks                 | 1.00 (Ref)       | 1.00 (Ref)          | 1.00 (Ref)              | 1.00 (Ref)          | 1.00 (Ref)       |         |
|                               | 25-26 weeks               | 0.34 (0.16–0.70) | 0.003               | 0.32 (0.16–0.66)        | 0.002               | 0.32 (0.16–0.67) | 0.002   |
|                               | 27-30 weeks               | 0.09 (0.03–0.26) | <0.001              | 0.08 (0.03–0.25)        | <0.001              | 0.09 (0.03–0.25) | <0.001  |
|                               | 31+ weeks                 |                  |                     |                          |                      |                   |         |
| Milk type          | Mother’s milk | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
|-------------------|---------------|------------|------------|------------|
| No enteral feed   |               | 0.15 (0.04–0.52) | 0.003 | 0.22 (0.06–0.87) | 0.030 | 0.23 (0.06–0.91) | 0.036 |
| Donor milk*       | -             | -          | -          | -          | -          | -          |
| Formula feed      |               | 0.85 (0.29–2.52) | 0.775 | 0.82 (0.28–2.43) | 0.724 | 0.85 (0.28–2.55) | 0.768 |
| Mixed             |               | 0.82 (0.41–1.64) | 0.576 | 0.80 (0.40–1.61) | 0.533 | 0.81 (0.40–1.62) | 0.549 |
| Birthweight       | <1000g        | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
|                  | 1000-1499g    | 0.71 (0.26–1.99) | 0.520 | 0.70 (0.25–1.94) | 0.491 | 0.70 (0.25–1.93) | 0.487 |
|                  | >1500g        | 1.12 (0.22–5.84) | 0.891 | 1.12 (0.21–5.81) | 0.896 | 1.11 (0.21–5.76) | 0.904 |
| Sex               | Male (vs Female) | 1.05 (0.59–1.86) | 0.872 | 1.04 (0.58–1.84) | 0.903 | 1.05 (0.59–1.87) | 0.878 |
| Antenatal steroids| At least one dose (vs never) | 1.10 (0.45–2.68) | 0.840 | 1.14 (0.47–2.80) | 0.772 | 1.12 (0.46–2.76) | 0.798 |
| NSAID             | None          | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
|                  | Indometacin   | 1.21 (0.47–3.08) | 0.694 | 1.14 (0.45–2.91) | 0.786 | 1.16 (0.43–3.11) | 0.768 |
|                  | Ibuprofen     | 1.20 (0.41–3.56) | 0.738 | 1.15 (0.39–3.43) | 0.796 | 1.15 (0.39–3.41) | 0.805 |
| PROM              | No            | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
|                  | Yes           | 0.53 (0.22–1.29) | 0.164 | 0.49 (0.20–1.20) | 0.119 | 0.49 (0.20–1.19) | 0.115 |
|                  | Not recorded  | 0.78 (0.33–1.88) | 0.583 | 0.78 (0.33–1.88) | 0.584 | 0.77 (0.32–1.87) | 0.568 |
| Mode of Birth     | Caesarean (vs vaginal) | 1.82 (0.92–3.60) | 0.086 | 1.72 (0.87–3.37) | 0.116 | 1.72 (0.87–3.37) | 0.118 |
* No baby received donor milk in the first epoch and there was no case of NEC among the infants (N=9) who were exclusively donor milk fed in the routine probiotics epoch.