# Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

## eAppendix. Sample Size Calculation

Sample size calculation was made by the Clinical Trial Unit of the University Hospital of Lausanne, Switzerland. The approach was to include enough newborns per network to be able to calculate the proportion of infants treated with antibiotics in relation to the incidence of early-onset sepsis with an adequate level of precision. Based on a review of the literature, we estimated that the proportion of proven infection would be around 1.25% (1/80) among infants treated with antibiotics. Considering that ± 1% precision around a proportion is acceptable, we calculated that the minimum sample size per network would be 475 infants treated with antibiotics. To calculate the minimal number of births that should be included in each network, we considered that 2% of infants receive antibiotics within the first postnatal week (lower end of reported data). The minimal sample size was estimated at 475*(100/2) = 23750 live births.

## eTable 1. Description of Networks

| Network | Country | Type of network[a] | Region, hospitals |
|---|---|---|---|
| Norway | Norway | Population-based data | Whole country |
| Stockholm County | Sweden | Population-based data | County |
| Central Switzerland | Switzerland | Population-based data | Canton Luzern, Uri, Schwytz, Unterwald |
| Emilia Romagna | Italy | 4 level ≥ III hospitals | Azienda Ospedaliero-Universitaria Policlinico, Modena<br>Azienda Ospedaliero-Universitaria Sant'Orsola, Bologna<br>Ospedale Maggiore, Bologna<br>Ospedale M Bufalini, Cesena |
| Western Switzerland | Switzerland | 3 level ≥ III, 1 level II hospitals | University Hospital of Geneva<br>Lausanne University Hospital<br>Inselspital, University Hospital of Bern<br>Hospital of Morges |
| Hamilton | Canada | 1 level ≥ III, 2 level II hospitals | McMaster Children's Hospital, Hamilton<br>St Joseph's Healthcare Hamilton<br>Niagara Health, St. Catharines |
| Rhode Island | USA | 1 level ≥ III hospital | Women & Infants Hospital of Rhode Island |
| Hungary | Hungary | 2 level ≥ III hospitals | University Hospital of Szeged<br>Semmelweis University Hospital |
| Apulia | Italy | 3 level ≥ III hospitals | Policlinico Bari<br>Ospedali Riuniti Foggia<br>Miulli |
| Wallonia | Belgium | 2 level ≥ III hospitals | Grand Hôpital de Charleroi<br>CHC Montlegia |
| Prague | Czech Republic | 1 level ≥ III, 1 level II hospital | Motol University Hospital, Prague<br>Thomayer Hospital, Prague |
| Perth | Australia | 1 level ≥ III hospital | King Edward Memorial Hospital for Women, Perth |
| Warsaw | Poland | 2 level ≥ III hospitals | Princess Anna Mazowiecka Hospital, Warsaw<br>Institute of Mother and Child, Warsaw |

[a]The level of care of hospitals was defined according to the classification of the American Academy of Pediatrics [reference #1].

## eTable 2. Strategies to Prevent and Treat EOS and Main Outcomes in the 13 Networks

| Country, region | GBS Screening[a] | GBS IAP[b] | Obstetrical guidelines to prevent EOS | Use of laboratory tests[c] | Antibiotics for chorioamnionitis[d] | Serial physical examination[e] | EOS calculator[f] | Neonatal guidelines to diagnose and treat EOS | Antimicrobial stewardship program[g] | Incidence of EOS[h] | Antibiotic exposure[i] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Norway | - | - | National guidelines[j] | + | - | - | - | - | - | 0.63 (0.53-0.74) | 115 (114-116) |
| Sweden, Stockholm County | - | - | National guidelines[k] | + | - | - | - | National guidelines[q] | - | 0.29 (0.21-0.39) | 54 (53-55) |
| Italy, Emilia Romagna | + | + | CDC guidelines[l] | - | - | + | - | Regional guidelines[r] | + | 0.45 (0.29-0.67) | 92 (90-95) |
| Western Switzerland | + | + | - | - | - | + | - | National guidelines[s] | -/+[w] | 0.37 (0.21-0.59) | 126 (123-129) |
| Canada, Hamilton | + | + | National guidelines[m] | + | - | + | - | National guidelines[m] | - | 0.54 (0.25-0.80) | 230 (227-234) |
| USA, Rhode Island | + | + | - | + | - | - | - | - | + | 0.18 (0.07-0.36) | 88 (85-90) |
| Central Switzerland | + | + | - | - | - | + | - | National guidelines[s] | - | 0.22 (0.10-0.44) | 107 (103-110) |
| Hungary | + | + | National guidelines | + | + | - | - | National guidelines | - | 0.57 (0.33-0.92) | 180 (175-184) |
| Italy, Apulia | + | + | CDC guidelines[l] | + | + | - | - | AAP guidelines[t] | - | 1.45 (1.05-1.96) | 387 (382-393) |
| Belgium, Wallonia | + | + | - | + | - | -/+[o] | - | National guidelines[u] | - | 0.39 (0.19-0.69) | 120 (116-123) |
| Czech Republic, Prague | + | + | Local guidelines | + | - | + | - | Local guidelines | + | 0.33 (0.15-0.63) | 88 (85-92) |
| Australia, Perth | + | + | Local guidelines | + | + | - | -/+[p] | Regional guidelines[v] | -/+[p] | 0.73 (0.44-1.14) | 491 (485-497) |
| Poland, Warsaw | + | + | National guidelines[n] | + | + | + | - | National guidelines | - | 0.43 (0.21-0.79) | 196 (191-201) |

[a]Maternal screening for colonization with Group B Streptococcus (GBS)
[b]Intrapartum antibiotic prophylaxis (IAP) in case of maternal GBS colonization
[c]Use of laboratory tests (such as complete blood count and/or C reactive protein) to decide whether or not to initiate antibiotic treatment
[d]Starting antibiotics in all infants born from mothers with chorioamnionitis
[e]Use of written protocol for standardized serial physical examination and observation of asymptomatic infants from mothers with risk factors
[f]Use of the neonatal early-onset sepsis (EOS) calculator
[g]Defined as an organizational strategy implemented in neonatal units to promote appropriate use of antimicrobials through the implementation of evidence-based interventions
[h]Number of EOS cases (all cases) per 1000 livebirths (95% CI)
[i]Number of antibiotic days per 1000 livebirths (95% CI)
[j]National Norwegian guidelines [reference # 2]
[k]National Swedish guidelines [reference #3]
[l]Guidelines of the Centers for Disease Control and Prevention [reference #4]
[m]Guidelines of the Canadian Pediatric Society [reference #5]

[n]Guidelines of the Polish Society of Gynecologists and Obstetricians [reference #6]
[o]Serial physical examination was implemented in 2015 in one out of two hospitals.
[p]The EOS calculator was implemented in July 2016 and an antimicrobial stewardship program was implemented in 2017.
[q]National Swedish guidelines [reference #7]
[r]Regional guidelines [reference #8]
[s]Guidelines of the Swiss Society of Neonatology [reference #9]
[t]Guidelines of the American Academy of Pediatrics [reference #10]
[u]Belgian pediatric GBS guidelines [reference #11]
[v]Guidelines of the Government of Western Australia [reference #12]
[w]An antimicrobial stewardship program was implemented in one out of four hospitals.

## eTable 3. Pathogens Identified in Blood and Cerebrospinal Fluid Cultures of Infants With Early-Onset Sepsis

| Pathogens | Number of EOS episodes | | | Postnatal age at blood culture, days |
|---|---|---|---|---|
| | All EOS episodes (n = 375) | Fatal episodes (n = 12) | Non-fatal episodes (n = 363) | |
| Gram-positive bacteria | 279 (74%) | 6 (50%) | 273 (75%) | |
| Group B streptococci | 126 (34%) | 2 (17%) | 124 (34%) | 0.5 (0-1) |
| Coagulase negative staphylococci | 65 (17%) | 1 (8%) | 64 (18%) | 1 (0-2) |
| *Staphylococcus aureus* | 23 (6%) | 0 | 23 (6%) | 3 (1-4) |
| Viridans group streptococci | 21 (6%) | 0 | 21 (6%) | 1 (0-2) |
| *Enterococcus* spp | 10 (3%) | 0 | 10 (3%) | 1 (0-2) |
| *Listeria monocytogenes* | 5 (1%) | 1 (8%) | 4 (1%) | 0 (0-1) |
| Other Gram-positive bacteria | 29 (8%) | 2 (17%) | 27 (7%) | 1 (1-1) |
| Gram-negative bacteria | 84 (22%) | 6 (50%) | 78 (21%) | |
| *Escherichia coli* | 62 (17%) | 5 (42%) | 57 (16%) | 1 (0-2) |
| *Klebsiella* spp | 8 (2%) | 1 (8%) | 7 (2%) | 3 (1-5) |
| Other Gram-negative bacteria | 14 (4%) | 0 | 14 (4%) | 1 (0-1) |
| *Candida albicans* | 2 (1%) | 0 | 2 (1%) | 2 (2-2) |
| Mixed pathogens | 5 (1%) | 0 | 5 (1%) | 1 (0-2) |
| Unidentified pathogens | 5 (1%) | 0 | 5 (1%) | 0 (0-1) |

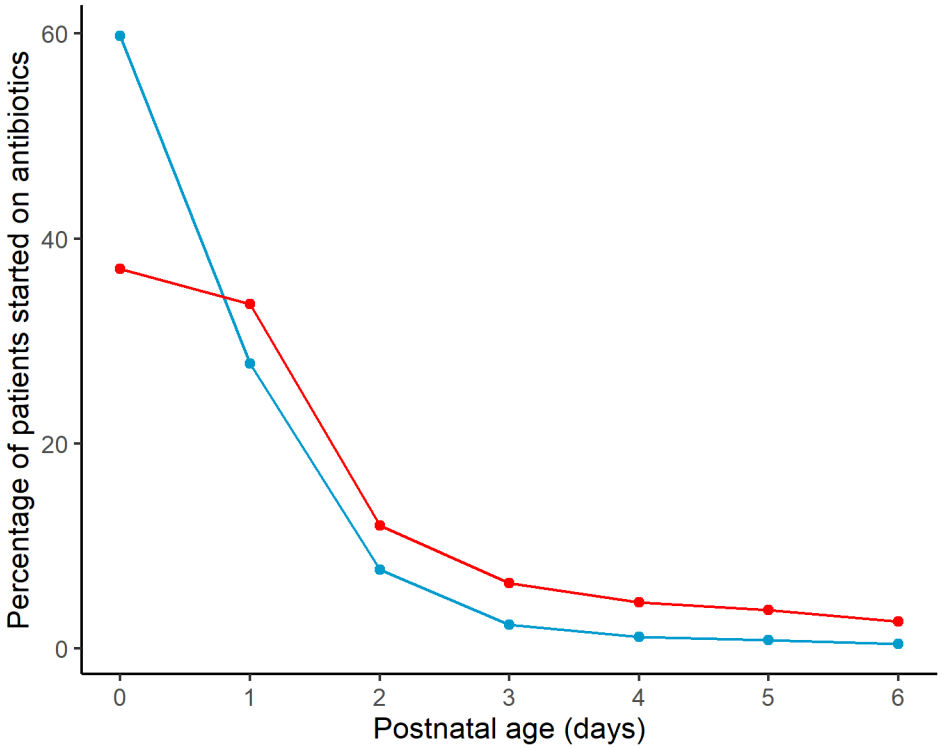
Categorical variables are presented as frequencies (%) and continuous variables as median (IQR). Column percentages are presented; percentages are based on available data for each variable.

## eTable 4. Main Outcomes in Infants Born in Level I-II vs III-IV Facilities From Stockholm County

| Outcomes | Level I-II facilities[a] | Level III-IV facilities[a] | Odds ratio or Median difference (95% CI) |
|---|---|---|---|
| Number of births | 104091 | 40326 | |
| Number of infants treated with antibiotics in all live births | 1144 (1.1%) | 557 (1.4%) | 1.26 (1.14 - 1.40) [b] |
| Number of antibiotic days (days/1000 live births) | 5250 (50) | 2542 (63) | 1.26 (1.14 - 1.39)[c]<br>1.25 (1.05 - 1.49)[d] |
| Number of EOS cases (per 1000 live births) | 26 (0.25‰) | 16 (0.40‰) | 1.59 (0.80 - 3.08) [b] |
| Number of all-cause deaths (per 1000 live births) | 24 (0.23‰) | 24 (0.60‰) | 2.58 (1.40 - 4.75)[b] |
| Duration of antibiotic treatment (days) | 4 (3-6) | 4 (3-5) | 0 (0 - 0)[e] |
| Number of antibiotic days (per treated infant) | 5250 (4.59) | 2542 (4.56) | 0.89 (0.75 - 1.07)[c]<br>0.99 (0.93 - 1.06)[d] |
| Number of EOS cases in infants treated with antibiotics | 26 (2.3%) | 16 (2.9%) | 1.27 (0.63 - 2.49)[b] |
| Number of all-cause deaths in all infants treated with antibiotics | 15 (1.2%) | 17 (3.1%) | 2.37 (1.10 - 5.13)[b] |
| Number of all-cause deaths in proven EOS cases | 2 (7.7%) | 0 (0.0%) | 0 (0 - 3.15)[b] |
| Number of all-cause deaths in cases without proven infection | 13 (1.2%) | 17 (3.1%) | 2.76 (1.25 - 6.22)[b] |

[a]The level of care of hospitals was defined according to the classification of the American Academy of Pediatrics [reference #1].
[b]Odds ratio for Level III-IV facilities (compared to Level I-II facilities) with 95% confidence interval
[c]Odds ratio, derived from an ordered logistic regression, for Level III-IV facilities (compared to Level I-II facilities) with 95% confidence interval
[d]Incidence rate ratio, derived from a negative binomial regression, for Level III-IV facilities (compared to Level I-II facilities) with 95% confidence interval
[e]Median difference with 95% confidence interval

## eFigure 1. Postnatal Age at Antibiotics Start

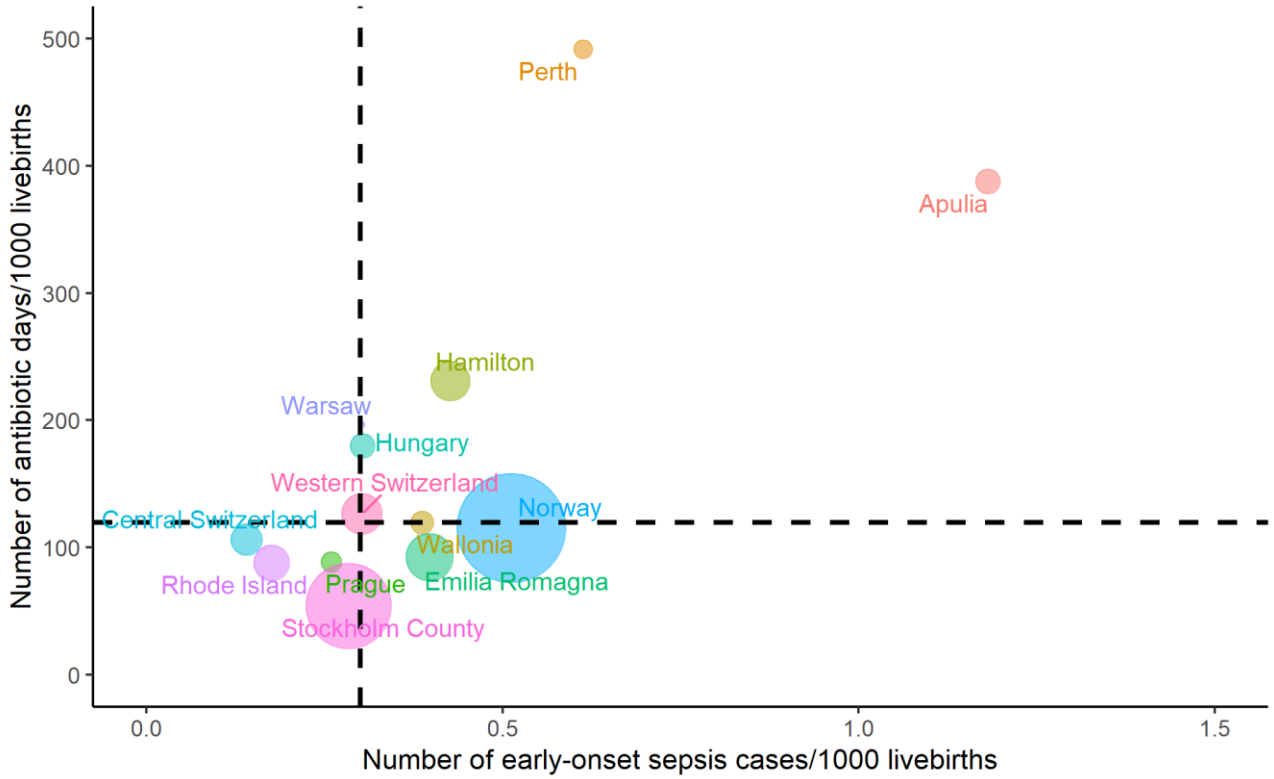



Number of infants started on antibiotics

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| EOS cases | 139 | 126 | 45 | 24 | 17 | 14 | 10 |
| Cases without proven EOS | 12752 | 5927 | 1636 | 497 | 244 | 170 | 102 |

Postnatal age at antibiotic start in infants with (red dots, n = 375) and without (blue dots, n = 21328) early-onset sepsis (EOS).

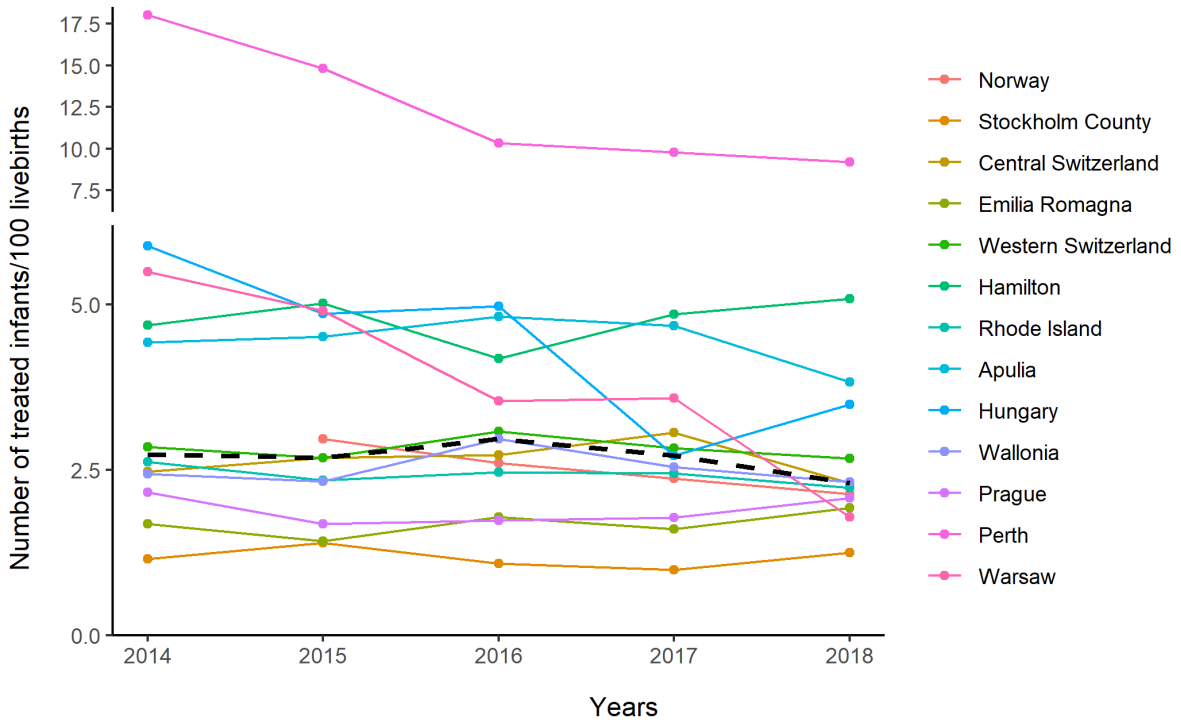
**eFigure 2. Relationship Between the Incidence of Early-Onset Sepsis Without Coagulase Negative Staphylococci and Exposure to Antibiotics**



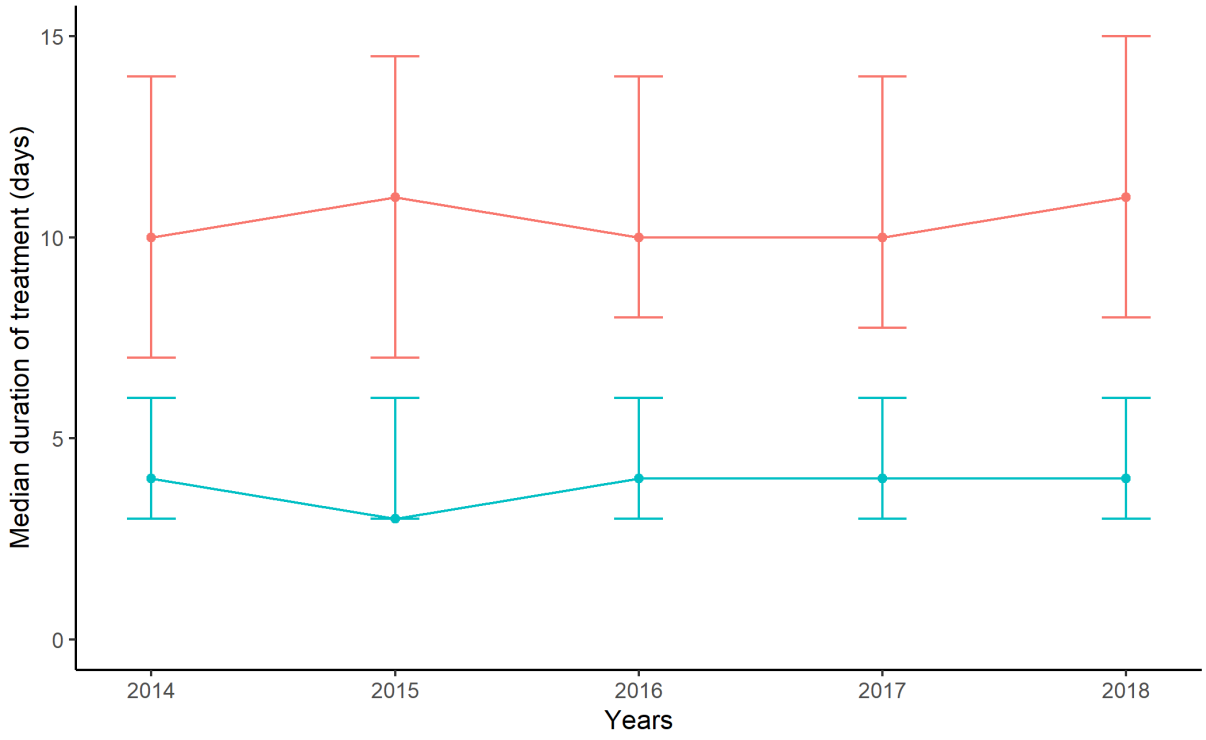

The size of the bubbles represents the number of births. The dotted lines represent the median of the 13 networks.

## eFigure 3. Burden of Treatment Over Time

A



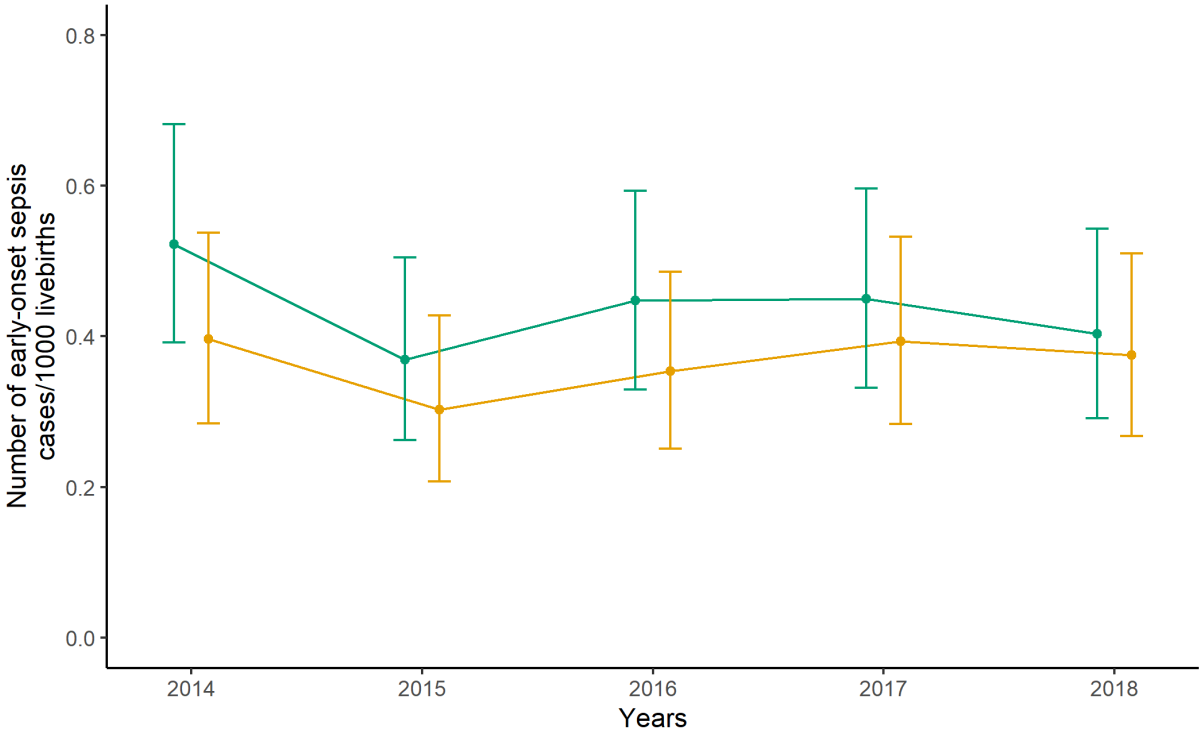

B



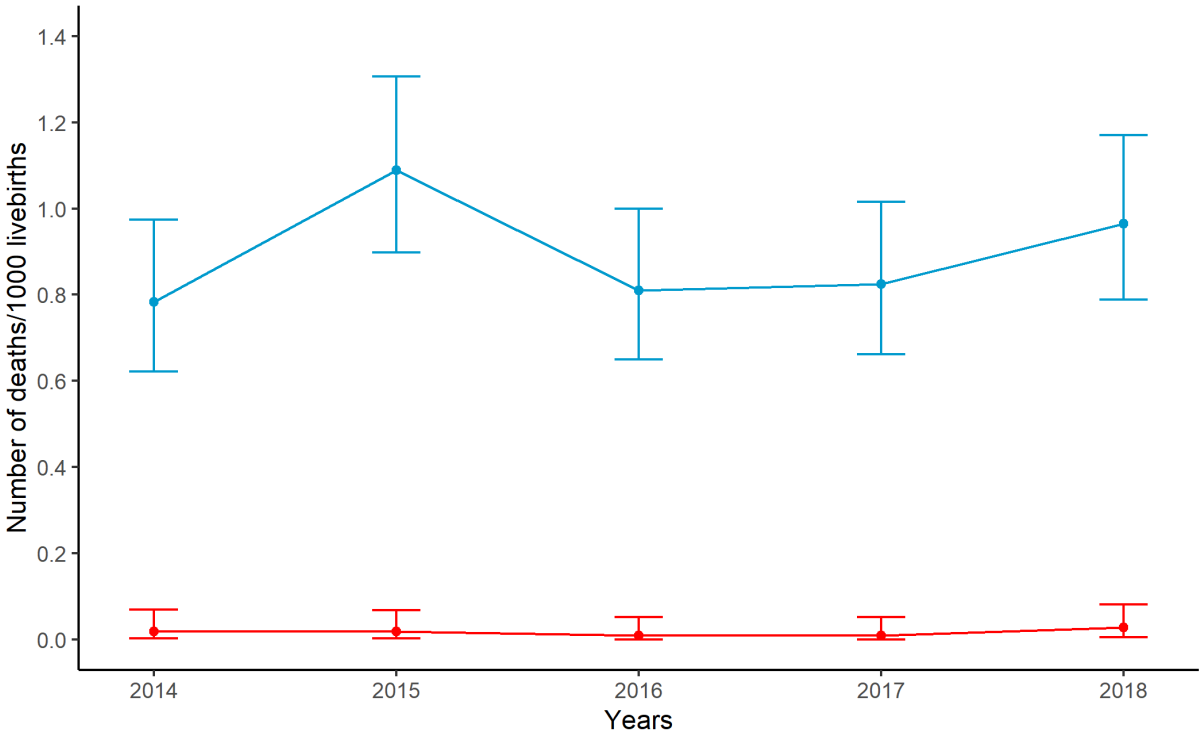

A) Proportion of infants treated with antibiotics by year in each network. The dashed line represent the median of the 13 networks. B) Duration of antibiotic treatment by year in infants with early-onset sepsis (in red), and in infants without early-onset sepsis (in blue). The median, 25$^{th}$ percentile, and 75$^{th}$ percentile are shown. Patients who died were not included this graph. Data on 529780/ 757979 births (69.9%) and 15936/21703 (73.4%) infants treated with antibiotics is presented, including 222/375 (59.2%) infants with proven EOS, and 15687/21328 (73.6%) infants without early-onset sepsis, as data from 2014 was not available for Norway.

## eFigure 4. Burden of Disease Over Time

A




B




A) Incidence of early-onset sepsis by year and 95% CI ; incidence calculated with all culture-proven early-onset sepsis episodes is presented in green, incidence calculated without inclusion of coagulase-negative staphylococci cases is presented in orange. B) Mortality per 1000 livebirths by year and 95% CI ; all-cause mortality is presented in blue, and mortality in early-onset cases is presented in red. Data on 529780/ 757979 births (69.9%) and 15936/21703 (73.4%) infants treated with antibiotics is presented, including 222/375 (59.2%) infants with proven early-onset sepsis, and 15687/21328 (73.6%) infants without proven early-onset sepsis, as data from 2014 was not available for Norway.

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