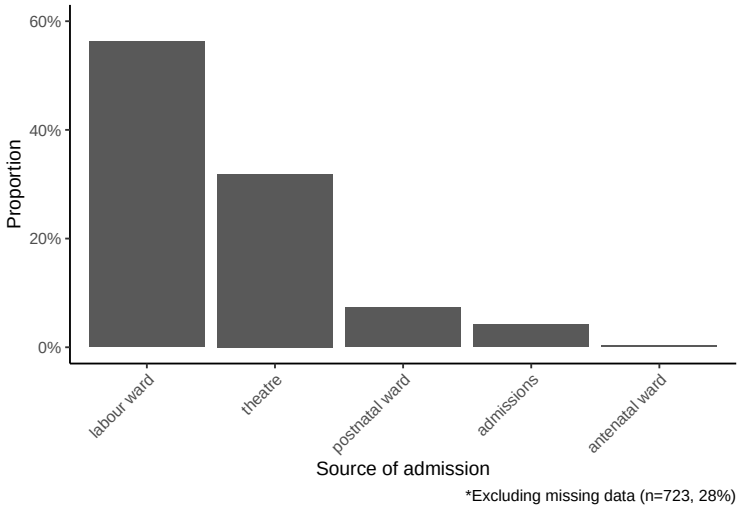
9-Reviewers

Additional analyses in response to reviewers' comments.

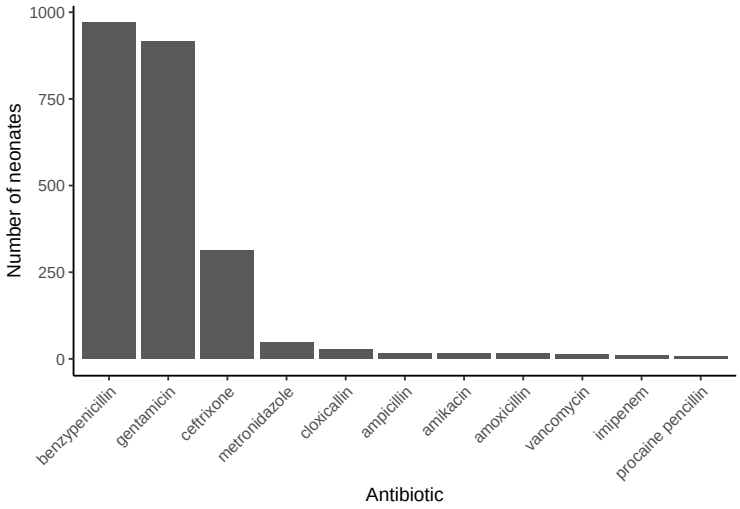
0.1 Source of admission

The below figure shows the source of admission for neonates included in our study.



0.2 Antibiotic usage

The below figure shows the distribution of antibiotic usage for neonates included in our study.



Below is the distribution of antibiotic usage for those with and without EOS.

```
##        sepsis (n)
## abx (n)   no  yes
##       0 1457   30
##       1  874  267
```

```
##        sepsis (%)
## abx (%) no yes
##       0 63  10
##       1 37  90
```

```
##
##  Pearson's Chi-squared test with Yates' continuity correction
##
## data:  table(abx_dat$abx, abx_dat$sepsis)
## X-squared = 292.36, df = 1, p-value < 2.2e-16
```

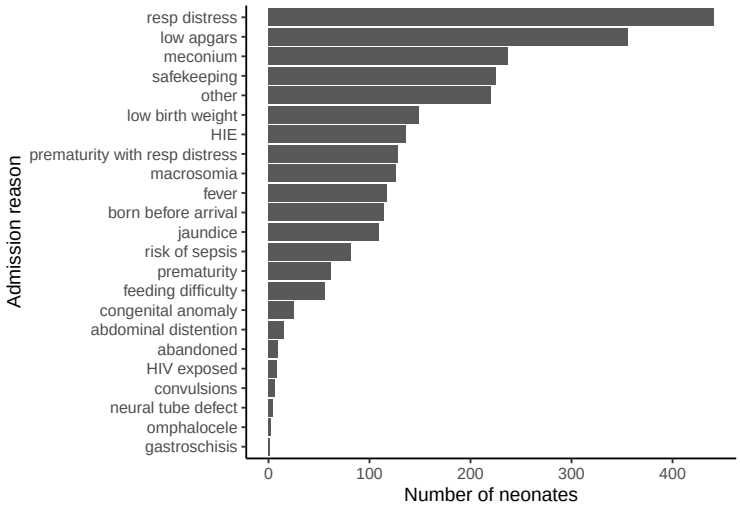
0.3 Characteristics of neonates in whom sepsis 'missed' by model

The table below compares characteristics between those with EOS who were classified as EOS by our model (true positives) and those with EOS who were classified as 'no EOS' by our model (false negatives, i.e. 'missed' EOS) at the optimal classification threshold determined by Youden's J statistic (0.121).

Characteristic	Overall, N = 297	0, N = 191	1, N = 106	p-value
Sex, n (%)				0.038
f	132 (44%)	76 (40%)	56 (53%)	
m	165 (56%)	115 (60%)	50 (47%)	
u	0 (0%)	0 (0%)	0 (0%)	
Gestational age, mean weeks (SD)	38.36 (2.29)	38.65 (2.13)	37.85 (2.48)	0.006
Birth weight, mean grams (SD)	2.95 (0.60)	3.02 (0.55)	2.82 (0.65)	0.007
Chronological age, n (%)				0.005
fnb	100 (34%)	55 (29%)	45 (43%)	
dol1	121 (41%)	76 (40%)	45 (43%)	
dol2	54 (18%)	44 (23%)	10 (9.6%)	
dol3	19 (6.5%)	15 (7.9%)	4 (3.8%)	
Type of birth, n (%)				>0.9
singleton	291 (98%)	187 (98%)	104 (98%)	
twin1	6 (2.0%)	4 (2.1%)	2 (1.9%)	
triplet1	0 (0%)	0 (0%)	0 (0%)	
Mode of delivery, n (%)				0.3
svd	226 (76%)	145 (76%)	81 (76%)	
electiveCS	12 (4.0%)	5 (2.6%)	7 (6.6%)	
emergencyCS	51 (17%)	36 (19%)	15 (14%)	
instrumental	8 (2.7%)	5 (2.6%)	3 (2.8%)	
Admission duration, median days [Q1-Q3]	6.0 [3.5-8.8]	5.3 [2.9-8.4]	6.9 [4.7-9.2]	0.006
Death, n (%)	37 (12%)	21 (11%)	16 (15%)	0.4
sepsis, n (%)	297 (100%)	191 (100%)	106 (100%)	>0.9

0.4 Reasons for admission

The below figure shows the reasons for admission of neonates included in our study.



0.5 Sample size calculations

The below code shows post hoc sample size calculations as per Riley *et al.* BMJ 2020 (doi: https://doi.org/10.1136/bmj.m441).

```
# a. estimate the overall outcome proportion with sufficient precision
# aiming for margin of error \leq 0.05
outprop <- sum(si$sepsis == "yes")/nrow(si) #outcome proportion
(1.96 / 0.05)^2 * outprop*(1-outprop) #=154
```

```
## [1] 154.0353
```

```
# b. target a small mean absolute prediction error (p \leq 30)
n <- nrow(si) #sample size of development dataset
P <- 9 #number of candidate predictor parameters
MAPE <- 0.05 #mean absolute prediction error
exp((-0.508 + 0.259*log(outprop) + 0.504*log(P) - log(MAPE))/0.544) #=263 for MAPE 0.05
```

```
## [1] 262.6125
```

```
# c. target a shrinkage factor of 0.9
# (although shrinkage not used in our study)
S <- 0.9 #target shrinkage factor of 10%
R2CS <- 0.1 #anticipated R2(CS) of at least 0.1
P / ((S-1) * log(1 - (R2CS/S))) #=764
```

```
## [1] 764.1168
```

```
# d. target small optimism of 0.05 in the apparent R2(Nagelkerke)
lnLnull <- (outprop*n)*log(outprop*n/n) + (n - outprop*n)*log(1 - outprop*n/n)
maxR2CS <- 1 - exp(2*lnLnull / n) #maximum possible value of R2CS
S2 <- R2CS / (R2CS + 0.05*maxR2CS) #assuming expected optimism \leq 0.05
P / ((S2 - 1)*log(1 - R2CS/S2)) #=333
```

```
## [1] 332.8419
```

0.6 Model calibration

The below statistics and figure shows calibration of our optimal model with a flexible calibration curve using a loess smoother.

```
##           Dxy       C (ROC)            R2             D      D:Chi-sq
##  4.615048e-01  7.307524e-01  1.495163e-01  7.831524e-02  2.068125e+02
##           D:p             U      U:Chi-sq          U:p             Q
##  0.000000e+00 -7.610350e-04 -6.821210e-13  1.000000e+00  7.907628e-02
##         Brier     Intercept         Slope          Emax  Brier scaled
##  8.914686e-02 -6.996109e-10  1.000000e+00  4.146973e-10  1.106800e-01
##          Eavg           ECI
##  1.729055e-02  4.155624e-02
```