Stratification of Culture-Proven Early-Onset Sepsis Cases by the Neonatal Early-Onset Sepsis Calculator: An Individual Patient Data Meta-Analysis

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Objectives To provide a comprehensive assessment of case stratification by the Neonatal Early-Onset Sepsis (EOS) Calculator, a novel tool for reducing unnecessary antibiotic treatment.

Study design A systematic review with individual patient data meta-analysis was conducted, extending PROSPERO record CRD42018116188. Cochrane, PubMed/MEDLINE, EMBASE, Web of Science, Google Scholar, and major conference proceedings were searched from 2011 through May 1, 2020. Original data studies including culture-proven EOS case(s) with EOS Calculator application, independent from EOS Calculator development, and including representative birth cohorts were included. Relevant (individual patient) data were extracted from full-text and data queries. The main outcomes were the proportions of EOS cases assigned to risk categories by the EOS Calculator at initial assessment and within 12 hours. Evidence quality was assessed using Newcastle-Ottawa scale, Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies, and GRADE tools.

Results Among 543 unique search results, 18 were included, totaling more than 459 000 newborns. Among 234 EOS cases, EOS Calculator application resulted in initial assignments to (strong consideration of) empiric antibiotic administration for 95 (40.6%; 95% CI, 34.2%-47.2%), more frequent vital signs for 36 (15.4%; 95% CI, 11.0%-20.7%), and routine care for 103 (44.0%; 95% CI, 37.6%-50.6%). By 12 hours of age, these proportions changed to 143 (61.1%; 95% CI, 54.5%-67.4%), 26 (11.1%; 95% CI, 7.4%-15.9%), and 65 (27.8%; 95% CI, 22.1%-34.0%) of 234 EOS cases, respectively.

Conclusions EOS Calculator application assigns frequent vital signs or routine care to a substantial proportion of EOS cases. Clinical vigilance remains essential for all newborns. *(J Pediatr 2021;234:77-84)*.

See related article, p 71

Clinical practice in management of suspected early-onset sepsis (EOS) is widely being reevaluated, because of declining incidence and increasing recognition that use of empiric antibiotics can have adverse consequences.[1,2] The Neonatal Early-Onset Sepsis Calculator developed by Kaiser Permanente is a novel tool for allocating antibiotics to newborns born at 34 or more weeks of gestation.[3-5] It provides clinicians with individualized, quantitative risk estimates based on maternal risk factors and objective neonatal clinical findings, along with recommendations for clinical management ranging from routine care to administration of empiric antibiotics.[6] A systematic review concluded that the implementation of the EOS Calculator was associated with a 44% decrease in empiric antibiotic use for suspected EOS.[7] Although evidence on safety was limited, a meta-analysis indicated noninferiority compared with conventional management, with a similar proportions of culture-proven EOS cases receiving antibiotic therapy within 24 hours after birth.

Potential delays in identification and treatment of culture-proven EOS are a major concern regarding the EOS Calculator.[8-11] The majority of 51 EOS cases in the largest implementation study to date had an estimated EOS Calculator risk below the threshold for empiric antibiotics at birth.[12] Much smaller studies have identified several more cases where the application of the EOS Calculator did not lead to the recommendation of empiric antibiotic therapy.[12-14] The aim of this study was to provide clinicians with a comprehensive and representative overview of how culture-proven EOS cases are stratified into different risk categories by the EOS Calculator. Because clinical monitoring using vital signs is included in EOS Calculator recommendations, the secondary aim was to

CHARMS	Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies
EOS	Early-onset sepsis

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A.v.R. reports personal fees from Oxford University and Karolinska Institute Stockholm and grants from the Coolsingel Foundation and the Sophia Foundation outside the submitted work. E.G. is supported by the Leenaards Foundation. The authors declare no conflicts of interest.

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https://doi.org/10.1016/j.jpeds.2021.01.065

explore the prevalence and timing of onset of clinical illness among those cases. The results provide important data regarding implementation and direct future research, and facilitate comparison with alternative strategies.

Methods

We performed a systematic review and individual patient meta-analysis of EOS cases reported in the literature evaluating the EOS Calculator, as detailed elsewhere in this article. For this study, we extended our previous systematic review analyzing the EOS Calculator,[7] which was registered in advance (CRD42018116188, PROSPERO database). We followed the PRISMA-IPD methodology,[15] described in detail in the PRISMA-IPD protocol (**Appendix 1**; available at www.jpeds.com). There was no funding source for this study.

Study Eligibility Criteria

We defined the study selection criteria as follows: studies reporting any original data on at least 1 culture-proven EOS case with application of the EOS Calculator, independent from EOS Calculator development, and including a representative birth cohort. Studies of preselected at-risk cohorts, such as newborns exposed to chorioamnionitis or prolonged rupture of membranes, those with clinical signs of illness, or newborns selectively admitted to a particular unit or level of care were excluded. This limitation was used to avoid oversampling of at-risk cases, which would distort overall assessment of the EOS Calculator recommendations. An EOS case was defined as a newborn with a positive blood or cerebrospinal fluid culture within 72 hours after birth.

Information Sources and Search Strategy

A systematic search of the EOS Calculator literature in the Cochrane, Embase, and PubMed/MEDLINE databases[7] and review of articles citing original EOS Calculator publications identified through Google Scholar and/or Web of Science search engines was updated to extend through May 1, 2020 (see protocol, **Appendix 1**). Databases were searched for equivalents of *EOS Calculator* in all fields. We also searched for *predictive*, *risk*, *quantitative*, or *stratification*, combined with *model* or *algorithm*, and equivalents of *EOS* in titles and abstracts. Available abstracts of large international conferences of pediatric societies since 2014 (Pediatric Academic Societies, American Academy of Pediatrics, European Society of Pediatric Infectious Diseases, European Academy of Paediatrics) were searched for *sepsis* and results were screened manually for eligibility. Citations were combined and duplicates excluded manually.

Study Selection and Data Collection

Publications not identified in the previous search were independently assessed for eligibility by at least 2 authors. Another author was consulted to resolve any disagreements.[7] Because of updated study eligibility criteria, we reassessed results previously excluded because of "no outcome data" and "no peer-review" results using the same procedure.

For each study, 2 authors independently extracted data on study location, study design, EOS Calculator implementation, number of births in the base population, and number of EOS cases. Individual patient data on maternal EOS Calculator input variables (maternal group B *Streptococcus* colonization status, duration of rupture of membranes, gestational age, maximum maternal intrapartum temperature, and administration and timing of intrapartum antibiotics), and clinical classification of the newborn (well-appearing, equivocal, or clinical illness) were extracted for each EOS case. The EOS Calculator uses detailed objective criteria and cut-offs for these classifications, with criteria including the (persistent) need for respiratory support or vasoactive drugs, presence of seizures or low Apgar scores, and/or the presence of persistent physiologic abnormalities in heart rate, respiratory rate, respiratory distress, and/or temperature instability.[4-6] For each newborn in this study, we used the clinical classification assigned by the original authors when they applied the EOS Calculator.

The occurrence and onset of EOS symptoms and isolated pathogen data were extracted when available. If data were incomplete, corresponding authors were queried using a standardized data collection form and/or single missing elements were inferred by application of the EOS Calculator to reproduce reported risk estimates (eg, inferring exact gestational age by calculating that required to reproduce the originally reported EOS risk). Additional or updated data revealed by author queries were included. For studies for which individual patient data could not be obtained, aggregate results on EOS Calculator recommendations were reviewed if available, but these subjects were not included in the individual patient meta-analysis.

Risk of Bias Assessment

To assess risk of bias within studies, we used applicable items from the Newcastle-Ottawa Scale for cohort studies, and the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist. To assess risk of bias across studies and for the accumulated evidence, we used the Grading of Recommendations Assessment, Development, and Evaluation method.[16,17] The risk of publication bias was not assessed separately, because the search included non-peer-reviewed results and outcome data were expected to be too rare to allow for a meaningful funnel plot.

Exclusion of Spurious or Transient Bacteremias

In cases in which cultures yielded potential nonpathogenic or contaminant isolates (such as coagulase-negative *Staphylococcus*), we deferred to the judgments of the original authors regarding the diagnosis of EOS. EOS cases clearly resembling transient bacteremia, defined as newborns with a positive blood culture obtained solely because of maternal risk factors who remained asymptomatic until discharge in the absence of antibiotic therapy and/or had a sterile follow-up blood culture obtained before initiation of treatment were excluded, with confirmation from the original authors.

Application of the EOS Calculator and Data Analysis

For each EOS case, the recommendations of the EOS Calculator (blood culture and empiric antibiotic therapy, strong consideration of empiric antibiotic treatment, blood culture and frequent vital signs, frequent vital signs alone, or routine care) were recalculated at the initial assessment (with examination), and separately including clinical signs over the first 12 hours. The proportions of EOS cases identified by the EOS Calculator at the initial assessment and by 12 hours of age were calculated, with exact 95% CIs (Clopper-Pearson method).[18] All data were analyzed using Excel (Microsoft) and R, version 3.6.0 (R Foundation for Statistical Computing).

The online EOS Calculator requires choice of a specific EOS population baseline incidence. For consistency, we used a homogenous incidence of 0.6 per 1000 live births, closest to that in the development sample.[19] The incidence can be adjusted to tailor the tool to a specific population, but this requires prior calibration and/or validation.[19] This is analogous to altering the threshold for treatment in the opposite direction (a higher incidence mimics a lower treatment threshold), which can be a clinical decision.[20] Additional analysis was performed to assess effects of different treatment thresholds or population incidences (as offered by the online EOS Calculator) on the proportion of EOS cases assigned treatment. We also assessed whether the results differed if the analysis was stratified by EOS pathogen or restricted to prospective data and explored the relationship between age at onset and EOS Calculator risk estimates.

Results

Included Studies and EOS Cases

The updated literature search revealed a total of 543 unique publications, of which 174 were selected for full-text review

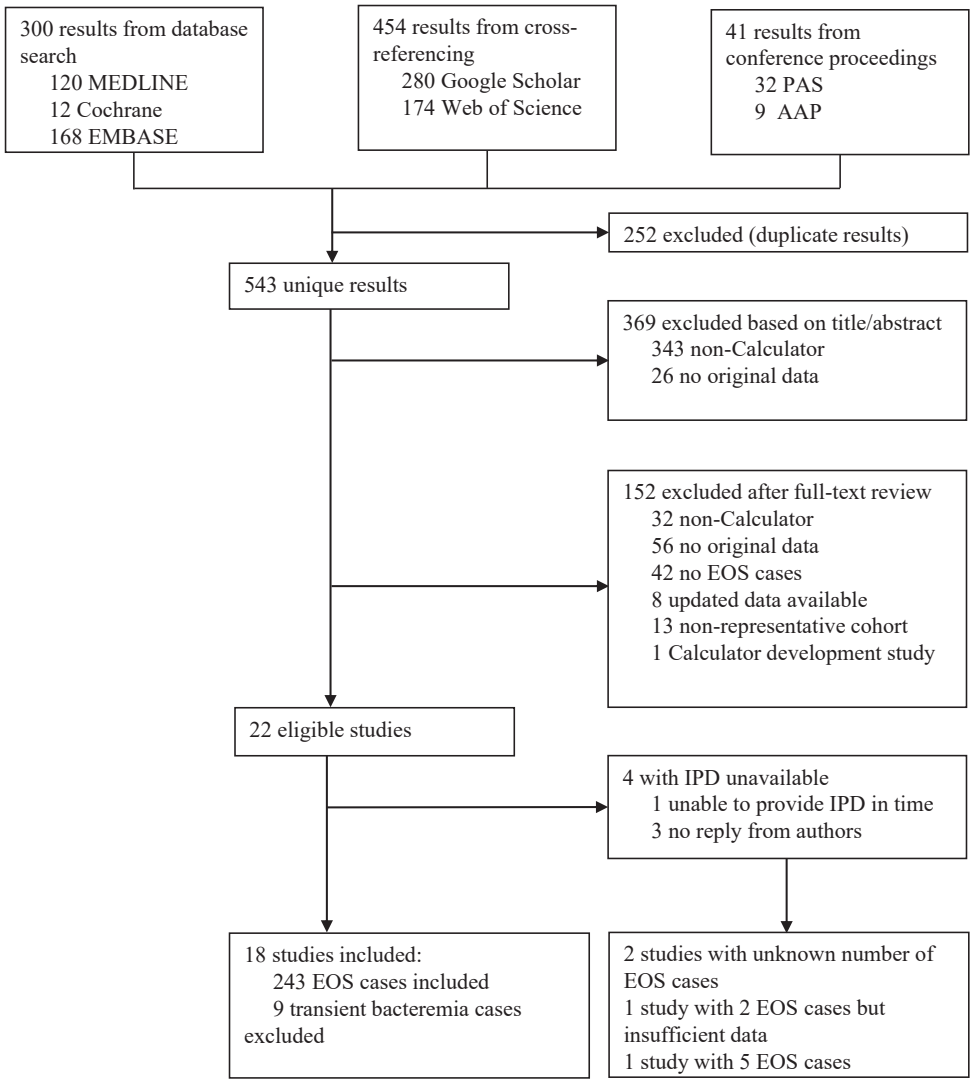

Figure 1. Flowchart of search results and study selection. *AAP*, American Academy of Pediatrics; *IPD*, Individual Patient Data; *PAS*, Pediatric Academic Societies.

(Figure 1). We excluded 152 of these for noneligibility, including 13 involving only nonrepresentative cohorts, and 8 because the same subjects were also described in subsequent publications.

Four studies were excluded from main analysis because individual patient data could not be obtained, leaving 18 studies for inclusion (Table I).[12,13,21-41] Eleven were from the US, 3 from the UK, and 4 from other countries. Individual patient data were obtained for a total of 243 EOS cases, from birth cohorts including more than 459 113 births. Of these, 9 were considered cases of transient bacteremia (Table II; available at www.jpeds.com), leaving 234 for analysis (Table III; available at www.jpeds.com). Birth cohort size was known for 17 studies, with an overall EOS incidence of 0.50 per 1000 live births. Among the 4 studies without individual patient data, 1 contained relevant aggregate results on the main outcome, describing 5 EOS cases.[23]

Risk of Bias

Studies were classified as having a high risk of bias for 11, low for 4, and unclear for 3 studies (Table IV; available at www.jpeds.com). We graded the overall quality of the evidence for the primary outcome as low, considering that data of 174 of 234 EOS cases (74.4%) were collected retrospectively. We identified 2 EOS cases with imputed highest maternal temperature (37.0°C), but no other issues compromising individual patient data integrity.[13,25]

Classification of EOS Cases by the EOS Calculator

At the initial assessment, the EOS Calculator application resulted in recommendation of empiric antibiotic treatment or strong consideration of treatment in 95 (40.6%; 95% CI, 34.2-47.2), frequent vital signs with or without blood cultures for 36 (15.4%; 95% CI, 11.0-20.7%), and routine care for 103 (44.0%; 95% CI, 37.6-50.6%) of 234 EOS cases (Figure 2 and Table V). There were no instances of treatment initiation because of a positive screening blood culture. After the incorporation of examination findings over the first 12 hours after birth (in accordance with its intended use), the EOS Calculator recommended antibiotic treatment or strong consideration of treatment in 143 (61.1%; 95% CI, 54.5%-67.4%), frequent vital signs with or without blood culture for 26 (11.1%; 95% CI, 7.4%-15.9%), and routine care for 65 (27.8%; 95% CI, 22.1%-34.0%) cases (Table V).[5]

EOS case classification was similar when restricted to prospectively collected data (Table VI; available at www.jpeds.com). Finally, the study providing only aggregate results indicated that the EOS Calculator identified 5 of 5 EOS cases, but without indicating the population incidence used.[23]

Effects of Adjusted Treatment Thresholds or Incidence Rates

Using treatment thresholds ranging from 0.45 to 18.0 cases per 1000 live births, which approximates use of population incidence rates ranging from 0.1 to 4.0 per 1000 live births (as offered in the online calculator), we found that lower treatment thresholds (at a fixed population incidence) or higher EOS incidence rates (at a constant treatment threshold) would increase the proportion of cases for which treatment is recommended (Table VII; available at www.jpeds.com).

Recommendations in the Context of Pathogen and Onset of Clinical Illness

Among included EOS cases for which the causative organism was reported, group B *Streptococcus* was the most common pathogen (116/228; 50.9%), followed by *Escherichia coli* (37/228; 16.2%) (Table V). For the 153 cases caused by

Table I. Included studies

Study		Country	Design	Gestational age	Birth cohort (n)	EOS cases	Implementation
Achten et al[25]	2018	NL	Retrospective + Prospective	≥35	3953	4	Before/after
Arora et al[26]	2019	US	Retrospective + Prospective	≥34	N/A	5	Before/after
Bajracharya et al[27]	2019	US	Retrospective	≥34	2066	7	No
Benaim et al[28]	2019	US	Retrospective	≥34	1367	5	No
Davidson et al[29]	2016	UK	Prospective	≥34	1351	3	No
Dhudasia et al[30]	2018	US	Retrospective	≥36	11 782	4	Before/after
Fischer et al[31]	2018	US	Retrospective	≥35	8240	5	No
Fowler et al[32]	2019	US	Retrospective	≥34	6517	6	Before/after
Goel et al[33]	2020	UK	Prospective	≥34	4992	6	No
Hershkovich-Shporen et al[34]	2019	Israel	Retrospective	≥35	7058	6	No
Joshi et al[35]	2019	US	Retrospective	≥34	19 996	7	No
Kopec et al[36]	2018	US	Retrospective	≥34	25 688	49	No
Kuzniewicz[12]		US	Prospective	≥35	204 685	42	Before/after
Morris et al[37]	2017	UK	Retrospective	≥34	142 333	70	No
Perez et al[38]	2019	US	Prospective	≥35	2916	2	Yes
Procianoy et al[39]	2019	Brazil	Retrospective	≥34	8321	9	No
Sharma et al[40]	2019	US	Prospective	≥36	5346	3	Before/after
Strunk et al[41]	2018	Australia	Prospective	≥35	2502	1	Yes
Total					>459 113	234	

N/A, not available; *NL*, The Netherlands.
Gestational age is the threshold for subject inclusion.

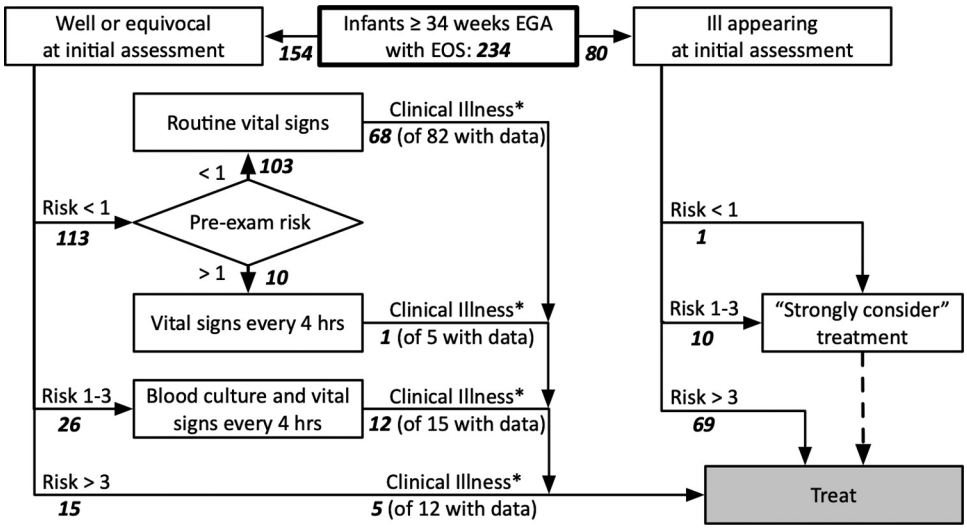

Figure 2. Pathways leading to treatment according to the EOS Calculator algorithm. Calculator recommendations at the initial assessment. Numbers in bold italics represent the number of cases within the adjacent branch of the flow diagram. Risk estimates expressed as cases per 1000 births. Infants with high initial risk estimates were much more likely to have clinical signs of illness immediately after birth ($P < .0001$). *Clinical signs of illness developing after initial assessment. *EGA*, estimated gestational age.

these typical EOS pathogens, the EOS Calculator recommended antibiotics for 54 patients (35.3%) at initial assessment and for 82 patients (53.6%) within 12 hours after birth. The initial recommendations across categories did not vary significantly by causative organism ($P = .13$).

The EOS Calculator paradigm partly depends on clinical vigilance for a period after birth. Of 180 cases with available data (**Figure 3**; available at www.jpeds.com), 149 (82.8%) exhibited clinical signs of illness at their initial assessment (n = 63) or later (n = 86); of these, 120 cases (80.5%) showed signs within 12 hours after birth, 133 (89.3%) within 24 hours, and 146 (98.0%) within 48 hours. Among the 104 cases with time of onset data who were neither clinically ill nor had a risk estimate of 3 or more per 1000

Table V. EOS Calculator recommendations for EOS cases management at birth, stratified according to pathogen

Pathogen No.	(% of total cases*)	Empiric antibiotics*	Strongly consider treatment	Blood culture and frequent vital signs	Frequent vital signs	Routine care
Recommendation at initial assessment, n (% of group)						
Group B *Streptococcus*†	116 (50.9)	36 (31.0)	4 (3.4)	14 (12.1)	3 (2.6)	59 (50.9)
E coli†	37 (16.2)	18 (47.1)	1 (2.7)	5 (13.5)	2 (5.4)	11 (29.7)
Viridans group streptococci	17 (7.5)	8 (47.1)	2 (11.8)	1 (5.9)	1 (5.9)	5 (29.4)
Coagulase-negative *Staphylococcus*	12 (5.3)	3 (25.0)	1 (8.3)	1 (8.3)	0 (0.0)	7 (58.3)
Enterococcus spp.	8 (3.5)	3 (37.5)	0 (0.0)	0 (0.0)	1 (12.5)	4 (50.0)
L monocytogenes	5 (2.2)	2 (40.0)	0 (0.0)	1 (20.0)	0 (0.0)	2 (40.0)
S aureus	5 (2.2)	0 (0.0)	0 (0.0)	1 (20.0)	2 (40.0)	2 (40.0)
Other	29 (12.7)	9 (30.0)	3 (13.3)	3 (10.0)	1 (3.3)	13 (43.3)
Total (known organisms)	228 (100.0)	78 (34.2)	11 (4.8)	26 (11.4)	10 (4.4)	103 (45.2)
All subjects	234 (100.0)	84 (35.9)	11 (4.7)	26 (11.1)	10 (4.3)	103 (44.0)
Recommendation in first 12 hours, n (% of group)						
Group B *Streptococcus*†	116 (50.9)	60 (51.7)	20 (17.2)	5 (4.3)	3 (2.6)	28 (24.1)
Escherichia coli†	37 (16.2)	22 (59.5)	3 (8.1)	4 (10.8)	2 (5.4)	6 (16.2)
Viridans group streptococci	17 (7.5)	8 (47.1)	2 (11.8)	1 (5.9)	1 (5.9)	5 (29.4)
Coagulase-negative *Staphylococcus*	12 (5.3)	3 (25.0)	1 (8.3)	1 (8.3)	0 (0.0)	7 (58.3)
Enterococcus spp.	8 (3.5)	3 (37.5)	0 (0.0)	0 (0.0)	1 (12.5)	4 (50.0)
L monocytogenes	5 (2.2)	2 (40.0)	0 (0.0)	1 (20.0)	0 (0.0)	2 (40.0)
S aureus	5 (2.2)	1 (20.0)	0 (0.0)	1 (20.0)	2 (40.0)	1 (20.0)
Other	29 (12.7)	10 (33.3)	3 (13.3)	3 (10.0)	1 (3.3)	12 (40.0)
Total (known organisms)	228 (100.0)	108 (47.6)	29 (12.7)	16 (7.0)	10 (4.4)	65 (28.4)
All subjects	234 (100.0)	114 (48.7)	29 (12.4)	16 (6.8)	10 (4.3)	65 (27.8)

*Identities of the causative organisms were not available for one study (6 EOS cases).
†One case with group B *Streptococcus* and *E coli* dual infection is counted in data for both pathogens.

at the initial assessment, clinical illness was apparent by 24 hours of age in 64 patients (61.5%) and by 48 hours of age in 80 patients (76.9%).

Thirty-one infants never had signs of illness. Two were treated based on risk estimates provided by the EOS Calculator.[30] For the other 29, the EOS Calculator (applied only in retrospect) would have recommended treatment in 5, blood culture for 5, frequent vital signs for 4, and routine care in 15. For the 24 infants for whom treatment would not have been recommended, it was given for maternal fever or more than 38°C (12 cases), rupture of membranes of more than 24 hours (7), encephalocele (1), group B *Streptococcus* colonization with no intrapartum prophylaxis (1), or without specified cause (3).

Discussion

With the association of the EOS Calculator with decreased use of empiric antibiotics clearly established, the primary question has become how well it performs in identifying EOS cases.[25] Using a consistent population risk estimate (0.6 per 1000 live births), the EOS Calculator recommends the administration of or strong consideration of antibiotics in 40.6% of EOS cases at the initial assessment after birth, increasing to 61.1% by 12 hours of age. Routine care was initially recommended for 103 infants with EOS (44.0%). The underlying prediction model performed better in the original data, with administration of antibiotics strictly recommended in 61% of EOS cases within 12 hours after birth.[4] Decreased performance of prediction models as they are implemented in clinical practice is common and does not imply lack of clinical utility. However, the initial assignment of more than 40% of newborns ultimately diagnosed with EOS to "routine care" indicates that vigilance is required for all newborns, not merely those identified as at risk.

The EOS Calculator involves clinical monitoring beyond the initial risk classification to ensure ascertainment of newborns who fall ill later on.[5,12,30] The optimal frequency and duration of observation needed to reliably detect such EOS cases remain uncertain.[42] We found that 88.6% of newborns who developed signs of illness after birth did so within 24 hours and 98.0% within 48 hours after birth (**Figure 3**), indicating that EOS cases not immediately allocated antibiotic therapy are likely to present within a reasonable timeframe, at which point treatment can be started. It is not possible to determine how many of the 24 persistently asymptomatic newborns with EOS would have developed signs of illness and thereby qualified for treatment had they gone without early empiric treatment; such instances could modestly increase the proportion of EOS cases identified as at risk or recommended treatment by the EOS Calculator.

Recommendations for blood cultures without antibiotic treatment did not lead to the identification of any EOS case. Among 1259 such cultures reported in the postimplementation experience, only a single case—excluded from our analysis as transient bacteremia—yielded a positive result.[12] This practice seems to have a very low yield.

Although not primary outcomes for this analysis, major short-term morbidity or mortality were described in 3 included studies.[12,34,37] Of the 118 EOS cases in those reports, all 3 infants who died and one who survived but required extracorporeal membrane oxygenation, were clinically ill at birth, so there were no reported instances of harm resulting from waiting for clinical signs to develop.[12,34,37] These potentially reassuring findings await confirmation by additional experience.

The strengths of this analysis include a comprehensive systematic search including conference proceedings and abstract databases, selective inclusion of representative birth cohorts, and rigorous collection and analysis of individual patient data with recalculation of the EOS Calculator results using consistent methodology. A prior meta-analysis focused on 1-sided disagreement between national guidelines and the EOS Calculator, included nonrepresentative cohorts, and used variable population incidence rates.[43]

Some limitations should be considered when interpreting these data. The majority of data were collected retrospectively or without actual EOS Calculator implementation, rendering the analysis for those cases hypothetical. Limiting our analysis to prospective data did not alter the results, but larger datasets are needed for confirmation. These data are aggregated from a diverse array of clinical settings and countries, and EOS Calculator performance may depend heavily on local circumstances. Our analysis is based on the arbitrary risk thresholds proposed by the EOS Calculator developers. Different thresholds would lead to different proportions of EOS cases being identified (**Table VII**). Potential contaminant cultures (eg, coagulase-negative *Staphylococcus*) were excluded from this analysis only if considered nonpathogenic by the original authors; a stricter exclusion of (potentially) spurious cases may increase the proportion of EOS cases identified as at risk or recommended treatment by the EOS Calculator. Finally, the available data are limited to results in subjects ultimately determined to have the disease in question, and corresponding risk estimates for the disease-free remainder of the population are not available, precluding robust methods. This analysis therefore is essentially observational in nature.

The EOS Calculator is increasingly being adopted and endorsed by professional societies. Our findings carry some important implications for clinical practice. First, when considering adoption of the EOS Calculator, clinicians and policy makers should evaluate the (expected) allocation of EOS to categories, and relate this to the (expected) reduction in empiric antibiotics. If, as our meta-analysis demonstrates, almost 41% of EOS cases are initially categorized as low risk, clinicians should be aware of this, and be cautious of a false sense of security.

Second, the EOS Calculator workflows should include at least 24 hours of clinical observation, because the vast

majority of EOS cases present within this timeframe. Because a substantial portion of EOS cases occur in low-risk, well-appearing infants, clinical vigilance should be universal, regardless of individual estimated risks. Whether this requires in-hospital observation or can be achieved with early discharge or home births with parent instruction and/or observation by healthcare providers at home may depend heavily on local circumstances and healthcare system organization; this factor requires further study.

Third, because 84% of the EOS cases assigned to receive antibiotics at initial assessment were already clinically ill, the recommendation of antibiotics by the EOS Calculator seems to lean heavily on signs of clinical illness. This finding suggests that the EOS Calculator paradigm is akin to approaches primarily dependent on physical examination, such as serial physical examinations.[35,44,45]

Finally, the EOS Calculator should be evaluated in the context of alternative approaches, be they more categorical (such as guidelines from the Centers for Disease Control and Prevention[46] or the National Institute for Health and Care Excellence[47]), or more focused on clinical signs (such as serial examinations).[35,44,45] Relevant data collected by Goel et al indicate that National Institute for Health and Care Excellence guidelines lead to 4-fold greater us of empiric antibiotics compared with the EOS Calculator, whereas antibiotics were started immediately in 3 of 6 EOS cases according to either strategy.[33] Strategies based on serial examinations (or frequent vital signs) have been found to reduce diagnostic testing and antibiotic use,[35,44,45] but prospective comparisons with calculator-based strategies in clinical practice are lacking. We recommend more comparisons between the EOS Calculator and alternative approaches, with detailed clinical follow-up, including re-admissions for sepsis.

In conclusion, in this large-scale individual patient meta-analysis from EOS cases derived from birth cohorts of newborns 34 or more weeks of gestation, the EOS Calculator application resulted in initial assignments to administration or strong consideration of empiric antibiotics for 40.6%, more frequent vital signs for 15.4%, and routine care for 44.0% of EOS cases. By 12 hours of age, these proportions change to 61.1%, 11.1%, and 27.8%, respectively. Most newborns with EOS presented with signs of illness within 24 hours after birth. Decisions regarding implementation of the EOS Calculator should consider these proportions in the context of local circumstances. Clinical vigilance remains essential for all newborns. Future studies should compare multiple strategies and involve careful monitoring and follow-up. ■

We thank Drs Vrinda Arora and Preetha Prazad (Park Ridge, IL), Surichhya Bajracharya (Brooklyn, NY), Ashley Fischer (Peoria, IL), Nyles Fowler and Joseph Kaempf (Portland, OR), Nitin Goel (Cardiff, Wales), Michael Hall (Southampton, UK), Gretchen Kopec (Cleveland, OH), Michael Kuzniewicz (Oakland, CA), Rachel Morris and Jean Matthes (Bath, UK), Eduardo Perez (Frisco, TX), Renato Procianoy (Porto Alegre, Brazil), Vinay Sharma (Minneapolis MN), Tobias Strunk (Perth, Australia), and Ajay Talati (Memphis, TN) for providing additional patient data.

Submitted for publication Nov 19, 2020; last revision received Dec 28, 2020; accepted Jan 27, 2021.

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Data Statement

Data sharing statement available at www.jpeds.com.

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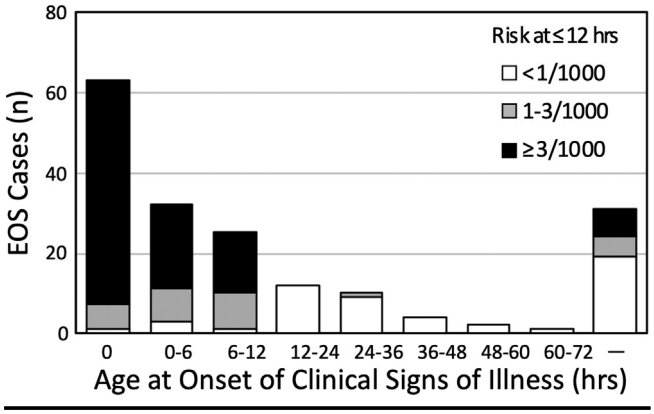

Figure 3. Age at onset of clinical signs in EOS, by estimated risk within 12 hours after birth. Data for 180 cases for which ages at onset are known. (—: Infants who did not develop signs of illness.)

Table II. Cases of transient bacteremia (excluded from analysis)

Organism	Gestational age (weeks)	Highest maternal temp (°C)	Maternal GBS status	ROM (h)	Maternal antibiotics and timing	Clinical status at initial assessment	Calculator risk at initial assessment (cases/1000)	Age at onset of clinical illness (h)	Repeat blood culture before treatment	Age at treatment (h)
E coli	$40^{3/7}$	36.8	Negative	51.1	None or <2 h	Well	0.11	—	Not done	37.6
GBS	$37^{0/7}$	36.7	Positive	0	None or <2 h	Well	0.04	—	Not done	33.2
E coli	$38^{2/7}$	38.6	Negative	11.7	None or <2 h	Well	0.99	—	Not done	40
GBS	$37^{2/7}$	37.2	Positive	22.8	None or <2 h	Well	0.36	—	Not done	30.3
GBS	$37^{0/7}$	36.3	Negative	9.7	None or <2 h	Well	0.04	—	Not done	25.4
K pneumoniae	$40^{5/7}$	36.8	Negative	17.9	None or <2 h	Well	0.07	20	Negative	49.1
E coli	$39^{0/7}$	37.6	Negative	13.2	None or <2 h	Equivocal	2.38	—	Negative	26.8
GBS	$41^{2/7}$	39.1	Positive	12.9	None or <2 h	Well	4.58	—	Negative	27.5
E coli	$40^{3/7}$	38.0	Negative	7.1	None or <2 h	Well	0.30	36	Negative	101

GBS, group B *Streptococcus*; *ROM*, rupture of membranes.

Table III. All EOS cases

Organism	Gestational age (wk)	Highest maternal temp (°C)	Maternal GBS status	ROM (h)	Maternal antibiotics and timing	Clinical status at initial assessment	Clinical status in first 12 h	Age at onset of clinical signs (h)	Calculator risk at initial assessment (cases/1000)	Calculator risk at 12 h (cases/1000)	Management recommended at birth	Management recommended at 12 h
Other	$40^{3/7}$	36.3	Unknown	0	None or <2 h	Well	Well	NR	0.01	0.01	Routine	Routine
E coli	$41^{2/7}$	36.4	Negative	0	None or <2 h	Well	III	3	0.01	0.50	Routine	Strongly
GBS	$38^{5/7}$	35.7	Unknown	10	None or <2 h	Well	III	3	0.01	0.50	Routine	Strongly
GBS	$39^{4/7}$	36.7	Unknown	0	None or <2 h	Well	III	11	0.01	0.63	Routine	Strongly
CoNS	$39^{1/7}$	36.7	Unknown	7	GBS abx >2 h	Well	Well	NR	0.01	0.01	Routine	Routine
Bacillus spp, CoNS	$38^{6/7}$	36.5	Negative	1.43	None or <2 h	Well	Well	50	0.02	0.02	Routine	Routine
E coli	$37^{5/7}$	37.1	Unknown	1	GBS abx >2 h	Well	Well	NR	0.02	0.02	Routine	Routine
L monocytogenes	$39^{0/7}$	37.0	Unknown	0	None or <2 h	Well	Well	16	0.02	0.02	Frequent VS	Routine
GBS	$41^{0/7}$	36.2	Negative	7	None or <2 h	Well	Well	1	0.02	0.02	Routine	Routine
Enterococcus spp	$40^{0/7}$	36.2	Negative	12.2	None or <2 h	Well	Well	48	0.02	0.02	Routine	Routine
GBS	$41^{6/7}$	36.1	Unknown	6	None or <2 h	Well	III	9	0.02	1.18	Frequent VS	Strongly
GBS	$40^{2/7}$	36.8	Unknown	1.6	None or <2 h	Well	III	6	0.03	1.53	Frequent VS	Strongly
GBS	$39^{3/7}$	36.6	Negative	6	None or <2 h	Well	III	5	0.03	1.53	Frequent VS	Strongly
L monocytogenes	$36^{0/7}$	36.6	Unknown	0	None or <2 h	Well	Well	15	0.03	0.03	Frequent VS	Routine
GBS	$40^{3/7}$	36.7	Unknown	4	None or <2 h	Well	III	7	0.03	1.75	Frequent VS	Strongly
GBS	$39^{0/7}$	37.0	Positive	0	None or <2 h	Well	Well	14.5	0.03	0.03	Frequent VS	Routine
GBS	$39^{0/7}$	36.6	Unknown	8	None or <2 h	Well	III	7	0.04	1.81	Frequent VS	Strongly
GBS	$40^{5/7}$	36.9	Unknown	1.8	None or <2 h	Well	III	10	0.04	1.98	Frequent VS	Strongly
GBS	$39^{5/7}$	36.8	Unknown	5	None or <2 h	Well	III	7	0.04	2.06	Frequent VS	Strongly
VGS	$38^{5/7}$	36.7	Unknown	8.0	None or <2 h	Well	Well	14	0.04	0.04	Frequent VS	Routine
CoNS	$39^{2/7}$	37.0	Negative	3	None or <2 h	Well	Well	NR	0.04	0.04	Routine	Routine
GBS	$39^{0/7}$	36.9	Negative	5	None or <2 h	Well	III	12	0.05	2.35	Frequent VS	Strongly
GBS	$38^{1/7}$	36.0	Unknown	79	None or <2 h	Well	III	7	0.05	2.41	Frequent VS	Strongly
GBS	$38^{4/7}$	36.8	Unknown	7	None or <2 h	Well	Well	22	0.05	0.05	Frequent VS	Routine
Other	$36^{4/7}$	36.8	Negative	1	None or <2 h	Well	Well	NR	0.05	0.05	Routine	Routine
GBS	$37^{3/7}$	37.0	Unknown	1	None or <2 h	Well	Well	—	0.05	0.05	Routine	Routine
GBS	$41^{3/7}$	36.7	Negative	8.3	None or <2 h	Well	III	9	0.05	2.76	Frequent VS	Strongly
E coli	$40^{6/7}$	36.7	Unknown	12	None or <2 h	Well	III	1	0.05	2.83	Frequent VS	Strongly
GBS	$37^{4/7}$	36.8	Unknown	5	None or <2 h	Well	III	1	0.06	2.86	Frequent VS	Strongly
GBS	$39^{4/7}$	37.0	Unknown	5.5	None or <2 h	Well	Well	36	0.06	0.06	Routine	Routine
Enterococcus spp	$39^{5/7}$	37.0	Unknown	6	None or <2 h	Well	Well	37	0.06	0.06	Routine	Routine
GBS	$40^{4/7}$	36.7	Negative	19	None or <2 h	Well	Well	—	0.06	0.06	Routine	Routine
GBS	$38^{0/7}$	37.0	Unknown	4	None or <2 h	Well	Well	52	0.06	0.06	Routine	Routine
GBS	$39^{0/7}$	37.2	Negative	3	None or <2 h	Well	III	5	0.06	3.19	Frequent VS	Treat
Other	$39^{0/7}$	37.3	Negative	2	None or <2 h	Well	Well	NR	0.06	3.31	Routine	Routine
GBS	$39^{1/7}$	37.2	Negative	3.5	None or <2 h	Well	III	6	0.06	0.06	Frequent VS	Treat
Moraxella	$38^{2/7}$	36.6	Positive	8	None or <2 h	Well	III	12	0.07	3.45	Frequent VS	Treat
GBS	$38^{0/7}$	36.9	Unknown	9	None or <2 h	Well	III	12	0.07	3.62	Frequent VS	Treat
GBS	$41^{5/7}$	36.9	Unknown	5	None or <2 h	Well	Well	24	0.07	0.07	Frequent VS	Routine
E coli	$39^{3/7}$	36.8	Negative	28	None or <2 h	Well	Well	NR	0.08	3.80	Routine	Routine
S aureus	$40^{6/7}$	36.6	Negative	36	None or <2 h	Well	III	6	0.07	3.85	Frequent VS	Treat
GBS	$36^{6/7}$	36.7	Unknown	8	None or <2 h	Well	III	6	0.07	3.87	Frequent VS	Treat
GBS	$38^{6/7}$	36.9	Unknown	16	None or <2 h	Well	III	8	0.08	0.08	Frequent VS	Treat
GBS	$40^{2/7}$	36.8	Unknown	23	None or <2 h	Well	III	6	0.08	0.08	Frequent VS	Treat
GBS	$42^{0/7}$	36.8	Unknown	7	None or <2 h	Well	III	11	0.08	3.93	Frequent VS	Treat
Other	$39^{2/7}$	37.2	Negative	6	None or <2 h	Well	Well	NR	0.08	3.94	Routine	Routine
GBS	$38^{6/7}$	36.7	Unknown	36	None or <2 h	Well	III	5	0.08	4.11	Frequent VS	Treat
GBS	$36^{1/7}$	37.3	Unknown	0	None or <2 h	Well	Well	44	0.09	0.09	Routine	Routine

(*continued*)

Table III. Continued

Organism	Gestational age (wk)	Highest maternal temp (°C)	Maternal GBS status	ROM (h)	Maternal antibiotics and timing	Clinical status at initial assessment	Clinical status in first 12 h	Age at onset of clinical signs (h)	Calculator risk at initial assessment (cases/1000)	Calculator risk at 12 h (cases/1000)	Management recommended at birth	Management recommended at 12 h
GBS	$36^{4/7}$	36.8	Unknown	5	None or <2 h	Well	Well	36	0.09	0.09	Routine	Routine
GBS	$38^{6/7}$	37.0	Unknown	16	None or <2 h	Well	Well	36	0.09	0.09	Routine	Routine
GBS	$41^{0/7}$	37.1	Positive	27	Broad abx 2-4 h	Well	Well	—	0.09	0.09	Routine	Routine
E coli	$41^{2/7}$	38.0	Unknown	3.1	GBS abx >2 h	Well	III	10	0.10	5.27	Frequent VS	Treat
GBS	$38^{0/7}$	37.2	Unknown	8	None or <2 h	Well	Well	16	0.11	0.11	Frequent VS	Routine
CoNS	$38^{4/7}$	37.2	Negative	13	None or <2 h	Well	Well	NR	0.11	0.11	Routine	Routine
S aureus	$35^{6/7}$	37.1	Unknown	17	GBS abx >2 h	Well	Well	NR	0.12	0.12	Routine	Routine
CoNS	$39^{2/7}$	37.5	Negative	6	None or <2 h	Well	Well	NR	0.12	0.12	Routine	Routine
GBS	$40^{0/7}$	37.4	Unknown	8.8	None or <2 h	Well	Well	—	0.13	0.13	Routine	Routine
GBS	$37^{2/7}$	37.1	Unknown	12	None or <2 h	Well	III	12	0.14	6.97	Frequent VS	Treat
GBS	$40^{0/7}$	37.4	Positive	50	Broad abx ≥4 h	Well	Well	—	0.14	0.14	Routine	Routine
E coli	$38^{6/7}$	37.8	Positive	9.5	GBS abx >2 h	Well	III	12	0.15	7.61	Frequent VS	Treat
GBS	$37^{3/7}$	37.2	Negative	14.8	None or <2 h	Well	Well	36	0.16	0.15	Routine	Routine
Other	$38^{0/7}$	36.6	Negative	0	None or <2 h	Equivocal	Equivocal	NR	0.15	0.16	Routine	Routine
VGS	$41^{1/7}$	37.7	Negative	2.4	None or <2 h	Well	Well	40	0.16	0.16	Routine	Routine
GBS	$37^{5/7}$	37.2	Unknown	17	None or <2 h	Well	Well	64	0.16	0.16	Routine	Routine
E coli	$37^{5/7}$	37.4	Unknown	8	None or <2 h	Well	III	12	0.16	8.20	Frequent VS	Treat
CoNS	$41^{1/7}$	38.0	Negative	14	Broad abx 2-4 h	Well	Well	NR	0.16	0.16	Routine	Routine
GBS	$38^{4/7}$	37.4	Unknown	16	None or <2 h	Well	Well	25	0.17	0.17	Routine	Routine
GBS	$38^{4/7}$	37.8	Unknown	3	None or <2 h	Well	Equivocal	5	0.17	2.12	Frequent VS	Blood culture
GBS	$37^{4/7}$	37.1	Negative	33	None or <2 h	Well	Well	24	0.18	0.18	Frequent VS	Routine
CoNS	$40^{1/7}$	36.5	Negative	1	None or <2 h	Equivocal	Equivocal	21	0.19	0.19	Routine	Routine
GBS	$40^{2/7}$	37.4	Unknown	22	None or <2 h	Well	Well	14	0.19	0.19	Frequent VS	Routine
GBS	$36^{0/7}$	36.6	Unknown	36	None or <2 h	Well	Well	—	0.20	0.20	Routine	Routine
GBS	$41^{0/7}$	37.3	Negative	27.6	None or <2 h	Well	III	3	0.20	10.23	Frequent VS	Treat
E coli	$35^{5/7}$	36.8	Unknown	14	None or <2 h	Well	Well	26	0.21	0.21	Routine	Routine
GBS	$41^{3/7}$	37.5	Unknown	10	None or <2 h	Well	Well	—	0.21	0.21	Routine	Routine
Other	$38^{4/7}$	36.9	Unknown	0	None or <2 h	Equivocal	Equivocal	NR	0.22	11.13	Routine	Routine
GBS	$37^{5/7}$	37.2	Unknown	34	None or <2 h	Well	III	6	0.22	0.22	Frequent VS	Treat
VGS	$41^{0/7}$	38.3	Negative	11.5	Broad abx 2-4 h	Well	Well	—	0.23	0.22	Routine	Routine
Other	$37^{3/7}$	37.2	Unknown	29	None or <2 h	Well	Well	NR	0.22	0.23	Routine	Routine
Other	$40^{5/7}$	39.3	Negative	0	GBS abx >2 h	Well	Well	NR	0.27	0.27	Routine	Routine
VGS	$41^{3/7}$	37.4	Negative	29.1	None or <2 h	Well	Well	—	0.27	0.27	Routine	Routine
GBS	$40^{5/7}$	37.3	Negative	59	None or <2 h	Well	Well	—	0.28	0.28	Routine	Routine
GBS	$40^{2/7}$	36.7	Unknown	2	None or <2 h	Equivocal	III	3	0.33	1.40	Frequent VS	Strongly
E coli	$41^{0/7}$	38.3	Unknown	25	Broad abx 2-4 h	Well	Well	—	0.33	0.33	Routine	Routine
GBS	$39^{0/7}$	38.3	Positive	0.2	None or <2 h	Well	Well	—	0.34	0.34	Routine	Routine
E coli	$41^{4/7}$	38.2	Negative	1.4	None or <2 h	Well	Well	—	0.34	0.34	Routine	Routine
E coli	$40^{0/7}$	36.3	Unknown	0	None or <2 h	III	III	0	0.35	0.35	Strongly	Strongly
GBS	$39^{2/7}$	37.9	Positive	49	GBS abx >2 h	Well	Well	—	0.35	0.35	Routine	Routine
GBS	$38^{3/7}$	37.9	Negative	14.7	None or <2 h	Well	III	4.5	0.35	17.96	Frequent VS	Treat
Other	$37^{6/7}$	36.5	Unknown	4	None or <2 h	Equivocal	Equivocal	NR	0.36	0.36	Routine	Routine
CoNS	$39^{5/7}$	37.9	Unknown	20	None or <2 h	Well	Well	NR	0.38	0.38	Routine	Routine
GBS	$40^{0/7}$	38.3	Positive	0.4	None or <2 h	Well	Well	24	0.38	0.38	Routine	Routine
E coli	$37^{6/7}$	38.1	Positive	22	GBS abx >2 h	Well	Well	NR	0.41	0.41	Routine	Enhanced
GBS	$40^{1/7}$	38.3	Positive	1	None or <2 h	Well	Well	15	0.46	0.46	Frequent VS	Enhanced
E coli	$40^{3/7}$	38.1	Negative	16	None or <2 h	Well	Well	NR	0.48	0.48	Routine	Enhanced
GBS	$38^{1/7}$	36.5	Negative	14	None or <2 h	Equivocal	III	9.0	0.50	2.14	Frequent VS	Strongly

(*continued*)

Table III. Continued

Organism	Gestational age (wk)	Highest maternal temp (°C)	Maternal GBS status	ROM (h)	Maternal antibiotics and timing	Clinical status at initial assessment	Clinical status in first 12 h	Age at onset of clinical signs (h)	Calculator risk at initial assessment (cases/1000)	Calculator risk at 12 h (cases/1000)	Management recommended at birth	Management recommended at 12 h
VGS	$41^{0/7}$	38.8	Unknown	15	Broad abx ≥4 h	Well	Well	—	0.51	0.51	Routine	Enhanced
E faecalis	$41^{6/7}$	37.9	Negative	16	None or <2 h	Well	Well	NR	0.53	0.53	Routine	Enhanced
GBS	$38^{5/7}$	37.9	Unknown	38	None or <2 h	Well	Well	—	0.55	0.55	Routine	Enhanced
S aureus	$40^{5/7}$	38.4	Negative	7	None or <2 h	Well	Well	NR	0.59	2.49	Routine	Enhanced
GBS	$38^{6/7}$	36.9	Unknown	5	None or <2 h	Equivocal	III	2	0.59	0.59	Frequent VS	Strongly
VGS	$38^{2/7}$	36.8	Negative	7.1	None or <2 h	Equivocal	Equivocal	24.5	0.60	0.59	Routine	Routine
Other	$34^{4/7}$	37.1	Unknown	65	GBS abx >2 h	Well	Well	NR	0.59	0.60	Routine	Enhanced
E faecalis	$38^{5/7}$	36.5	Unknown	25	None or <2 h	Equivocal	Equivocal	NR	0.61	0.61	Routine	Routine
GBS	$38^{3/7}$	36.8	Negative	8.9	None or <2 h	Equivocal	Equivocal	33.9	0.63	0.63	Routine	Routine
Other	$37^{4/7}$	36.8	Negative	6	None or <2 h	Equivocal	Equivocal	NR	0.69	0.69	Routine	Routine
Enterococcus spp	$37^{0/7}$	36.6	Negative	8.1	None or <2 h	Equivocal	Equivocal	—	0.70	0.70	Routine	Routine
GBS	$37^{3/7}$	36.5	Negative	19	None or <2 h	Equivocal	III	3	0.71	3.02	Frequent VS	Treat
GBS	$38^{2/7}$	38.2	Unknown	22	None or <2 h	Well	Well	—	0.72	0.72	Routine	Enhanced
GBS	$38^{0/7}$	37.1	Negative	3.1	None or <2 h	Equivocal	Equivocal	27.6	0.78	0.78	Routine	Routine
E coli	$36^{5/7}$	37.2	Unknown	14	Broad abx ≥4 h	Equivocal	Equivocal	NR	0.81	0.81	Routine	Routine
Other	$38^{5/7}$	37.1	Negative	6	None or <2 h	Equivocal	Equivocal	NR	0.84	0.84	Routine	Routine
S aureus	$42^{3/7}$	38.3	Unknown	59	Broad abx 2-4 h	Well	Well	—	0.89	0.89	Routine	Enhanced
GBS	$37^{3/7}$	36.7	Negative	17.1	None or <2 h	Equivocal	III	6.9	0.93	3.94	Frequent VS	Treat
S aureus	$40^{5/7}$	37.0	Negative	13	None or <2 h	Equivocal	Equivocal	NR	1.02	1.02	Blood culture	Blood culture
Other	$37^{2/7}$	37.0	Negative	6	None or <2 h	Equivocal	Equivocal	NR	1.05	1.05	Blood culture	Blood culture
GBS	$35^{6/7}$	37.0	Positive	83	None or <2 h	Well	Well	33	1.07	1.07	Blood culture	Blood culture
GBS	$39^{1/7}$	37.2	Unknown	8	None or <2 h	Equivocal	III	3	1.08	4.57	Blood culture	Treat
GBS	$40^{4/7}$	37.0	Unknown	15	None or <2 h	Equivocal	III	1	1.10	4.65	Blood culture	Treat
GBS	$42^{2/7}$	38.5	Unknown	63	GBS abx >2 h	Well	Well	—	1.18	1.18	Blood culture	Blood culture
GBS	$39^{3/7}$	37.1	Negative	17.68	None or <2 h	Equivocal	III	4	1.20	5.08	Blood culture	Treat
E coli	$39^{5/7}$	38.9	Negative	9	None or <2 h	Well	Well	NR	1.25	5.20	Blood culture	Blood culture
GBS	$38^{4/7}$	37.1	Unknown	14	None or <2 h	Equivocal	III	10	1.23	1.25	Blood culture	Treat
Other	$37^{0/7}$	36.8	Unknown	0	None or <2 h	III	III	NR	1.29	1.29	Strongly	Strongly
CoNS	$34^{4/7}$	36.9	Unknown	2	GBS abx >2 h	Equivocal	Equivocal	NR	1.29	1.29	Blood culture	Blood culture
VGS	$36^{6/7}$	36.8	Negative	0	None or <2 h	III	III	0	1.32	1.32	Strongly	Strongly
E coli	$39^{0/7}$	39.5	Unknown	14.0	GBS abx >2 h	Well	III	12	1.42	68.62	Blood culture	Treat
GBS	$39^{6/7}$	39.0	Positive	27	Broad abx 2-4 h	Well	Well	—	1.46	1.46	Blood culture	Blood culture
GBS	$41^{0/7}$	37.3	Negative	9	None or <2 h	Equivocal	III	3	1.51	6.38	Blood culture	Treat
GBS	$39^{5/7}$	37.5	Negative	7.37	None or <2 h	Equivocal	III	8	1.59	6.71	Blood culture	Treat
E coli	$40^{0/7}$	39.0	Negative	12.3	None or <2 h	Well	Well	—	1.68	1.68	Blood culture	Blood culture
GBS	$40^{1/7}$	37.4	Negative	6	Broad abx ≥4 h	III	III	0	1.69	1.69	Strongly	Strongly
Other	$39^{0/7}$	36.7	Negative	5	None or <2 h	III	III	NR	1.72	1.72	Strongly	Strongly
CoNS	$40^{1/7}$	36.8	Positive	13.78	GBS abx >2 h	III	III	0	1.85	1.85	Strongly	Strongly
L monocytogenes	$35^{3/7}$	39.2	Unknown	1.7	GBS abx >2 h	Well	Well	—	1.86	1.86	Blood culture	Blood culture
Other	$37^{0/7}$	36.6	Negative	2	None or <2 h	III	III	NR	1.90	1.90	Strongly	Strongly
GBS	$42^{0/7}$	37.0	Unknown	20	None or <2 h	Equivocal	III	1	1.94	8.17	Blood culture	Treat
VGS	$40^{1/7}$	37.4	Unknown	0	None or <2 h	III	III	0	1.95	1.95	Strongly	Strongly
GBS	$34^{2/7}$	37.0	Unknown	72	None or <2 h	Well	Well	—	1.97	1.97	Blood culture	Blood culture
GBS	$36^{3/7}$	37.2	Negative	5.3	None or <2 h	Equivocal	III	7.3	2.04	8.61	Blood culture	Treat
E coli	$36^{4/7}$	37.2	Negative	10	None or <2 h	Equivocal	Equivocal	NR	2.39	9.75	Blood culture	Blood culture
GBS	$36^{0/7}$	37.0	Unknown	8	None or <2 h	Equivocal	III	3	2.32	2.33	Blood culture	Treat
GBS	$39^{5/7}$	37.0	Negative	3.18	None or <2 h	III	III	0	2.33	2.37	Strongly	Strongly
GBS	$40^{3/7}$	36.9	Negative	4.4	None or <2 h	III	III	0	2.37	2.39	Strongly	Strongly

(*continued*)

Table III. Continued

Organism	Gestational age (wk)	Highest maternal temp (°C)	Maternal GBS status	ROM (h)	Maternal antibiotics and timing	Clinical status at initial assessment	Clinical status in first 12 h	Age at onset of clinical signs (h)	Calculator risk at initial assessment (cases/1000)	Calculator risk at 12 h (cases/1000)	Management recommended at birth	Management recommended at 12 h
GBS	$40^{2/7}$	37.0	Unknown	84	None or <2 h	Equivocal	III	1	2.50	10.51	Blood culture	Treat
Other	$37^{0/7}$	39.1	Negative	7	None or <2 h	Well	Well	NR	2.71	2.71	Blood culture	Blood culture
Other	$36^{5/7}$	37.6	Negative	3	None or <2 h	Equivocal	Equivocal	NR	2.75	2.75	Blood culture	Blood culture
VGS	$40^{1/7}$	37.8	Negative	9.5	None or <2 h	Equivocal	Equivocal	NR	2.87	2.87	Blood culture	Blood culture
E coli	$36^{1/7}$	37.3	Unknown	58.08	GBS abx >2 h	Equivocal	Equivocal	5	2.94	2.94	Blood culture	Blood culture
GBS	$39^{5/7}$	36.9	Negative	10	None or <2 h	III	III	NR	2.96	2.96	Strongly	Strongly
GBS	$42^{2/7}$	37.3	Unknown	14	None or <2 h	Equivocal	Equivocal	—	3.03	3.03	Treat	Treat
GBS	$39^{4/7}$	37.8	Negative	13	None or <2 h	Equivocal	III	6	3.15	13.21	Treat	Treat
E coli	$40^{0/7}$	39.4	Negative	14	None or <2 h	Well	Well	10	3.31	3.31	Treat	Treat
GBS	$38^{6/7}$	36.8	Unknown	16	None or <2 h	III	III	0	3.31	3.31	Treat	Treat
GBS	$40^{2/7}$	37.6	Unknown	26	None or <2 h	Equivocal	III	3	3.43	14.37	Treat	Treat
Bacillus spp	$37^{1/7}$	37.0	Unknown	2	None or <2 h	III	III	0	3.48	3.48	Treat	Treat
E coli	$39^{2/7}$	37.5	Unknown	18.8	GBS abx >2 h	III	III	0	3.59	3.59	Treat	Treat
GBS	$41^{4/7}$	36.7	Negative	15.2	None or <2 h	III	III	0	3.68	3.68	Treat	Treat
GBS	$36^{3/7}$	37.2	Negative	24.2	None or <2 h	Equivocal	Equivocal	—	3.74	3.74	Treat	Treat
GBS	$38^{4/7}$	37.1	Unknown	6	None or <2 h	III	III	0	3.77	3.77	Treat	Treat
GBS	$41^{0/7}$	37.4	Unknown	1	None or <2 h	III	III	0	4.01	4.01	Treat	Treat
GBS	$40^{2/7}$	37.1	Negative	9	None or <2 h	III	III	NR	4.07	4.07	Treat	Treat
Oral flora	$39^{3/7}$	37.0	Negative	15.75	None or <2 h	III	III	0	4.14	4.14	Treat	Treat
GBS	$38^{0/7}$	39.3	Negative	25.5	None or <2 h	Well	III	6	4.42	4.31	Treat	Treat
VGS	$38^{5/7}$	39.5	Negative	16.6	None or <2 h	Well	Well	12	4.31	4.35	Treat	Treat
GBS	$40^{4/7}$	37.0	Unknown	12.75	None or <2 h	III	III	0	4.35	186.69	Treat	Treat
GBS	$40^{5/7}$	37.3	Unknown	3.5	None or <2 h	III	III	0	4.50	4.50	Treat	Treat
GBS	$41^{3/7}$	36.9	Unknown	12	None or <2 h	III	III	0	4.54	4.51	Treat	Treat
VGS	$38^{2/7}$	37.0	Negative	14.25	None or <2 h	III	III	0	4.53	4.51	Treat	Treat
L monocytogenes	$39^{6/7}$	37.1	Negative	13	None or <2 h	III	III	NR	4.51	4.53	Treat	Treat
L monocytogenes	$39^{6/7}$	37.1	Negative	13	None or <2 h	III	III	NR	4.51	4.54	Treat	Treat
GBS	$37^{0/7}$	37.7	Unknown	11	None or <2 h	Equivocal	III	5	4.59	19.16	Treat	Treat
GBS	$41^{0/7}$	37.1	Unknown	10	None or <2 h	III	III	0	5.08	5.08	Treat	Treat
E coli	$36^{1/7}$	37.0	Negative	1.83	None or <2 h	III	III	0	5.39	5.38	Treat	Treat
Group G *Streptococcus*	$39^{6/7}$	36.9	Negative	40.98	None or <2 h	III	III	0	5.58	5.39	Treat	Treat
E coli	$40^{1/7}$	39.3	Negative	53	None or <2 h	Well	Well	—	5.38	5.58	Treat	Treat
Not specified	$37^{6/7}$	37.0	Negative	21	None or <2 h	III	III	0	5.97	5.97	Treat	Treat
GBS	$38^{1/7}$	37.1	Unknown	16	None or <2 h	III	III	NR	6.00	5.98	Treat	Treat
GBS	$40^{2/7}$	37.2	Negative	16	None or <2 h	III	III	0	5.98	6.00	Treat	Treat
GBS	$37^{0/7}$	37.0	Negative	12	None or <2 h	III	III	NR	6.45	6.45	Treat	Treat
VGS	$41^{4/7}$	37.1	Unknown	12	None or <2 h	III	III	0	6.50	6.50	Treat	Treat
E coli	$41^{4/7}$	39.7	Negative	10.5	None or <2 h	Well	Well	—	6.63	6.63	Treat	Treat
GBS	$42^{1/7}$	39.4	Unknown	17	None or <2 h	Well	Well	—	6.67	6.67	Treat	Treat
GBS	$38^{3/7}$	36.8	Unknown	63	None or <2 h	III	III	0	6.90	6.78	Treat	Treat
E coli	$41^{0/7}$	37.2	Unknown	14	None or <2 h	III	III	NR	6.78	6.90	Treat	Treat
GBS	$37^{2/7}$	37.2	Unknown	9	None or <2 h	III	III	0	7.28	7.28	Treat	Treat
Other	$39^{5/7}$	37.3	Negative	22	None or <2 h	III	III	NR	7.65	7.53	Treat	Treat
E coli	$41^{4/7}$	37.2	Negative	13.1	None or <2 h	III	III	0	7.53	7.59	Treat	Treat
VGS	$40^{3/7}$	37.0	Unknown	45	None or <2 h	III	III	0	7.59	7.64	Treat	Treat
GBS + *E coli*	$40^{6/7}$	37.3	Negative	15.45	None or <2 h	III	III	0	7.64	7.65	Treat	Treat
Other	$41^{0/7}$	37.4	Unknown	9	None or <2 h	III	III	NR	7.77	7.71	Treat	Treat
E coli	$39^{5/7}$	38.2	Negative	9.52	GBS abx >2 h	III	III	0	7.71	7.77	Treat	Treat

(*continued*)

Table III. Continued

Organism	Gestational age (wk)	Highest maternal temp (°C)	Maternal GBS status	ROM (h)	Maternal antibiotics and timing	Clinical status at initial assessment	Clinical status in first 12 h	Age at onset of clinical signs (h)	Calculator risk at initial assessment (cases/1000)	Calculator risk at 12 h (cases/1000)	Management recommended at birth	Management recommended at 12 h
CoNS	$38^{2/7}$	37.4	Negative	13	None or <2 h	III	III	NR	8.12	8.12	Treat	Treat
GBS	$38^{0/7}$	36.9	Unknown	60	None or <2 h	III	III	0	8.65	8.65	Treat	Treat
VGS	$36^{4/7}$	37.2	Negative	6.8	None or <2 h	III	III	0	8.72	8.72	Treat	Treat
GBS	$37^{3/7}$	37.1	Unknown	23	None or <2 h	III	III	NR	8.72	8.72	Treat	Treat
VGS	$35^{3/7}$	37.5	Unknown	0	None or <2 h	III	III	0	9.52	9.52	Treat	Treat
GBS	$35^{1/7}$	36.8	Unknown	45	GBS abx >2 h	III	III	0	9.75	9.75	Treat	Treat
GBS	$42^{1/7}$	37.2	Unknown	13	None or <2 h	III	III	0	9.87	9.87	Treat	Treat
GBS	$37^{6/7}$	37.5	Unknown	10	None or <2 h	III	III	NR	9.94	9.94	Treat	Treat
E coli	$36^{1/7}$	37.1	Negative	8.6	None or <2 h	III	III	0	10.31	10.31	Treat	Treat
CoNS	$34^{1/7}$	37.0	Negative	0	None or <2 h	III	III	NR	12.17	12.17	Treat	Treat
VGS	$35^{0/7}$	37.0	Unknown	2	None or <2 h	III	III	0	12.62	12.62	Treat	Treat
VGS	$38^{5/7}$	37.6	Negative	22.6	None or <2 h	III	III	0	13.01	13.01	Treat	Treat
E coli	$38^{6/7}$	37.6	Negative	25	None or <2 h	III	III	0	13.36	13.36	Treat	Treat
Enterococcus spp	$41^{0/7}$	37.8	Unknown	8	None or <2 h	III	III	0	13.81	13.81	Treat	Treat
E coli	$38^{1/7}$	38.1	Negative	2.5	None or <2 h	III	III	0	14.10	14.10	Treat	Treat
GBS	$36^{2/7}$	37.3	Unknown	12	None or <2 h	III	III	0	15.26	15.26	Treat	Treat
E coli	$41^{6/7}$	37.5	Negative	18.2	None or <2 h	III	III	0	15.34	15.34	Treat	Treat
Not specified	$39^{0/7}$	38.0	Negative	12	None or <2 h	III	III	0	17.82	17.82	Treat	Treat
GBS	$37^{5/7}$	37.2	Unknown	89	None or <2 h	III	III	0	18.70	18.70	Treat	Treat
GBS	$40^{0/7}$	38.3	Unknown	50	GBS abx >2 h	III	III	0	20.10	20.10	Treat	Treat
GBS	$35^{4/7}$	37.0	Negative	27	None or <2 h	III	III	0	20.41	20.41	Treat	Treat
E coli	$41^{1/7}$	39.1	Positive	17.1	GBS abx >2 h	Equivocal	Equivocal	—	20.74	20.74	Treat	Treat
Enterococcus spp	$39^{1/7}$	38.7	Negative	25.5	Broad abx ≥4 h	III	III	0	22.18	22.18	Treat	Treat
GBS	$37^{1/7}$	38.9	Negative	8	None or <2 h	Equivocal	Equivocal	NR	23.44	23.36	Treat	Treat
GBS	$41^{6/7}$	37.8	Unknown	15	None or <2 h	III	III	0	23.36	23.44	Treat	Treat
H influenzae	$40^{2/7}$	38.5	Unknown	62	Broad abx 2-4 h	III	III	0	31.53	31.53	Treat	Treat
CoNS	$39^{4/7}$	39.4	Negative	11	None or <2 h	Equivocal	Equivocal	NR	34.72	34.72	Treat	Treat
H influenzae	$38^{3/7}$	39.4	Negative	9	None or <2 h	Equivocal	Equivocal	—	35.64	35.64	Treat	Treat
Not specified	$41^{4/7}$	38.2	Unknown	16	None or <2 h	III	III	0	39.46	37.15	Treat	Treat
E coli	$40^{4/7}$	38.8	Negative	39.1	Broad abx 2-4 h	III	III	0	39.14	39.14	Treat	Treat
Enterococcus spp	$40^{3/7}$	38.3	Negative	21	None or <2 h	III	III	0	37.15	39.46	Treat	Treat
GBS	$40^{0/7}$	39.0	Unknown	24	Broad abx 2-4 h	III	III	0	40.76	40.76	Treat	Treat
E coli	$37^{3/7}$	39.0	Negative	18	Broad abx ≥4 h	III	III	0	42.98	42.98	Treat	Treat
GBS	$39^{1/7}$	39.3	Negative	16	GBS abx >2 h	III	III	0	51.21	51.21	Treat	Treat
GBS	$39^{0/7}$	39.5	Positive	2.78	GBS abx >2 h	III	III	0	66.31	66.31	Treat	Treat
Pneumococcus	$38^{4/7}$	38.9	Negative	15.8	None or <2 h	III	III	0	80.62	80.62	Treat	Treat
Not specified	$39^{2/7}$	39.3	Negative	14	None or <2 h	III	III	0	126.23	126.23	Treat	Treat
E coli	$40^{0/7}$	39.3	Negative	16.6	None or <2 h	III	III	0	136.13	136.13	Treat	Treat
Other	$40^{3/7}$	39.4	Negative	17	None or <2 h	III	III	NR	163.94	163.94	Treat	Treat
E coli	$40^{3/7}$	39.3	Negative	162.7	Broad abx 2-4 h	III	III	0	167.71	167.71	Treat	Treat
Not specified	$34^{1/7}$	37.2	Negative	197	None or <2 h	III	III	0	225.89	225.89	Treat	Treat
Not specified	$34^{1/7}$	37.3	Positive	322	None or <2 h	III	III	0	411.84	411.84	Treat	Treat

abx, antibiotics; *Blood culture*, blood culture and frequent vital signs; *CoNS*, coagulase-negative staphylococcus; *GBS*, group B *Streptococcus*; *NR*, not reported for any subjects in source report; *ROM*, duration of ruptured membranes at birth; *Strongly*, strongly consider starting empiric antibiotics; *VGS*, viridans group streptococci; *VS*, vital signs; —, data not available for this subject. Temperatures reported in Fahrenheit were converted to Celsius and rounded to the first decimal place for use in risk calculations.

Table IV. Risk of bias assessments for included studies

Study	Year	Data source	Outcome			Predictors		Missing data	Overall
			Definition	Follow-up duration	Blinding	Definition	Blinding		
Achten et al[25]	2018	Unclear	Low	Unclear	Low	Unclear	High	Unclear	Unclear
Arora et al[26]	2019	Unclear	Low	Low	Low	Low	Unclear	Unclear	Low
Bajracharya et al[27]	2019	High	High	Low	Low	Low	High	Low	High
Benaim et al[28]	2019	High	High	Low	Low	Low	High	High	High
Davidson et al[29]	2016	Low	High	Unclear	Low	High	High	Low	Unclear
Dhudasia et al[30]	2018	High	Low	Low	Low	Low	High	Low	High
Fischer et al[31]	2018	High	Low	Low	Low	Low	High	Low	High
Fowler et al[32]	2019	High	High	Low	Low	Low	High	Unclear	High
Goel et al[33]	2020	High	Low	Low	Low	Low	Low	Low	Low
Hershkovich-Shporen et al[34]	2019	High	High	Low	Low	Low	High	Unclear	High
Joshi et al[35]	2019	High	Low	Low	Low	Low	High	Low	High
Kopec et al[36]	2018	High	Low	Unclear	Low	Low	High	Low	High
Kuzniewicz[12]		Low	Low	Low	Low	Low	Unclear	Low	Low
Morris et al[37]	2017	High	Low	Low	Low	Low	Unclear	Unclear	High
Perez et al[38]	2019	Low	Low	High	Low	Low	Unclear	Unclear	Unclear
Procianoy et al[39]	2019	High	High	Low	Low	Unclear	High	Low	High
Sharma et al[40]	2019	High	High	High	Low	Low	High	Unclear	High
Strunk et al[41]	2018	Low	High	Low	Low	Low	Low	Low	Low

ROM, rupture of membranes.
Data source: prospective low, combined unclear, retrospective or unknown: high.
Outcome definition: low if handling of contaminants explained, unclear if not explained.
Follow-up duration: low if <72 hours timeframe specified, unclear if not specified, high if other definition.
Outcome blinding: low for all, given blood culture results considered unlikely to be affected by bias as a lack of blinding.
Predictor definition: low if according to development studies, high if different from original development studies.
Predictor blinding: low if any blinding or prospective study, high if no blinding, unclear if not described.
Missing data: low if none, unclear if undescribed or imputed, high if missing data, inadequately imputed or excluded.
Overall: consensus judgment depending on severity of bias issues, emphasis on data source.

Table VI. Results of analysis restricted to prospectively collected data

Recommendations	n (%; 95% CI)
At initial assessment	
Empiric treatment	25 (41.7; 29.1-55.1)
Strongly consider treatment	6 (10.0; 3.8-20.5)
Give or strongly consider treatment	31 (51.7; 38.4-64.8)
Blood culture and frequent vital signs	5 (8.3; 2.8-18.4)
Frequent vital signs	0 (0.0; 0.0-4.9)
Routine care	24 (40.0; 27.6-53.5)
Total	60 (100.0)
Within first 12 hours	
Empiric treatment	36 (60.0; 46.5-72.4)
Strongly consider treatment	8 (13.3; 5.9-24.6)
Give or strongly consider treatment	44 (51.7; 38.4-64.8)
Blood culture and frequent vital signs	2 (3.3; 0.4-11.5)
Frequent vital signs	0 (0.0; 0.0-4.9)
Routine care	14 (23.3; 13.4-36.0)
Total	60 (100.0)

Table VII. Effects of alternative treatment thresholds or population EOS incidence rates on the sensitivity of EOS Calculator recommendations

Treatment threshold* (cases/1000 births)	Corresponding population EOS incidence* (cases/1000 births)	Probability of recommendations at initial assessment (%)			Probability of recommendations at by 12 hours of age (%)		
		All infants		Infants without clinical illness	All infants		Infants without clinical illness
		Treat	Treat or "strongly consider"	Treat or "strongly consider"	Treat	Treat or "strongly consider"	Treat or "strongly consider"
0.45	4.0	60.3 (53.7-66.6)	60.7 (54.1-67.0)	40.3 (32.4-48.5)	79.1 (73.3-84.1)	79.5 (73.7-84.5)	47.3 (36.7-58.0)
0.90	2.0	51.7 (45.1-58.3)	52.1 (45.5-58.7)	27.3 (20.4-35.0)	70.5 (64.2-76.3)	72.6 (66.5-78.3)	29.7 (20.5-40.2)
1.80	1.0	42.7 (36.3-49.3)	45.3 (38.8-51.9)	16.9 (11.3-23.8)	61.5 (55.0-67.8)	69.2 (62.9-75.1)	20.9 (13.1-30.7)
2.00	0.9	40.6 (34.2-47.2)	44.0 (37.6-50.6)	14.9 (9.7-21.6)	59.0 (52.4-65.3)	68.4 (62.0-74.3)	18.7 (11.3-28.2)
2.25	0.8	40.2 (33.8-46.8)	43.6 (37.1-50.2)	14.3 (9.2-20.8)	57.3 (50.7-63.7)	67.9 (61.6-73.9)	17.6 (10.4-27.0)
2.57	0.7	37.6 (31.4-44.2)	41.9 (35.5-48.5)	11.7 (7.1-17.8)	53.8 (47.2-60.4)	67.1 (60.7-73.1)	15.4 (8.7-24.5)
3.00	**0.6**	35.9 (29.8-42.4)	40.6 (34.2-47.2)	9.7 (5.6-15.6)	50.9 (44.3-57.4)	65.8 (59.3-71.9)	12.1 (6.2-20.6)
3.60	0.5	32.9 (26.9-39.3)	38.9 (32.6-45.5)	7.1 (3.6-12.4)	47.0 (40.5-53.6)	65.0 (58.5-71.1)	9.9 (4.6-17.9)
4.50	0.4	29.1 (23.3-35.3)	37.6 (31.4-44.2)	5.2 (2.3-10.0)	39.7 (33.4-46.3)	64.1 (57.6-70.2)	7.7 (3.1-15.2)
6.00	0.3	24.4 (19.0-30.4)	36.8 (30.6-43.3)	3.9 (1.4-8.3)	32.9 (26.9-39.3)	63.7 (57.2-69.8)	6.6 (2.5-13.8)
9.00	0.2	16.2 (11.8-21.6)	35.9 (29.8-42.4)	2.6 (0.7-6.5)	21.8 (16.7-27.6)	62.8 (56.3-69.0)	4.4 (1.2-10.9)
18.00	0.1	10.3 (6.7-14.9)	35.9 (29.8-42.4)	2.6 (0.7-6.5)	12.0 (8.1-16.8)	62.8 (56.3-69.0)	4.4 (1.2-10.9)

Bold values represent treatment threshold and corresponding population EOS incidence used in main analysis.
*With low population incidence rates, effects of changes in treatment thresholds closely approximate effects of inverse changes in the population incidence rates stipulated in the Calculator. Results presented for threshold values are based on a fixed population incidence of 0.6 per 1000, those for incidence rates on a fixed treatment threshold of 3 per 1000.