

## Sepsis calculator to support antibiotic stewardship in early-onset neonatal sepsis: a meta-analysis

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### Abstract

**Background** Establishing a diagnosis of neonatal sepsis is difficult. As such, appropriate timing of antibiotic therapy remains the biggest challenge. As a consequence of non-definitive diagnoses, inappropriate antibiotic administration is common. Recently, a sepsis calculator to estimate risk of early-onset sepsis (EOS) based on both maternal risk factors and infants' clinical presentation was established.

**Objective** To determine the impact of the sepsis calculator in daily clinical settings, especially with regards to antibiotic usage.

**Methods** A literature search of Pubmed, EBSCO, Embase, and Scopus database from January 2011 (after sepsis calculator was established) to June 2018 was performed. We included observational studies that compared the sepsis calculator to recent neonatal sepsis guidelines in terms of antibiotic administration, blood culture, and admission to the neonatal intensive care unit (NICU). The literature search, validation study, and assessment risk of bias were done independently by our four authors, while the first author did the statistical analysis.

**Results** Of the 35 studies identified, 5 cohort studies met the criteria, with a total sample size of 18,352 infants from various countries. We developed a fixed-effect meta analysis of the data. The use of the sepsis calculator significantly reduced inappropriate use of antibiotics [RR 0.46; 95%CI 0.41 to 0.51;  $z=13.57$ ;  $P<0.001$ ], blood culture sampling [RR 0.46; 95%CI 0.40 to 0.52;  $z=12.11$ ;  $P<0.001$ ], and higher neonatal care level admissions [RR 0.68; 95%CI 0.59 to 0.78];  $z=5.47$ ;  $P<0.001$ ). No safety issues were reported from studies using the sepsis calculator.

**Conclusion** The new EOS risk estimation using a neonatal sepsis calculator is an easy, effective, and safe tool to improve appropriate antibiotic use and outcomes. This calculator is ready to be implemented in all levels of neonatal care units. [Paediatr Indones. 2018;58:286-97; doi: <http://dx.doi.org/10.14238/pi58.6.2018.286-97> ].

**Keywords:** antibiotic stewardship; early-onset neonatal sepsis; NICU; sepsis calculator

Early-onset neonatal sepsis (EOS) is an invasive microorganism infection in blood or cerebrospinal fluid in the first 72 hours of life.<sup>1-3</sup> The most common etiologies of EOS are group B streptococcus (GBS), followed by *Escherichia coli*.<sup>1</sup> Early onset neonatal sepsis is usually acquired in the perinatal period shortly before or during birth, due to transplacental, ascending, or intrapartum transmission.<sup>4-6</sup> Early onset neonatal sepsis has one of the highest burdens of neonatal care worldwide.<sup>7-10</sup> With the incidence of culture-proven sepsis ranging from 0.5 to 1.2 cases/1,000 live births, EOS contributes 3 to 40% of mortality in neonatal populations.<sup>11-14</sup> In well-appearing newborns with EOS risk factors, the rate of proven EOS was 0.02 to 0.19%.<sup>15-18</sup>

Following the Centers for Disease Control and Prevention (CDC) guidelines for GBS screening and intrapartum antibiotic prophylaxis (IAP), there was a significant decline in both the incidence of overall and GBS-specific neonatal EOS cases.<sup>3,8,15-16</sup> But, these

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guidelines raised physician awareness about antibiotic stewardship, leading to a 200-fold higher antibiotic administration than the incidence of EOS.<sup>19</sup> This phenomenon was contradictory to the antimicrobial stewardship principle endorsed by the *American Academy of Pediatrics* (AAP) since 2007, which consists of maternal antibiotic prophylaxis, antibiotic for neonates suspected to have sepsis (type, duration, rationale), and the approach to the asymptomatic newborn.<sup>20</sup> The critical issue in treatment is rooted in the difficulty to definitively diagnose EOS cases. Clinical presentation of sepsis in neonates is not always indicative of current infection status. Neonates could appear with or without persistent physiologic abnormalities, hemodynamic instability, seizures, and persistent need for supplemental oxygen/mechanical ventilation.<sup>1</sup> Blood culture, along with antibiotic sensitivity test, as the gold standards for sepsis diagnosis and definitive therapy, take time. To date, the *Committee on the Fetus and Newborn* AAP and CDC algorithms do not specify how to interpret the recommended laboratory tests or how to evaluate EOS in terms of duration and severity.<sup>3,21-22</sup>

Another consideration in EOS diagnosis is maternal chorioamnionitis (CAM). It is a clinical, traditional, and yet less reliable predictor of upcoming neonatal EOS. Due to wide variations in the diagnostic criteria, no single consensus has been reached. Regarding clinical signs and symptoms of CAM, they were found in less than 50% of proven EOS cases.<sup>23</sup> The advances in intrapartum antibiotic treatment since the CDC recommendation was implemented, although associated with lower EOS rate in newborns from CAM mothers, have raised the issue of antibiotic stewardship.<sup>10,24-25</sup> However, given the difficulty of diagnosis, it is not surprising that EOS can often be misdiagnosed, and ergo, mistreated. To date, risk stratification based on maternal factors and neonatal clinical findings is still the best approach to assess the possibility of EOS.<sup>26</sup> In 2011, Escobar *et al.* made a breakthrough in perinatal medicine by launching the neonatal sepsis calculator, widely known as the *Kaiser Permanente Neonatal Sepsis Calculator*.<sup>13</sup> The calculator was constructed from a nested case-control study analyzing 350 culture-positive cases and 1,063 matched controls. It is now available on a website and/or mobile-phone based system. The simple and user-friendly calculator is a more efficient approach to

measure the probability of EOS in infants born >34 weeks gestation. By entering values from five objective maternal risk factors (of chorioamnionitis) at the time of birth as well as the infant's evolving clinical presentations during the first 12 hours of life, the model results in risk for sepsis per 1,000 live births. The risk is classified into three groups: <0.65 (low risk), 0.65-1.54 (medium risk), and >1.54 (high risk) and the score is classified as "well-appearing," "equivocal," or "clinical illness." This handy EOS risk predictive model helps clinicians to reduce overtreatment by immediately stratifying neonates into 1 of 3 category treatment strategies (continue observation, evaluate with treatment conditional on further information, or treat empirically with antibiotics) efficiently.<sup>11,13,19,27-29</sup> After a validation study in 2016, neonatal centers across the world began to implement this calculator in daily practice.

The aim of this meta-analysis study was to estimate the impact of sepsis calculator usage in routine clinical settings, focusing on antibiotic stewardship. First, we evaluated if inappropriate antibiotic use could be clinically reduced without missing any cases of positive blood culture as the safety issue. Second, we assessed if the sepsis calculator application would minimize over-diagnosis of EOS, thus reducing blood culture sampling and unneeded higher neonatal care level admissions, according to each institution standard.

## Methods

We followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) guideline in constructing this meta-analysis.<sup>30</sup> We did a comprehensive electronic literature search from PubMed, EBSCO, EMBASE, and Scopus about studies on associations between the use of the neonatal sepsis risk calculator and outcomes related to antibiotic stewardship, consisting of inappropriate antibiotic use, blood drawn for culture, and higher neonatal level care admission. We used a combination of vocabularies or any possible keywords for early-onset neonatal sepsis, neonatal sepsis calculator, risk stratification, antibiotic use, blood culture, and higher neonatal care admission. The search dates were set from 1 January 2011 to June 2018, with no language restriction. We chose this

time range because the neonatal sepsis calculator was first established in 2011. We also manually searched references from relevant publications to ensure that no publication was missed. We did not seek information from conference proceeding abstracts nor unpublished studies, as these data may not hold up in the peer review process. This literature search was done in June 2018. When a number of publications from the same institution with similar or overlapping patient populations were spotted, only the report published with the largest series was included.

We included any observational cohort studies that compared the sepsis calculator to recent neonatal sepsis guidelines, in terms of either one or more of following outcomes: antibiotic administration, blood culture, and admission to higher level neonatal care. We allowed prospective cohort, retrospective cohort, historical cohort, or any modified cohort with countable relative risk as predetermined effect size for meta-analysis. Exclusion criteria were studies with unclear methods, studies that enrolled neonates <34 weeks of gestation, and studies that included only healthy neonates or neonates without probable infection. We also excluded retrospective chart review or retrospective simulation, reviews, case reports, and non-original studies, such as expert opinions, correspondences, and editorials.

Neonatal sepsis guidelines referred to any guideline used by the neonatal care unit, whether CDC guideline or the institution's own guideline. Early-onset neonatal sepsis was defined by blood or cerebrospinal fluid (CSF) culture with positive results for pathogenic bacteria or fungi, or sepsis in a newborn during the first 72 hours of life. Other common skin pathogens from culture results were regarded as contaminants. Inappropriate antibiotic was defined as the gap between the number of patients given antibiotics compared to the number of patients advised to receive antibiotics from the neonatal sepsis calculator, of those who did not present with clinical deterioration for the first 72 hours of life. We did not assess the type of antibiotic or the duration of antibiotic administration to determine the appropriateness of antibiotic administration, since those values were based on clinical findings of which several considerations could bias the result. Higher neonatal care level admission was defined as the admission of newborns to higher level of neonatal care

level compared to each center's policy. For example, several institutions had protocols of care that preterm newborn should be hospitalized in the perinatology unit (Level II), so that higher level was referred to as NICU admission (Level I). Four investigators (HGH, DUN, SMA, and AY) independently evaluated and reviewed the studies found from the literature search. Disagreements, if any, would be resolved by consensus of all authors and by using the Delphi method.

Each author performed individual literature searches, followed by a detailed review of all studies that met our criteria. Details of individual study characteristics included authors, year of publication, study design, sample size, main characteristics of the study population, study outcomes, and study limitations. We extracted data on sample size, relative risk/risk ratio of outcomes, and associated 95% confidence intervals for our statistical analyses.

In cases in which major discrepancies between the data reported in the included studies and the data calculated were observed, or any additional information needed was not reported in the published articles, an electronic-mail was sent to the corresponding authors requesting clarification regarding the raw data of the studied patient group. If we received no reply, such articles were excluded from the meta-analysis. Quality of the studies was assessed with the *Newcastle-Ottawa Scale* for non-randomized controlled trials and the *GRADE* system for evidence ranking.<sup>31-32</sup> Any disagreements were resolved by the Delphi method.

The main effect size of this meta-analysis was relative risk. We extracted relative risk values of each outcome and calculated each study weight based on their standard of error. We manually calculated relative risk values for studies that did not implicitly report them, since it was possible that a study only reported the relative reduction of outcomes. We log-transformed each relative risk and upper-lower confidence interval of each study before conducting the meta-analysis. Weighing of each study was done using the inverse-variance method. Results are presented in forest plots. Besides the quantitatively reported data on those outcomes, we also assessed the safety of implementing the neonatal sepsis calculator by finding any missed case identification or fatal outcome in newborns that had low risk of sepsis and no advice on antibiotic administration according to the sepsis calculator.

To investigate any potential presence of publication bias, we chose funnel plot, Begg’s rank test, or Egger’s regression test as the most suitable methods for bias assessment, according to the literature search result. The heterogeneity of outcomes from studies was expressed by Cochran Q-statistic and inconsistency tests (I2 test). A result was considered to have significant variation if the I2 score was > 20%. We did not conduct subgroup analyses since the neonatal sepsis calculator was aimed for use in the general newborn population. Statistical analysis was done using *STATA 14 software for Windows* and conducted by authors (RR and HGH).

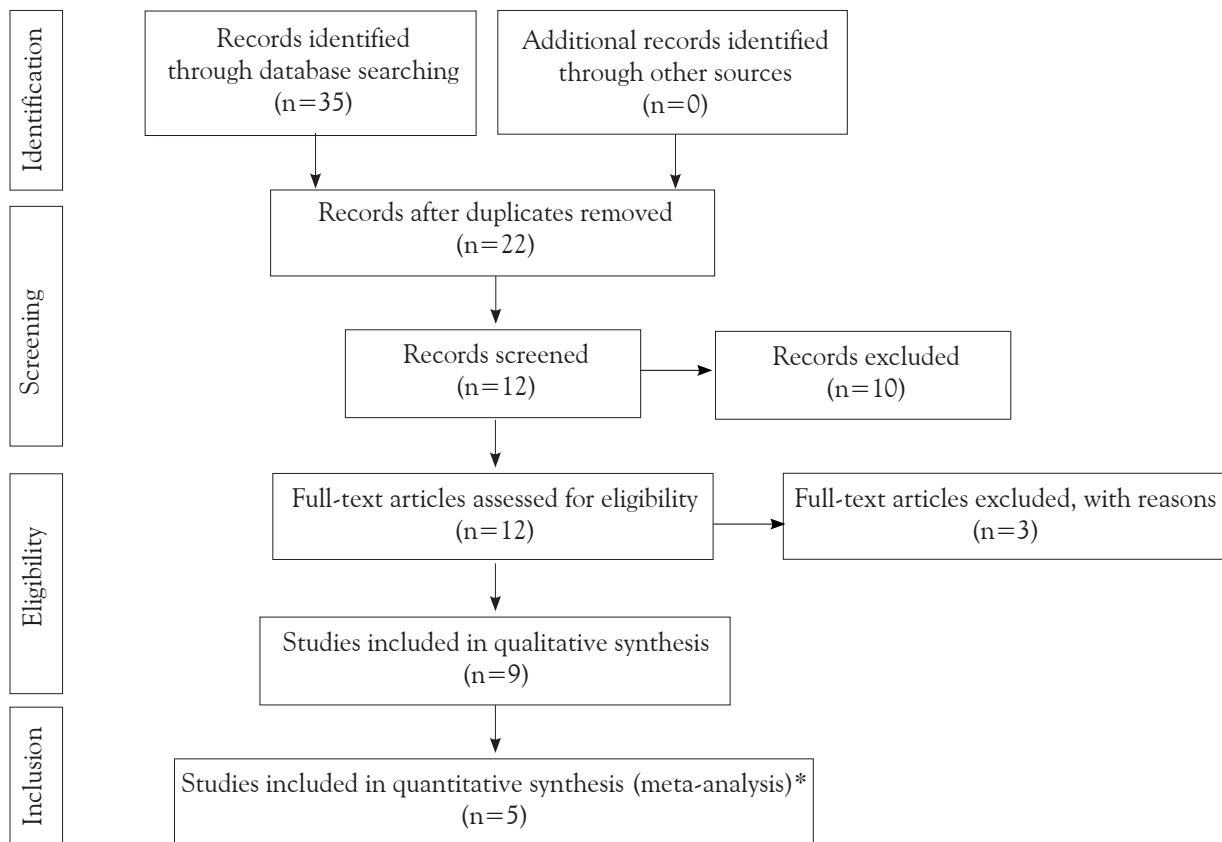
## Results

Of the 35 studies, five cohort studies met our predetermined criteria and were eligible for the meta-analysis (Figure 1). These studies principally originated from the United States (1 from Arkansas,

1 from Portland, and 1 from Philadelphia), 1 from Australia, and 1 from The Netherlands. All five studies were published between 2016 and 2018 and made use of the neonatal sepsis calculator. Study designs were prospective cohort (1 study) and historical cohort (4 studies).

Study characteristics, outlined in Table 1, showed nearly similar patient baseline characteristics. Two studies only included newborns of 35 and 36 weeks gestational age, however, we concluded that these studies were valid for inclusion.<sup>33,36</sup> According to Escobar *et al.*, more than 90% of the study population were newborns with term gestational age.<sup>13</sup> The quality of evidence analysis revealed that all studies had good quality and met the criteria for further data analysis, as shown in Table 2.

The outcomes in each study are presented in Table 3. We then developed a fixed-effect meta-analysis based on two main reasons: 1) the study populations did not differ much among the studies, and 2) the procedure was reproducible (same



**Figure 1.** Flowchart of study selection  
\*reasons for exclusion showed in **Supplementary Appendix 1**

**Table 1 .** Summary of study characteristics

Author (year of publication & place of study)	Study design	Inclusion criteria	Exclusion criteria	Calculator	EOS incidence (per 1,000 live birth)	Outcomes studied	Conclusion
Strunk et al. <sup>33</sup> (2018, Australia)	Prospective historical cohort	Infant > 35 weeks	Not clearly stated	Kaiser	0.44	Differences in admission and readmission rates, antibiotic administration, and blood culture sampling	No discrepancy between sepsis calculator and newborn with proven-EOS
Beavers et al. <sup>34</sup> (2018, Arkansas-US)	Prospective historical cohort	Infant > 34 weeks, maternal chorioamnionitis	Congenital anomaly	Kaiser	Not clearly stated	NICU admission rate, blood culture drawn, antibiotic administration, total charges, and length of stay	No escalation of care associated with calculator use
Warren et al. <sup>35</sup> (2016, Portland-US)	Prospective cohort	Infant > 34 weeks	Antibiotic indication other than EOS	Kaiser	0.5	Comparing antibiotic administration based on CDC guideline and Kaiser calculator, association between i;T ratio > 0.3, and calculator recommendation	No discrepancy between sepsis calculator and newborn with full-course of antibiotics (>5 days)
Dhudasia et al. <sup>36</sup> (2018, Philadelphia-US)	Prospective historical cohort	Infant > 36 weeks	Infant underwent CBC testing only	Kaiser	0.49	Proportion of newborns in each risk stratification category, antibiotic use, laboratory testing (blood culture, CBC, CRP, differential count, or combination)	One patient developed clinical deterioration at 36 hours of age, previously categorized as low risk sepsis by calculator (Negative GBS status, no intrapartum antibiotic and no maternal fever)
Achten et al. <sup>37</sup> (2018, Netherlands)	Prospective historical cohort	Infant > 35 weeks, elevated maternal EOS risk (based on maternal fever, positive GBS status, rupture of membranes <24 hours before birth, or presumed chorioamnionitis)	Congenital anomaly	Kaiser	0.6	Antibiotic use in each EOS risk category, duration of antibiotics, time to start of treatment, newborn completed 7 days or more of antibiotic treatment, and physician adherence to calculator recommendation	No discrepancy between sepsis calculator and newborns with proven EOS

**Table 2.** Assessment of study quality using NOS Scale and GRADE system

Author (year of publication)	Quality assessment (NOS) scale				Risk of bias	Final GRADE evidence ranking
	Selection (max. 4)	Comparability (max. 2)	Outcome (max. 3)	Overall score (total 9)		
Strunk <i>et al.</i> <sup>33</sup> (2018)	4	2	3	9	Low	Moderate +++
Beavers <i>et al.</i> <sup>35</sup> (2018)	4	2	3	9	Low	Moderate +++
Warren <i>et al.</i> <sup>35</sup> (2016)	4	1	3	9	Low	Moderate +++
Dhudasia <i>et al.</i> <sup>36</sup> (2018)	4	2	3	9	Low	Moderate +++
Achten <i>et al.</i> <sup>7</sup> (2018)	4	2	3	9	Low	Moderate +++

**Table 3.** Results of studies and limitations

Author (year of publication)	Sample size	Culture proven EOS	Results, RR (95%CI)			Safety issue	Study limitation
			Use of AB	Blood culture sampling	Higher neonatal care level admission		
Strunk <i>et al.</i> <sup>33</sup> (2018)	4,233	2	0.55 (0.42 to 0.71)	0.67 (0.55 to 0.82)	0.79 (0.67 to 0.92)	No	Low sample size relative to proven EOS incidence
Beavers <i>et al.</i> <sup>34</sup> (2018)	255	0	0.39 (0.29 to 0.52)	0.54 (0.43 to 0.68)	0.40 (0.30 to 0.54)	No	Not clearly stated
Warren <i>et al.</i> <sup>35</sup> (2016)	202	0	0.25 (0.19 to 0.32)	-	-	No	Not clearly stated
Dhudasia <i>et al.</i> <sup>36</sup> (2018)	11,782	4	0.58 (0.50 to 0.69)	0.24 (0.19 to 0.30)	-	No	No assessment of post-discharge infants
Achten <i>et al.</i> <sup>37</sup> (2018)	1,877	4	0.46 (0.18 to 0.88)	-	-	No	High missing data rate

neonatal sepsis calculator used and same definition of outcomes), such that any variety among studies was believed to arise from different population sampling only.

From five studies, the use of sepsis calculator reduced inappropriate use of antibiotics [RR 0.46 (95%CI 0.41 to 0.51);  $P < 0.001$ ;  $z = 13.57$ ], as shown in **Figure 2**. Blood culture sampling was also found to be reduced in three studies [RR 0.46 (95%CI 0.40 to 0.52);  $P < 0.001$ ;  $z = 12.11$ ], as was reduced higher level neonatal care admissions [RR 0.68 (95%CI 0.59 to 0.78);  $P < 0.001$ ;  $z = 5.47$ ], shown in **Figure 3** and 4, respectively. The lower risk of blood culture was similar to lower antibiotic use. Although significant, less studies investigate on neonatal care admission

since several neonatal center have a protocol of neonatal admission based on gestational age, not on clinical condition or current working diagnosis.

We found no reports of safety issues in any studies, as shown in **Table 3**. Although the safety rate of the neonatal sepsis calculator was not implicitly stated, one study reported a newborn with clinical deterioration at 36 hours of age who had been previously stratified as “no need of antibiotic” by the calculator. This infant was eventually admitted to the NICU. All the studies reported that this neonatal sepsis calculator was well implemented in each of their neonatal care centers.

We did not assess publication bias using funnel plot or any advanced regression-based assessment,



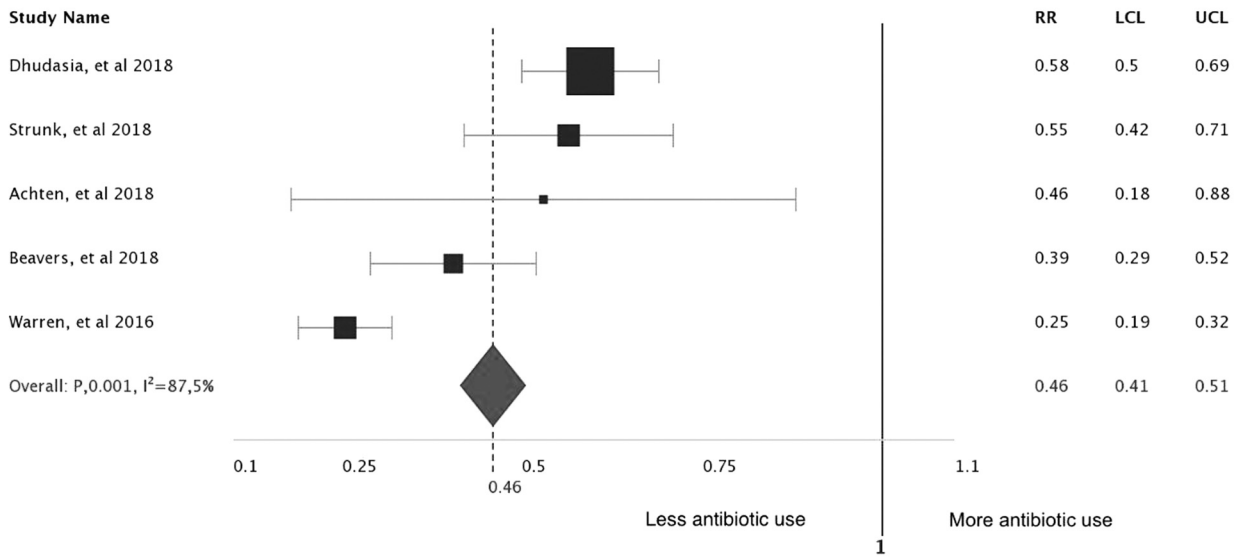


Figure 2. Forest plot of first outcome: use of antibiotics

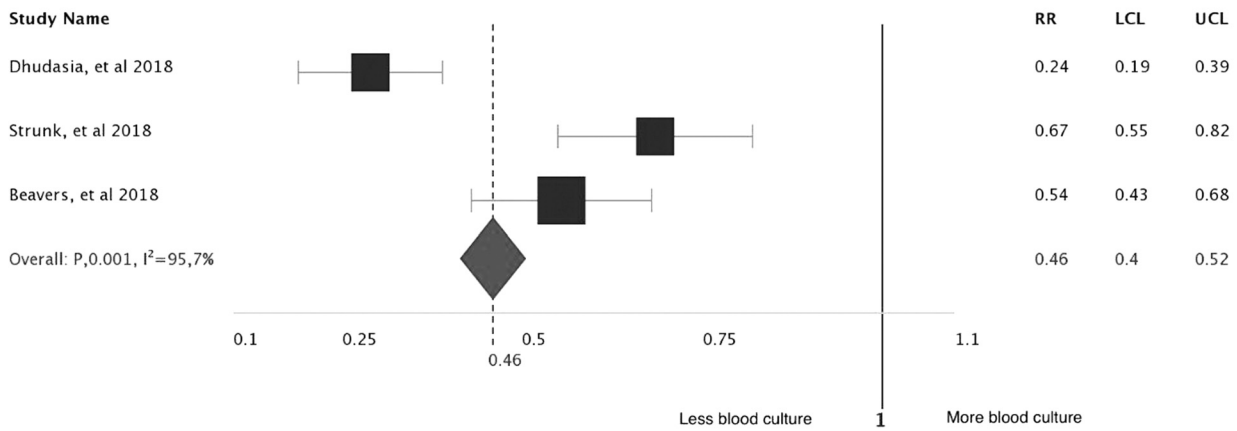


Figure 3. Forest plot of second outcome: blood culture sampling

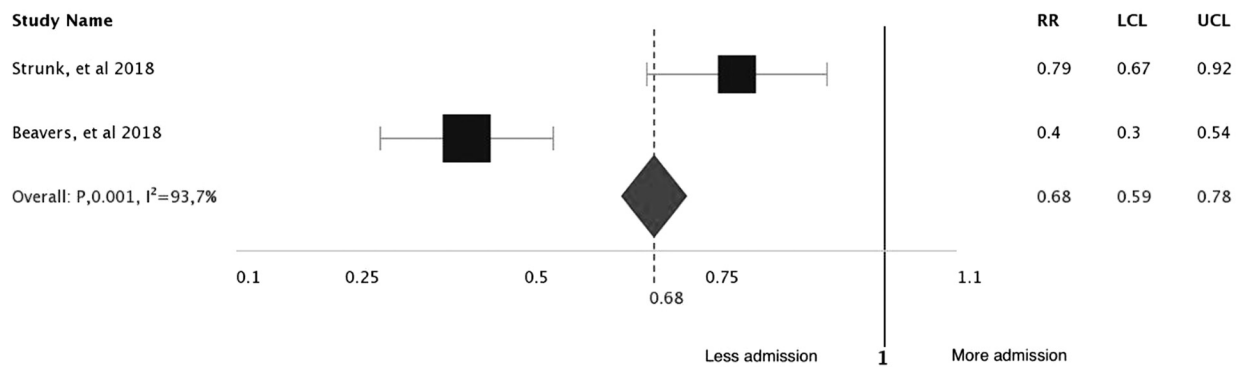


Figure 4. Forest plot of third outcome: higher level neonatal care admission

as the number of studies was inadequate. High heterogeneity level between studies was not an issue since all of the studies had an effect size of less than 1 (including the upper limit of 95% confidence intervals).

## Discussion

This study was the first meta-analysis to assess the role of the neonatal sepsis calculator to support antibiotic stewardship since its establishment in 2011 and validity study in 2016. By analyzing results from studies across countries with different EOS incidence and different standards of neonatal care quality, the result of this meta-analysis gave us assurance of the applicability, benefits, and safety of the neonatal sepsis calculator implementation. This meta-analysis would also help both neonatologists and obstetricians in decision-making during daily clinical practice.

Our analysis showed that inappropriate antibiotic administration was decreased after using the neonatal sepsis calculator. The pooled relative risk of "inappropriate antibiotic administration" was less than 0.5. As such, this finding provides marked evidence that the sepsis calculator significantly guided clinicians to implement antibiotic stewardship. Likewise, clinicians became more confident to not administer antibiotics in doubtful clinical situations, notably with an estimated quantification of risk provided by this calculator. It is also possible that clinicians' tendency to give empirical antibiotics would be altered in the near future with greater acceptance of this calculator.<sup>38</sup>

This result was also reiterated by some studies reporting shorter antibiotic use after sepsis calculator implementation (<53 hours).<sup>35</sup> Previously, an international survey showed that 45% of clinicians administer antibiotics if the laboratory result is abnormal, rising to 99% in high-risk situations. Most of them (56%) continued antibiotics to 5-7 days. Since the neonatal sepsis calculator provides guidance, an inappropriate treatment of EOS should be reduced in the near future. Lower inappropriate antibiotic administration could reduce the emergent antimicrobial resistance rate and harmful effect on the neonatal microbiome. In contrast, inappropriate antimicrobial use led to late-onset neonatal sepsis.<sup>39-40</sup>

Lower antibiotic administration also minimized intravenous (IV) access and lowered the adverse events from excessive drug administration.<sup>41</sup> Moreover, studies have also reported that inappropriate antibiotic administration during infancy increased the risk of developing asthma,<sup>42</sup> autoimmune disease,<sup>43</sup> and obesity<sup>44</sup> in the future.

We found that the blood culture sampling rate was significantly reduced with the implementation of the sepsis calculator. The amount of blood, taken merely to perform blood cultures, was relatively large for a newborn, especially for preterm infants. Not only did decreased blood sampling allow avoidance of a painful venous puncture, it also reduced the unnecessary cost and hospital stay just to wait for the results. This was imperative since blood culture sampling rate was routinely done, regardless of culture results' low positivity rate and lack of usefulness in altering our approach in patient management. A multicenter survey of neonatal units showed that the most ordered laboratory exam in newborns with suspected EOS was complete blood count (97.2%), followed by blood culture (80.3%), and C-reactive protein (29.6%).<sup>45</sup> Therefore, blood sampling for culture was an important issue and any reduction could improve antibiotic stewardship.

Some literature about biomarkers in EOS also stated that gestational age and other physiologic processes, including maternal and perinatal factors, influenced the levels of CRP in the first three days of life after birth.<sup>46-49</sup> With a cutoff value of 10 mg/L and when combined with other biomarkers, CRP had a superior diagnostic accuracy.<sup>46</sup> The CRP response was noted to be higher in gram-negative than in gram-positive infections.<sup>46</sup> By lowering the blood culture rate, the use of other laboratory parameters such as CRP, procalcitonin (PCT), or immature-to-total neutrophil ratio (I/T ratio) could be optimized, as those were faster and simpler tests that involved less blood volume.<sup>4</sup> These results could then lead to optimization of laboratory examinations directly during the observation phase when an infant presented a clinical deterioration later, after 12 hours of life.

Sepsis was the most common diagnosis that led to newborn neonatal unit admissions, mainly the NICU. The presence of sepsis, even only in suspected cases, indeed warranted admission to a higher level of neonatal care. In our review, the pooled risk ratio



for higher neonatal care was 0.68, following the use of neonatal sepsis calculator. Through a more detailed analysis, this ratio was higher than antibiotic administration (RR 0.46), meaning that although not given antibiotics, several clinicians still decided on a higher neonatal care level to observe high-risk newborns. We found that reduced neonatal care admission had several consequences both for the newborn and parents. Higher neonatal care admission led to longer hospital stay, raised parental anxiety, and created a huge burden in terms of health care cost.<sup>41</sup> Moreover, these factors could lead to disruption in maternal-infant bonding and delayed early breastfeeding.<sup>41</sup> In developing countries, an admission to a neonatal unit (especially NICU) also increased the risk of nosocomial infection, known as late-onset neonatal sepsis.

The goal of all existing approaches in neonatal sepsis risk assessment is newborn safety. The devastating effects of neonatal sepsis on morbidity and mortality prompt clinicians to start antibiotic regimens as soon as there is a suspicion of sepsis. Several journals reported cases of neonatal sepsis who were not given antibiotic recommendation by the sepsis calculator. However, those studies were retrospective chart reviews. We preferred to not rely on chart review studies, since the high bias between clinical and calculator decision. A previous study also evidenced an improvement in antibiotic stewardship through close monitoring of at-risk newborns only by physical examination.<sup>50</sup> We also noted that the neonatal sepsis calculator could not be used as a single parameter to predict EOS without considering laboratory or routine physical examination results. Further multicenter research on the calculator's safety is needed.

Based on the evidence provided above, we concluded that the neonatal sepsis calculator was ready to be implemented in daily clinical practice. An added benefit was that this calculator could be implemented at no extra cost. It led to a robust improvement in antibiotic stewardship in the neonatal unit and did not cause any potential harm to newborns. This neonatal sepsis calculator also guided clinicians to a more efficient decision-making process, especially in doubtful and dilemmatic situations when facing suspected early-onset neonatal sepsis, for example, in "well-appearing" babies born from

mothers with suspected CAM.<sup>17</sup> The calculator also decreased improper diagnosis of maternal CAM, since merely elevated maternal temperature sometimes led clinicians to CAM diagnoses. Frequent re-evaluations, mainly of clinical findings, were necessary in newborns who received a no antibiotic recommendation, since EOS could develop anytime during the first 72 hours of life.<sup>44</sup> Kuzniewicz *et al.* reported that 50% of newborns with culture-proven EOS were asymptomatic at birth.<sup>29</sup> Wortham *et al.* found that 22% of full term neonates with culture-proven EOS and CAM exposure remained asymptomatic at 72 hours after birth and 28% presented no signs of sepsis within 6 hours after birth.<sup>51</sup>

The main obstacle reported during the implementation of the sepsis calculator was clinician compliance in using such a real-time, decisive tool. This change of habit takes time and should never be rushed. In addition, it requires training, resources, manpower, and an uptick in provider workload to compensate for any medical error resulting from a miscalculation of EOS risk.

This meta-analysis yielded a favorable result for neonatal sepsis calculator implementation. However, several aspects have not been investigated. Some potential further studies would be about the type of antibiotics used, time to switch to stronger antibiotics, and the duration of antibiotic administration. Indirectly, these components affect both newborn length of stay in the hospital (shorter duration reduced the risk of late-onset neonatal sepsis) and cost during hospitalization. Another potential field for further study is the post-discharge analysis of infants not receiving antibiotics based on the calculator recommendation, although a previous study in *Kaiser Permanente Northern California* (KPNC, an original sample population of neonatal sepsis calculator) reported similar readmission rates between the use of CDC guidelines and the neonatal sepsis calculator.<sup>29</sup> A 'wash-out' period was recommended for any further study to investigate the efficiency of using this calculator to improve data quality when conducting a historical cohort. This approach was also done by KPNC from 2012 to 2014 before they completely implemented this calculator.

Risk stratification using the neonatal sepsis calculator is an effective way to improve antibiotic stewardship in the neonatology unit. By reducing

the administration of inappropriate antibiotics, blood sampling for cultures, and admission to higher-level neonatal care, this calculator can help clinicians to evaluate and make decisions for EOS treatment. A prospective meta-analysis in upcoming years is needed to give stronger evidence from a high quality study on the impact of the neonatal sepsis calculator on antibiotic stewardship.

## Conflict of Interest

None declared.

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**Supplementary Appendix 1.** Excluded studies for meta-analysis and reasons for exclusion

Author (year of publication)	Reason for exclusion
Shakib <i>et al.</i> (2015)	Excluded patients admitted to NICU; no exact proportion of newborn recommended to receive antibiotic by neonatal sepsis calculator
Kerste <i>et al.</i> (2016)	A chart review; unable to calculate relative risk since all sample receive antibiotics
Carola <i>et al.</i> (2017)	A chart review; all samples were given antibiotics, underwent blood culture, and admitted to NICU
Money <i>et al.</i> (2017)	A chart review where all samples were given antibiotics and admitted to NICU