

## Supplementary Online Content

Brown JVE, Meader N, Wright K, Cleminson J, McGuire W. Assessment of C-reactive protein diagnostic test accuracy for late-onset infection in newborn infants: a systematic review and meta-analysis. *JAMA Pediatr*. Published online February 3, 2020. doi:10.1001/jamapediatrics.2019.5669

**eAppendix 1.** Search Strategy

**eAppendix 2.** Changes Between Protocol and Review

**eTable.** Post-Test Probabilities for Late-Onset Infection for a Sample of Population Prevalence

**eFigure 1.** SROC Plot for Studies With CRP Threshold 5-10 mg/L (Bivariate Meta-analysis)

**eFigure 2.** SROC Plot of CRP for Preterm Infants Only

**eFigure 3.** Deeks' Funnel Plot (Asymmetry Test)

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

## eAppendix 1. Search Strategy

### MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

- 1 exp Infant, Newborn/ (507086)
- 2 Premature Birth/ (7396)
- 3 (neonat\$ or neo nat\$).ti,ab. (204089)
- 4 (newborn\$ or new born\$ or newly born\$).ti,ab. (135419)
- 5 (preterm or preterms or pre term or pre terms).ti,ab. (50291)
- 6 (preemie\$ or premie or premies).ti,ab. (121)
- 7 (prematu\$ adj3 (birth\$ or born or deliver\$)).ti,ab. (12210)
- 8 (low adj3 (birthweight\$ or birth weight\$)).ti,ab. (26659)
- 9 (lbw or vlbw or elbw).ti,ab. (5938)
- 10 infan\$.ti,ab. (345004)
- 11 (baby or babies).ti,ab. (54493)
- 12 "Intensive Care Units, Neonatal"/ (10315)
- 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (854743)
- 14 C-Reactive Protein/ (32529)
- 15 c-reactive protein.ti,ab. (44280)
- 16 CRP.ti,ab. (30090)
- 17 Interleukin-6/ (48141)
- 18 IL-6.ti,ab. (71459)
- 19 interleukin-6.ti,ab. (35713)
- 20 acute phase reactant\$.ti,ab. (3064)
- 21 Biological Markers/ (172550)
- 22 biomarker\$.ti,ab. (113562)
- 23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (371276)
- 24 exp Sepsis/ (95928)
- 25 sepsis.ti,ab. (68288)
- 26 infection\$.ti,ab. (1022808)
- 27 exp Bacterial Infections/ (745229)
- 28 (bacteraemia or bacteremia).ti,ab. (22257)
- 29 (fungaemia or fungemia).ti,ab. (1664)
- 30 exp Candidiasis/ (27375)
- 31 candidiasis.ti,ab. (12078)
- 32 exp Meningitis/ (48258)
- 33 meningitis.ti,ab. (42079)
- 34 Pneumonia, Bacterial/ (8792)
- 35 Urinary Tract Infections/ (32771)
- 36 Catheter-related Infections/ (2533)
- 37 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (1653493)
- 38 13 and 23 and 37 (3447)
- 39 exp animals/ not humans.sh. (4037496)
- 40 38 not 39 (3184)

### Embase via Ovid

- 1 exp Infant/ (898706)
- 2 Prematurity/ (76784)
- 3 (neonat\$ or neo nat\$).ti,ab. (253737)
- 4 (newborn\$ or new born\$ or newly born\$).ti,ab. (162735)
- 5 (preterm or preterms or pre term or pre terms).ti,ab. (66105)
- 6 (preemie\$ or premie or premies).ti,ab. (165)
- 7 (prematu\$ adj3 (birth\$ or born or deliver\$)).ti,ab. (15808)
- 8 (low adj3 (birthweight\$ or birth weight\$)).ti,ab. (31872)
- 9 (lbw or vlbw or elbw).ti,ab. (7572)
- 10 infan\$.ti,ab. (406724)
- 11 (baby or babies).ti,ab. (71539)
- 12 newborn intensive care/ (22338)
- 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1220384)
- 14 C Reactive Protein/ (98704)
- 15 c-reactive protein.ti,ab. (59724)

16 CRP.ti,ab. (53596)  
 17 Interleukin 6/ (140947)  
 18 IL-6.ti,ab. (98082)  
 19 interleukin-6.ti,ab. (41784)  
 20 acute phase reactant\$.ti,ab. (4241)  
 21 Biological Marker/ (150561)  
 22 biomarker\$.ti,ab. (170601)  
 23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (472866)  
 24 exp Sepsis/ (181816)  
 25 newborn sepsis/ (4927)  
 26 sepsis.ti,ab. (96170)  
 27 infection\$.ti,ab. (1249750)  
 28 exp Bacteremia/ (35078)  
 29 exp Fungemia/ (4805)  
 30 (bacteraemia or bacteremia).ti,ab. (27114)  
 31 (fungaemia or fungemia).ti,ab. (2019)  
 32 exp Candidiasis/ (40057)  
 33 candidiasis.ti,ab. (15095)  
 34 exp Meningitis/ (75363)  
 35 meningitis.ti,ab. (49821)  
 36 Pneumococcal meningitis/ (908)  
 37 Urinary Tract Infection/ (75050)  
 38 Catheter infection/ (11655)  
 39 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (1501019)  
 40 13 and 23 and 39 (5912)  
 41 animal/ (1656079)  
 42 human/ (15731222)  
 43 41 not (41 and 42) (1247837)  
 44 40 not 43 (5877)

#### Science Citation Index via Web of Science

# 1,256 #3 AND #2 AND #1  
 4 *Indexes=SCI-EXPANDED Timespan=1900-2015*  
 # 194,557 TOPIC: (sepsis) OR TOPIC: ("bacterial infection\*") OR TOPIC: (bacteremia or bacteraemia) OR  
 3 TOPIC: (fungaemia or fungemia) OR TOPIC:(candidiasis) OR TOPIC: (meningitis) OR TOPIC:  
 ("pneumococcal meningitis") OR TOPIC: ("urinary tract infection\*") OR TOPIC: ("catheter  
 infection\*")  
*Indexes=SCI-EXPANDED Timespan=1900-2015*  
 # 241,196 TOPIC: ("c reactive protein") OR TOPIC: ("Interleukin 6") OR TOPIC: ("acute phase reactants")  
 2 OR TOPIC: ("biological markers") OR TOPIC:(biomarker\*)  
*Indexes=SCI-EXPANDED Timespan=1900-2015*  
 # 616,040 TOPIC: ((neonat\* or neo nat\* or newborn\* or new born\* or newly born\*)) OR TOPIC: ((preterm  
 1 or preterms or pre term or pre terms or premie\* or premie\* or premies)) OR TOPIC:  
 ("premature birth" or "premature delivery") OR TOPIC: (low birthweight\* or "low birth  
 weight\*") OR TOPIC: (lbw or vlbw or elbw) OR TOPIC: (infant or infants or infancy or baby or  
 babies) OR TOPIC: ("neonatal intensive care")  
*Indexes=SCI-EXPANDED Timespan=1900-2015*

## **eAppendix 2. Changes Between Protocol and Review**

We used a hierarchical summary receiver operating characteristic model rather than the proposed bivariate random-effects approach because included studies did not use a common cut-off.

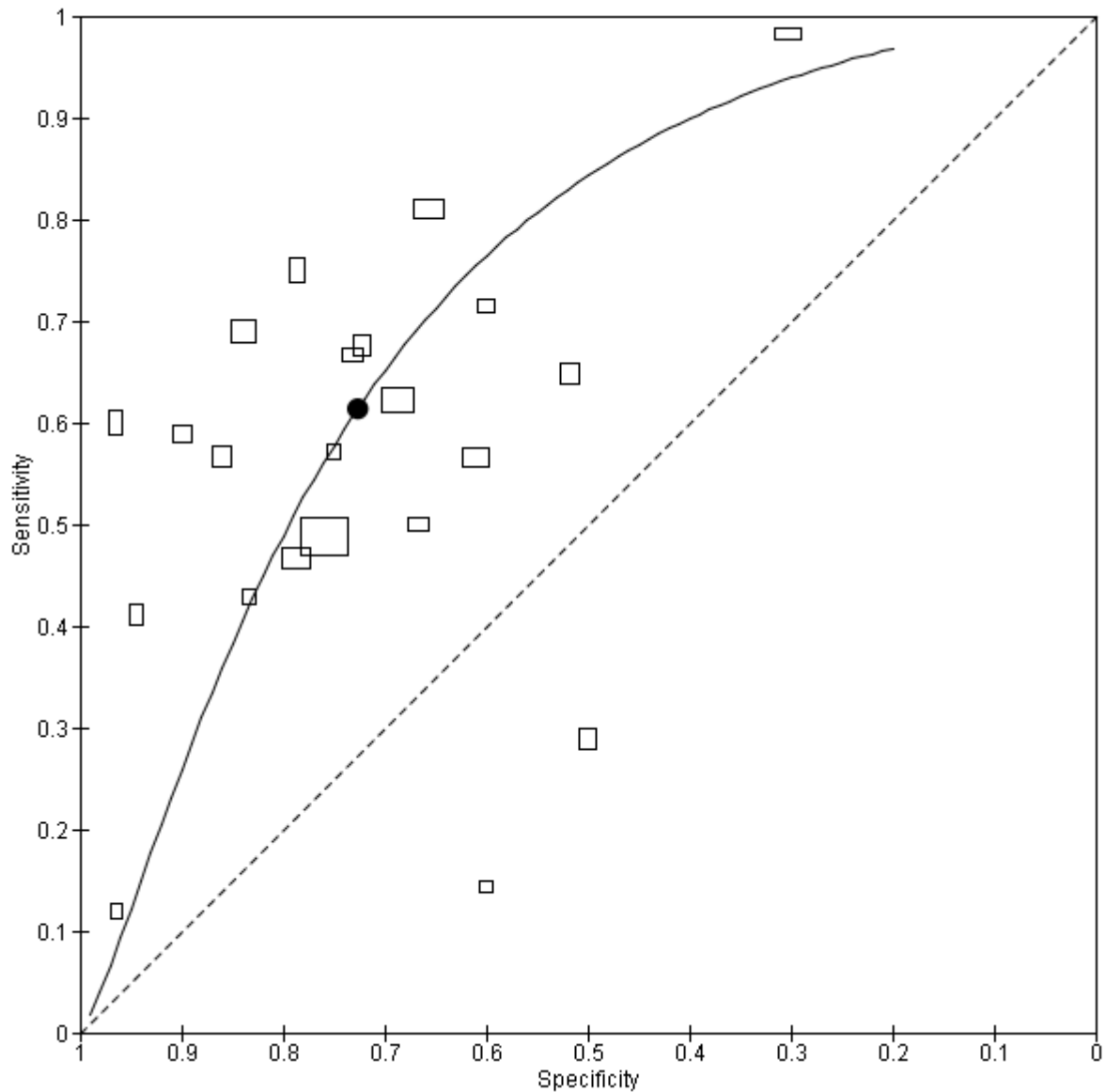
We included studies in which infants with urinary tract infection or radiologically confirmed pneumonia fulfilled the case definition for late-onset infection. These studies typically had none or very few participants with these diagnoses in the absence of bacteraemia.

We accepted the primary study authors' definition of late-onset infection with regards to the infant's age when evaluated (range from 48 hours to six days after birth).

**eTable. Post-test probabilities for late-onset infection for a sample of population prevalence**

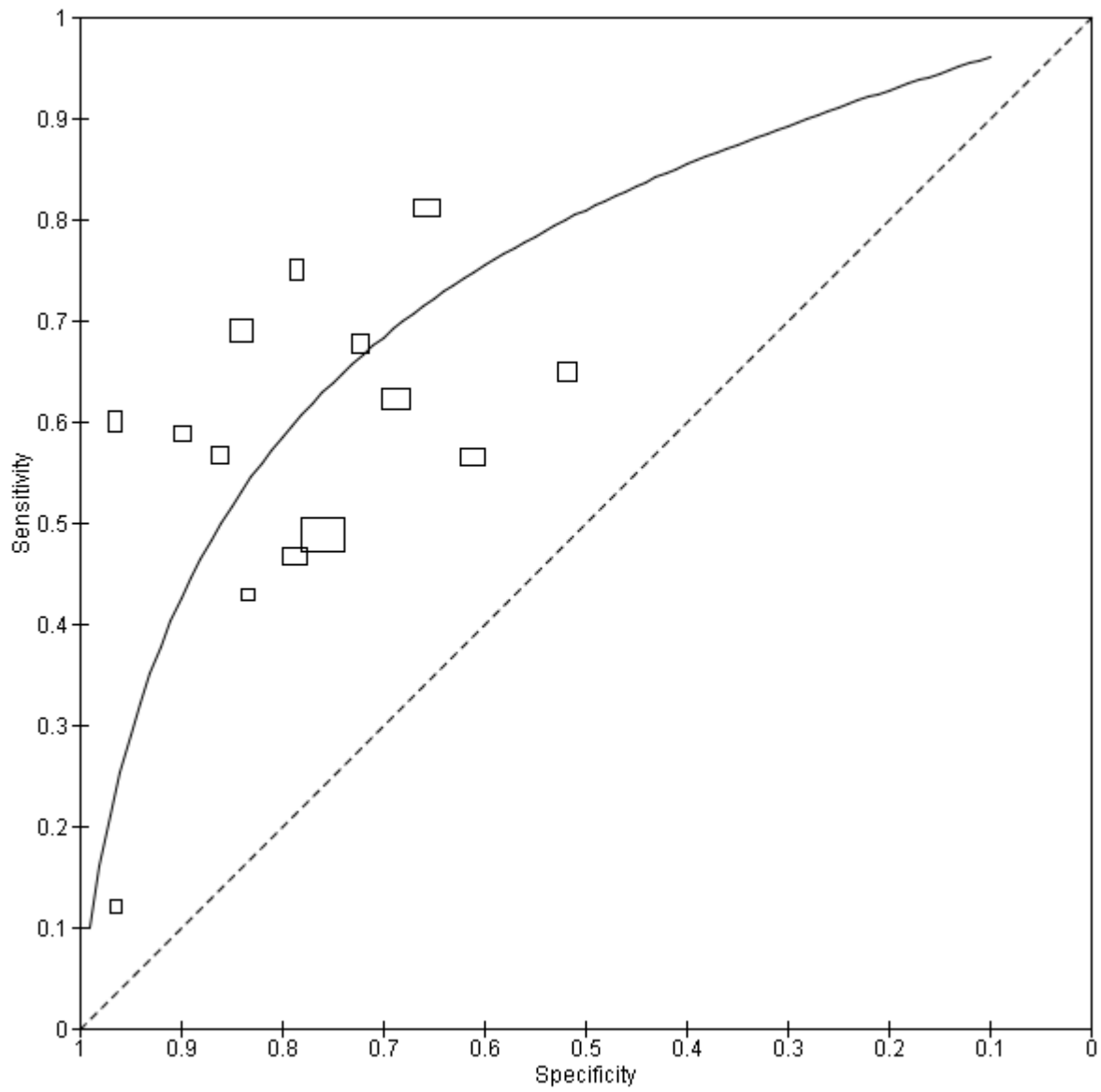
<b>Pretest probability</b>	<b>Post-test probability after a positive result</b>	<b>Post-test probability after a negative result</b>
0.2	0.37	0.11
0.3	0.51	0.18
0.4	0.61	0.26
0.5	0.70	0.34
0.6	0.78	0.44

**eFigure 1. SROC plot for studies with CRP threshold 5-10 mg/l (bivariate meta-analysis)**



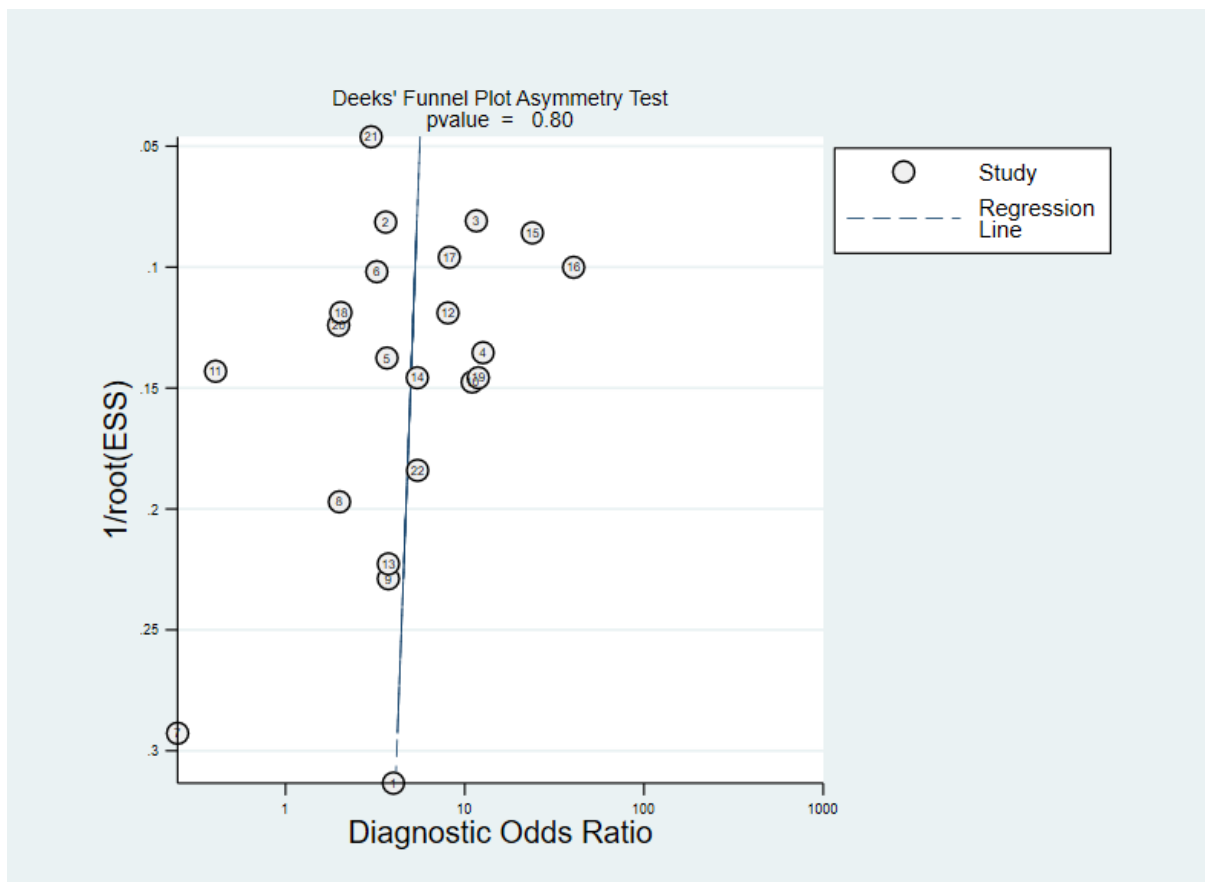
eFigure 1: Summary receiver operating characteristics curve for studies with CRP threshold 5-10 mg/l (with summary point from bivariate meta-analysis). Study estimates of sensitivity and specificity are shown with the SROC curve (size of rectangle is scaled by the inverse standard error)

**eFigure 2. SROC plot of CRP for preterm infants only**



eFigure 2: SROC plot of CRP for preterm infants only.

**eFigure 3. Deeks' Funnel Plot (Asymmetry Test)**



eFigure 3: Deeks' funnel plot (asymmetry test).