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ORIGINAL RESEARCH

Validation of the ICD-10 Diagnoses of Early-Onset Neonatal Infection in the Danish National Patient Register from 2010 to 2018

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Purpose: To examine the accuracy of the diagnoses of early-onset neonatal infection in the Danish National Patient Register.

Patients and Methods: All Danish neonates born after 35 weeks of gestation with an ICD10 diagnosis of sepsis or meningitis within the first week of life between 2010 and 2018 were identified. To examine the validity of the diagnoses, medical records were reviewed for 500 neonates diagnosed with sepsis and all 63 neonates diagnosed with meningitis. Proven infection was defined by bacterial pathogens identified from blood or cerebrospinal fluid. Probable sepsis was defined as at least 5 days of antibiotic treatment, two clinical signs of infection, and one abnormal blood biomarker. Probable meningitis was defined as at least 14 days of antibiotics, neurological affection, and cerebrospinal fluid analysis consistent with meningitis. Positive predictive values (PPVs) with 95% CI were estimated using the proven definition of infection as well as the criteria for either proven or probable infection.

Results: The PPV for sepsis diagnoses using the proven definition was 0.04 (0.02, 0.06), while the PPV using both the proven and probable definition was 0.52 (0.45, 0.58). Sepsis diagnoses with a specified pathogen showed the highest PPV for proven sepsis at 0.36 (0.29, 0.43) and for proven or probable sepsis at 0.65 (0.58, 0.72). The PPV for meningitis diagnoses using the proven definition was 0.24 (0.13, 0.37), while the PPV using both the proven and probable definition was 0.38 (0.25, 0.52).

Conclusion: We found a poor validity for the ICD10 diagnoses of early-onset neonatal infection in the Danish National Patient Register. This highlights that the diagnoses should be used cautiously in future research and surveillance and emphasises the need for supporting information on microbiological samples. Additionally, this highlights the importance of establishing a consensus definition of neonatal sepsis to improve diagnostic accuracy.

Keywords: neonatal sepsis, neonatal meningitis, validation study, health administrative data

Introduction

Early-onset neonatal infection may be defined as an invasive bacterial infection within the first week of life including conditions such as sepsis and meningitis.[1] The infections are mainly caused by Group B *Streptococcus* (GBS) or *Escherichia coli* acquired from the mother prior to or during birth.[2,3] These early infections are amongst the leading causes of mortality during the neonatal period and are associated with long-term neurodevelopmental impairment.[4–6]

Despite this significant global burden, no consensus definition of neonatal sepsis and meningitis exists.[1,7] The gold standard for diagnosing invasive neonatal bacterial infection is the detection of the pathogen in cultures from blood or cerebrospinal fluid or by molecular testing of cerebrospinal fluid.[8] However, studies have reported that for each culture-positive neonate, between 15 to 30 times as many culture-negative neonates are treated with antibiotics.[9,10] In Denmark, it has been estimated that about 2% of all neonates are treated with antibiotics.[11] The low yield of blood cultures may be explained by difficulties in obtaining samples from critically ill neonates, small sample volumes compared with adults,

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and low levels of bacteriemia possibly due to the use of intrapartum maternal antibiotics.[12–14] However, false positive diagnoses may also be a potential explanation, especially since the diagnosis of early-onset infection relies on non-specific clinical symptoms and biomarkers when no pathogen is identified.[15–18] The Danish National Patient Register contains information on all hospital contacts in Denmark including time of admission and physician-assigned diagnoses based on the International Classification of Diseases 10th revision (ICD10).[19] The registry is frequently used in epidemiological research and enables nationwide population-based observational studies. Through the personal identification number assigned to all Danish citizens at birth, information from the registry can be combined with data from several other national registers and medical records.[20,21] Diagnoses of early-onset infection are often used to study disease burden, determinants, and long-term outcomes.[4,5,22–30] However, given that the diagnosis of early-onset infection is often non-specific and largely reliant on clinical judgement, it would be valuable to investigate the validity of these diagnoses in the Danish National Patient Register to identify and evaluate potential sources of bias associated with their use.[19] Such estimates may provide important information for future research into neonatal infections, as well as for assessing the reliability of the diagnoses for disease surveillance.

The aim of this study was therefore to estimate the accuracy of the diagnoses of early-onset neonatal sepsis and meningitis in neonates born after 35 weeks of gestation by estimating the positive predictive value (PPV) of the ICD10 diagnoses based on pre-specified criteria related to microbiology, clinical signs, biomarkers, and treatment.

Materials and Methods

Population

The eligible study population consisted of all liveborn singletons in Denmark from 2010 to 2018 born after at least 35 completed gestational weeks. Neonates were included if they were admitted within the first week of life with a primary or secondary ICD10 diagnosis of bacterial infection, as recorded in the Danish National Patient Register.[19] An overview of the included diagnoses is provided in the supplement (Supplemental Table S1). Neonates with an ICD10 diagnosis of congenital malformation (Q*) received within the first year of life were excluded. A total of 500 neonates with a diagnosis of sepsis were randomly sampled for validation. The admission duration was required to be at least five days (unless death occurred prior to this) to exclude those who were assigned a diagnosis due to suspected infection but could not have received at least 5 days of intravenous antibiotics. The neonates were sampled from different diagnosis groups including 200 with an ICD10 diagnosis of newborn bacterial sepsis with an unspecified pathogen (P36.9) (Group 1), 200 with newborn bacterial sepsis with a specified pathogen (P36.0-P36.8) (Group 2), and 100 with *Streptococcal* sepsis (A40), other sepsis (A41), bacterial pneumonia (J15), or congenital pneumonia (P23.1-DP23.9) (Group 3). Diagnoses of pneumonia were considered as no clear clinical distinction can be made between pneumonia and sepsis within the first week of life, which is in accordance with the Neonatal Sepsis and Meningitis guidelines from the Danish Pediatric Society.[31] We aimed to include sample sizes equal to or larger than those of previous validation studies.[32–35] By including a total of 500 children with sepsis, the width of the 95% CIs for the PPVs would not exceed 0.14 for the diagnosis groups including 200 neonates and 0.20 for the group including 100 neonates. A priori, this was considered to be an adequate precision of the estimates. All neonates with an ICD10 diagnosis of meningitis were selected for validation including diagnoses of bacterial meningitis (G00) and unspecified meningitis (G03.9). The admission duration was required to be at least 14 days for diagnoses of meningitis.

Collection of Healthcare Administrative Data

Medical records for each neonate were identified by their personal identification number and were obtained following contact to each Danish Department of Pediatric and Adolescent Medicine.[20] One investigator (MA) examined all records from the North Denmark Region, Central Denmark Region, Region Zealand, and the Capital Region of Denmark. Another investigator (MM) examined 50 of these records to evaluate interrater agreement. All discrepancies were reassessed by a second review of the records, ensuring that the correct information was retained. Due to specific regulations for the Region of Southern Denmark, these medical records were examined by a third investigator (AH). The data were entered into a predefined structured data-collection template made by the Research Electronic Data

Capture (REDCap).[36] All investigators were medical doctors and were blinded to the specific diagnosis in the registry. The development of the REDCap database and all interpretational issues during data collection were handled in close collaboration with an expert in neonatology (TBH) and clinical microbiology (SYN).

Criteria for Early-Onset Sepsis

Table 1 provides an overview of the definitions of proven and probable sepsis.

Table 1 Study Criteria for Assessing ICD10 Diagnoses of Early-Onset Neonatal Sepsis Using Medical Record Data Within the First week of Life

Identification of bacteria			**Checkbox**
Identification of bacterial pathogen in blood by culture			☐
Duration of antibiotics			
A total of ≥5 days of antibiotic treatment or died while receiving antibiotics			☐
Clinical signs of infection			
Respiratory	Apnea	Statement of apnea or cessation of breathing	☐
	Tachypnoea	Statement of tachypnoea or respiratory rate ≥60/min	
	Respiratory distress	Statement of retractions, grunting, nasal flaring, or cyanosis	
	Respiratory support	Statement of continuous positive airway pressure (CPAP), supplemental oxygen, other non-invasive ventilation, or invasive ventilation	
Heart rate	Tachycardia	Statement of tachycardia or heart rate >160/min	☐
	Bradycardia	Statement of bradycardia or heart rate <100/min	
Arterial hypotension	Hypotension	Statement of hypotension, systolic blood pressure <55 mmHg, or mean arterial blood pressure <35 mmHg	☐
	Signs of hypotension	Statement of use of fluid bolus, use of inotropes, lactate >3 mM, or capillary refill time ≥3 seconds	
Neurological	Neurological signs	Statement of seizures, hypertonia, hypotonia, lethargy, irritability, or bulging fontanelle	☐
Temperature	Hyperthermia	Statement of hyperthermia or ≥38 °C	☐
	Hypothermia	Statement of hypothermia or <36 °C	
	Instability	Statement of temperature instability	
Other symptoms	Skin	Statement of petechia, purpura, or pustules	☐
	Gastrointestinal	Statement of feeding intolerance, vomiting, or ileus	
Biomarkers in blood			
C-reactive protein ≥35 mg/l			☐
WBC $<5*10^9$/l			☐
ANC $<1.5*10^9$/l			☐

(*Continued*)

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Table 1 (Continued).

Certainty	Culture	Antibiotics	Clinical signs	Biomarkers	
Proven	Positive	–	–	–	☐
Probable	Negative	≥5 days	≥2	≥1	☐
None	Negative	0-4 days	0-1	0	☐

Abbreviations: ICD10, International Classification of Diseases 10th revision; WBC, white blood cell; ANC, absolute neutrophil count.

Proven Sepsis

Proven sepsis was defined as a bacterial pathogen identified in the blood including *Enterobacterales* (eg *Escherichia coli), Enterococcus faecalis, Enterococcus faecium, Haemophilus influenzae, Listeria monocytogenes, Pseudomonas aeruginosa, Staphylococcus aureus*, GBS, *Streptococcus dysgalactiae, Streptococcus pneumoniae*, and *Streptococcus pyogenes*. Some bacteria (eg coagulase-negative *Staphylococci*) were considered non-pathogenic as they most likely represent contamination in the near-term to term population. A list of all identified bacteria is provided in the supplement (Supplemental Table S2).

Probable Sepsis

Probable sepsis was defined as a condition without any identified pathogen in the blood, but 1) at least 5 days of antibiotic treatment, 2) at least two clinical signs of infection within two different organ categories, and 3) at least one blood biomarker indicating sepsis. The treatment duration was determined based on guidelines from the Danish Pediatric Society as well as local departmental guidelines.[31] Clinical signs and biomarkers were based on previous definitions by Stocker et al 2017 with some modifications eg maternal risk factors were not part of the definition in the present study.[37] Clinical signs were divided into six different categories including respiratory, heart rate, arterial hypotension, neurological, body temperature, and other symptoms. Biomarkers indicative of sepsis included C-reactive protein (CRP) ≥35 mg/l, white blood cell count (WBC) $<5*10^9$/l, or absolute neutrophil count (ANC) $<1.5*10^9$/l.[17,18,31]

Table 2 Study Criteria for Assessing ICD10 Diagnoses of Early-Onset Neonatal Meningitis Using Medical Record Data Within the First week of Life

Identification of bacteria					Checkbox
Identification of bacterial pathogen in cerebrospinal fluid by culture or molecular testing					☐
Duration of antibiotics					
A total of ≥14 days of antibiotic treatment or died while receiving antibiotics					☐
Neurological affection					
Statement of seizures, hypertonia, hypotonia, lethargy, irritability, or bulging fontanelle					☐
Biomarkers in the cerebrospinal fluid					
WBC $>15*10^6$/l and either >80% neutrophiles, glucose <1.7 mmol/l, or protein >1.3 g/l					☐
Certainty	**Bacterial identification**	**Antibiotics**	**Neurological sign**	**Biomarkers**	
Proven	Positive	–	–	–	☐
Probable	Negative	≥14 days	≥1	1	☐
None	Negative	0-13 days	0	0	☐

Abbreviations: ICD10, International Classification of Diseases 10th revision; WBC, white blood cell.

Criteria for Early-Onset Meningitis

Table 2 provides an overview of the definitions of proven and probable meningitis.

Proven Meningitis

Proven meningitis was defined as any bacterial pathogen identified in the cerebrospinal fluid.

Probable Meningitis

Probable meningitis was defined as a condition without any identified pathogen in the cerebrospinal fluid, but 1) at least 14 days of antibiotic treatment, 2) at least one neurological sign, and 3) analysis of the cerebrospinal fluid consistent with meningitis including WBC >15*10^6/l and either >80% neutrophiles, glucose <1.7 mmol/l, or protein >1.3 g/l.[31,38,39]

Additional Data

Additional information on all neonates with a diagnosis of early-onset infection were obtained from the Danish Medical Birth Register.[40] This included sex, birth year, birth region, mode of delivery, gestational age at birth, birthweight, 5-min Apgar score, umbilical cord pH, maternal age, parity, maternal smoking status, and maternal body mass index.

Statistical Methods

Different reference standards were applied to estimate the validity of the ICD10 diagnoses of sepsis and meningitis. PPVs with 95% CIs were estimated using two definitions: one based solely on proven infection, and another combining both proven and probable infection. The PPVs for all sepsis diagnoses were weighted according to the prevalence of the different diagnosis groups in the total eligible study population. Weighing was unnecessary for meningitis as all patients during the study period were included. PPVs were also calculated separately for the different diagnosis groups of sepsis. For sepsis diagnoses, sensitivity analyses were conducted with probable sepsis 1) only requiring one clinical sign and 2) only requiring C-reactive protein ≥10 mg/l. For meningitis diagnoses, a sensitivity analysis was conducted with probable meningitis only requiring WBC >15*10^6/l in the cerebrospinal fluid as the only biochemical criteria. To assess potential predictors of misclassified diagnoses, the weighted PPVs for sepsis diagnoses were also stratified by calendar year (2010–2014 and 2015–2018), region (Northern, Central, Southern, Zealand, and Capital), type of hospital (regional and university), and type of diagnosis (primary and secondary). Interrater agreement was evaluated by Cohen's kappa. Analyses were performed in Stata (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC).

Approvals and Reporting

The study was approved by the Central Region Denmark (1–16-02-403-21) and Regional Council (1–45-70-106-21). Register-data were received from The Danish Health Data Authority (FABID-00000382). The study was reported in accordance with the revised version of the Standards for Reporting of Diagnostic accuracy (STARD) guidelines (Supplemental Table S3).[41]

Results

Population

Figure 1 provides a flowchart of the study population. The total population consisted of 3,230 neonates identified with an ICD10 diagnosis of early-onset infection between 2010 and 2018, resulting in a prevalence of about 7 per 1,000 live births. Of these, 2,756 neonates (85%) had diagnoses of newborn sepsis with an unspecified pathogen, 220 (7%) had newborn sepsis with a specified pathogen, 190 (6%) had other sepsis, and 64 (2%) had meningitis. Among diagnoses with specified pathogen, the majority specified GBS as the causative bacteria (56%). Four neonates in the validation sample were excluded due to admission after the first week of life. All neonates with no or insufficient data were also excluded (n = 35) with the most of these being from the Southern Region of Denmark (80%) and born between 2010 and 2013 (62%). These missing neonates were likely due to changes in medical record software implemented after the study period. This resulted in a validation sample of 525 neonates including 192 with diagnoses of newborn sepsis with an

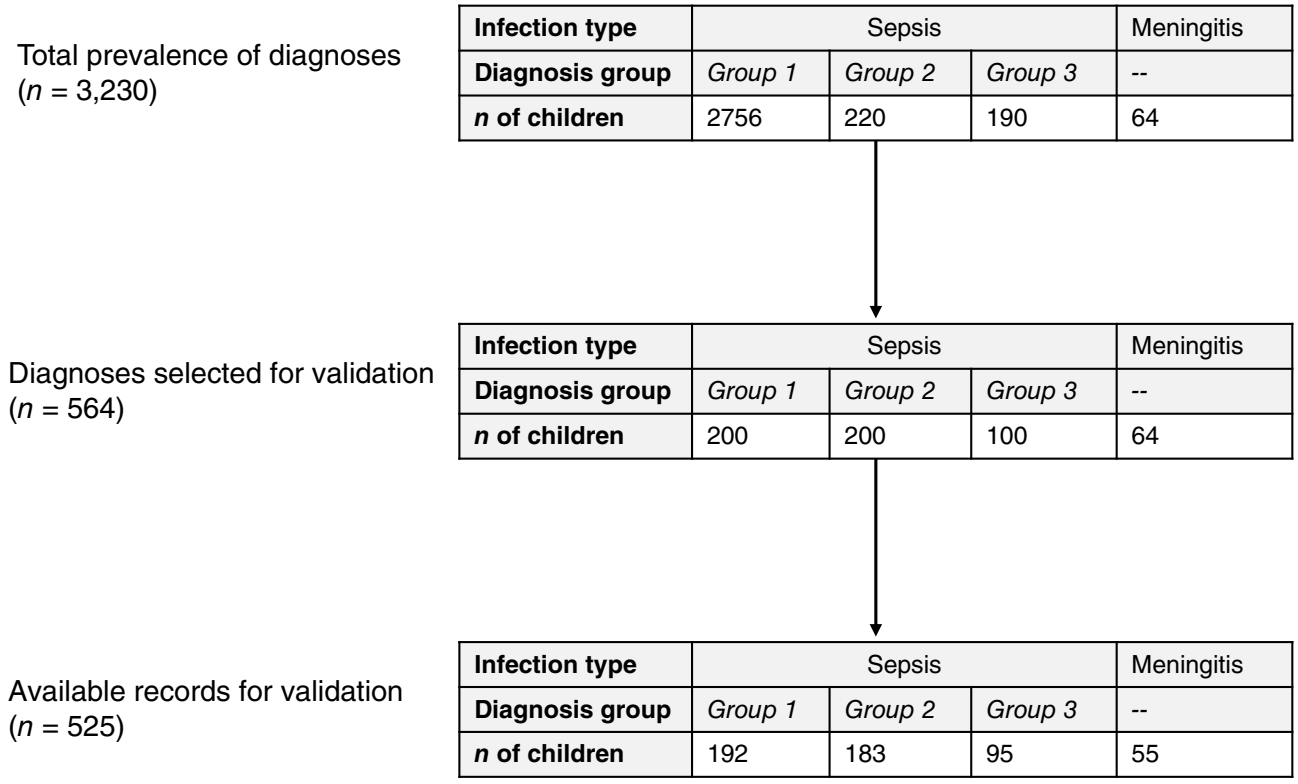

Figure 1 Flowchart of the study population consisting of Danish near-term to term neonates with an ICD10 diagnosis of early-onset neonatal infection from 2010 to 2018.
Notes: Group 1 = ICD10 diagnoses of newborn sepsis with an unspecified pathogen; Group 2 = ICD10 diagnoses of newborn sepsis with a specified pathogen, Group 3 = other ICD10 diagnoses of sepsis.
Abbreviations: ICD10, International Classification of Diseases 10th revision.

unspecified pathogen, 183 with newborn sepsis with a specified pathogen, 95 with other sepsis, and 55 with meningitis. Table 3 shows the characteristics of the neonates included in the validation sample compared to the total eligible study population. Table 4 summarizes the clinical information from the medical records for those included in the validation sample.

Validity of Diagnoses

Table 5 shows the PPVs for the ICD10 diagnoses of early-onset sepsis and meningitis. The weighted PPV for diagnoses of sepsis using the proven definition was 0.04 (95% CI: 0.02, 0.06), while the weighted PPV using both the proven and probable definition was 0.52 (95% CI: 0.45, 0.58). The PPV for diagnoses of meningitis using the proven definition was 0.24 (95% CI: 0.13, 0.37), while the PPV using both the proven and probable definition was 0.38 (95% CI: 0.25, 0.52). Table 5 also shows the PPVs for the different diagnosis groups of sepsis. The estimates varied by diagnosis groups with newborn sepsis with a specified pathogen showing the highest PPV for proven sepsis at 0.36 (95% CI: 0.29, 0.43) and for proven or probable sepsis at 0.65 (95% CI: 0.58, 0.72).

Sensitivity Analyses

When modifying the criteria for probable sepsis to only require one clinical sign, the weighted PPV for diagnoses of sepsis increased to 0.64 (95% CI: 0.58, 0.70). When requiring C-reactive protein to be only >10 mg/l, the weighted PPV increased to 0.63 (95% CI: 0.57, 0.68). When combining the two modified criteria, the weighted PPV increased to 0.75 (95% CI: 0.70, 0.81). When defining probable meningitis with WBC $>15*10^6$/l in the cerebrospinal fluid as the only biochemical criteria, the PPV for diagnoses of meningitis increased to 0.58 (95% CI: 0.44, 0.71).

Table 3 Characteristics of All Danish Near-Term to Term Neonates with an ICD10 Diagnosis of Early-Onset Neonatal Infection From 2010 to 2018

	Sampling frame (n = 2,705)	Validation sample of sepsis (n = 470)	Validation sample of meningitis (n = 55)
Child characteristics			
Male	1,673 (62%)	300 (65%)	36 (63%)
Birth year			
2010-2012	833 (31%)	105 (22%)	14 (25%)
2013-2015	901 (33%)	149 (32%)	15 (27%)
2016-2018	971 (36%)	216 (46%)	26 (47%)
Gestational age, median (IQR), wk	40.6 (39.6–41.4)	40.6 (39.4–41.4)	40.1 (38.6–41.0)
Birth weight, mean (SD), g	3638 (561)	3670 (552)	3578 (661)
5-min Apgar score			
10-7	2,504 (94%)	439 (94%)	–
6-4	107 (4%)	19 (4%)	–
3-0	57 (2%)	8 (2%)	–
pH-value below 7.0	97 (4%)	19 (4%)	–
Region			
Northern	48 (2%)	9 (2%)	–
Central	1,018 (38%)	146 (31%)	–
Southern	302 (11%)	72 (15%)	–
Zealand	318 (12%)	70 (15%)	–
Capital	980 (37%)	173 (37%)	–
University hospital	964 (36%)	153 (33%)	15 (27%)
Maternal characteristics			
Maternal age, mean (SD), years	30 (5.1)	30 (4.9)	31 (5.7)
Nulliparous	1,901 (70%)	299 (64%)	31 (56%)
Smoking during pregnancy	197 (7%)	28 (6%)	–
Body mass index, median (IQR)	24 (21–28)	24 (21–27)	25 (22–30)
Delivery characteristics			
Caesarean section	851 (31%)	139 (30%)	15 (27%)
Induction of labor	1,228 (45%)	216 (46%)	27 (49%)

Notes: Continuous values were reported with means and standard deviations (SD) or medians and interquartile ranges (IQR), while categorical variables were reported as numbers and percentages. Blanks represent values that was not allowed to be reported due to fewer than five observations within categories, in accordance with regulations from the Danish Health Authority.
Abbreviation: ICD10, International Classification of Diseases 10th revision.

Predictors of Misclassified Diagnosis

No significant difference was observed in the weighted PPVs for diagnoses of early-onset sepsis when the estimates were stratified according to calendar year, region, hospital type, or diagnosis type (Table 6).

Table 4 Clinical Information From Medical Records of Danish Near-Term to Term Neonates with a Validated ICD10 Diagnosis of Early-Onset Neonatal Infection From 2010 to 2018

	Validation sample of sepsis (n = 470)	Validation sample of meningitis (n = 55)
Pathogens		
Most common pathogens		
GBS	47 (14%)	6 (11%)
S. aureus	13 (3%)	–
E. coli	8 (2%)	–
Treatment		
Most common antibiotics		
Gentamicin	457 (97%)	50 (91%)
Ampicillin	383 (81%)	46 (84%)
Penicillin	84 (18%)	26 (47%)
Cefuroxime	64 (14%)	–
Treatment duration, median (IQR), days	8 (7–8)	15 (13–21)
Clinical signs of infection		
Respiratory [a]	397 (84%)	50 (91%)
Heart rate [b]	131 (28%)	25 (45%)
Arterial hypotension [c]	156 (33%)	30 (55%)
Neurological [d]	275 (59%)	48 (87%)
Temperature [e]	135 (29%)	33 (60%)
Other symptoms [f]	92 (20%)	17 (31%)
Biomarkers of infection		
C-reactive protein ≥35 mg/l	341 (73%)	40 (73%)
WBC $<5*10^9$/l	15 (3%)	9 (16%)
ANC $<1.5*10^9$/l	–	–
Maternal risk factor of infection		
GBS colonization	59 (13%)	–
PROM	93 (20%)	5 (9%)
Maternal fever	132 (28%)	9 (16%)
Intrapartum antibiotics	130 (28%)	9 (16%)

Notes: Continuous values were reported with medians and interquartile ranges (IQR), while categorical variables were reported as numbers and percentages. Blanks represent values that was not allowed to be reported due to fewer than five observations within categories, in accordance with regulations from the Danish Health Authority. [a]Apnea, tachypnoea, respiratory distress, or respiratory support. [b]Tachycardia or bradycardia. [c]Hypotension or signs hereof. [d]Seizures, hypertonia, hypotonia, lethargy, irritability, or bulging fontanelle. [e]Hyperthermia, hypothermia, or temperature instability. [f]Symptoms from skin or gastrointestinal tract.

Abbreviations: ICD10, International Classification of Diseases 10th revision; WBC, white blood cells; ANC, absolute neutrofile count; GBS, Group B *Streptococcus*; PROM, prolonged rupture of membranes.

Interrater Agreement

A 96% agreement for classifying proven infection was found between the primary and secondary investigator with a Cohen's kappa of 0.84, while an 88% agreement was found for classifying probable infection with a Cohen's kappa of 0.75.

Table 5 The Positive Predictive Values of ICD10 Diagnoses of Early-Onset Sepsis and Meningitis in Near-Term to Term Neonates Born in Denmark from 2010 to 2018 Using Definitions of Proven and Probable Infection as Reference Standards

Diagnosis	Total n	Validation sample n	Proven infection (95% CI)	Proven or probable infection (95% CI)
Sepsis [a]	3,166	470	0.04 (0.02, 0.06)	0.52 (0.45, 0.58)
Group 1	2756	192	< 0.03 [b]	0.51 (0.43, 0.58)
Group 2	220	183	0.36 (0.29, 0.43)	0.65 (0.58, 0.72)
Group 3	190	95	< 0.05 [b]	0.55 (0.44, 0.65)
Meningitis	64	55	0.24 (0.13, 0.37)	0.38 (0.25, 0.52)

Notes: Group 1 = ICD10 diagnoses of newborn sepsis with an unspecified pathogen; Group 2 = ICD10 diagnoses of newborn sepsis with a specified pathogen, Group 3 = other ICD10 diagnoses of sepsis. [a]Weighted estimates based on the distribution of the different diagnosis groups in the sampling frame. [b]The exact positive predictive value was not allowed to be reported due to fewer than five observations within categories, in accordance with regulations from the Danish Health Authority.
Abbreviation: ICD10, International Classification of Diseases 10th revision.

Table 6 Weighted Positive Predictive Values of ICD10 Diagnoses of Early-Onset Sepsis in Near-Term to Term Neonates Born in Denmark from 2010 to 2018 Stratified According to Different Categories

	Total n	Validation sample n	Proven infection (95% CI)	Proven or probable infection (95% CI)
Birth year				
2000-2014	1,599	198	0.05 (0.02, 0.08)	0.49 (0.39, 0.58)
2015-2018	1,567	272	0.04 (0.02, 0.07)	0.54 (0,46, 0.62)
Region				
Northern	57	9	–	–
Central	1,168	146	0.03 (0.01, 0.06)	0.46 (0.36, 0.57)
Southern	398	72	0.04 (0.01. 0.06)	0.53 (0.38, 0.67)
Zealand	388	70	0.07 (0.00, 0.14)	0.51 (0.34, 0.68)
Capital	1,155	173	0.05 (0.01, 0.09)	0.51 (0.40, 0.61)
Hospital				
University hospital	1,121	153	0.02 (0.01, 0.04)	0.53 (0.42, 0.63)
Regional hospital	2,045	317	0.05 (0.03, 0.08)	0.51 (0.43, 0.59)
Diagnose				
Primary diagnosis	2,241	349	0.04 (0.02, 0.05)	0.51 (0.44, 0.59)
Secondary diagnosis	925	121	0.06 (0.01, 0.11)	0.53 (0.42, 0.64)

Notes: Blanks represent values that was not allowed to be reported due to fewer than five observations within categories, in accordance with regulations from the Danish Health Authority.
Abbreviation: ICD10, International Classification of Diseases 10th revision.

Discussion

Key Results

Low PPVs were observed for the ICD10 diagnoses of early-onset neonatal infection in the Danish National Patient Register using the pre-specified reference standards.[19] Our findings suggest that only 4% of neonates with a diagnosis of sepsis have a positive blood culture with a relevant pathogen, while only 52% fulfilled the criteria for either proven or probable sepsis. A similar concern was observed for diagnoses of meningitis with only 24% of neonates having an identified pathogen from the cerebrospinal fluid and only 38% fulfilling the criteria for either proven or probable meningitis.

Interpretation

Only 4% of neonates diagnosed with early-onset sepsis was estimated to have a positive culture from blood, which is in line with the observation that the vast majority had a diagnosis with an unspecified pathogen. However, even the diagnoses with a specified pathogen showed a low PPV with only 36% fulfilling the criteria for a proven infection. An identified pathogen was also rare for diagnoses of meningitis, only found in about 24% of the neonates. Several Danish studies have previously used diagnostic codes for sepsis and meningitis with specified pathogens to examine associations between specific neonatal bacterial infections and neurodevelopmental impairment.[22–27] Most of these studies focused on GBS infections due to the prospect of a future maternal vaccine protecting the neonate against invasive bacterial infection.[42] Our study suggests that estimates from these previous studies could be biased. The reported incidence of GBS infections in Denmark may be overestimated, while the non-differential misclassification of the exposure may have resulted in associations being underestimated. It remains unclear why the treating clinician would decide to include a pathogen in the diagnostic coding, when no pathogen has been identified. In Denmark, no billing incentives exist to code neonatal sepsis as pathogen-specified rather than unspecified. Also, no severity scoring systems rely on the use of these codes. GBS was the pathogen most commonly specified in the ICD10 diagnoses. One could speculate that the clinician specified this pathogen as it is the most common bacteria causing early-onset sepsis in most westerns populations.[28] However, the presence of maternal risk factors for neonatal GBS infection, such as GBS colonization, could also prompt the clinician to assume that this specific bacteria was the most likely agent. At last, some local or institutional coding practices may favor the routine use of pathogen-specific codes when infection is strongly suspected based on these maternal risk factors or characteristic clinical features. Studies from a recent meta-analysis as well as previous studies by the authors have investigated associations between different definitions of neonatal infection and neurodevelopmental outcomes.[6,28–30,43,44] All studies indicated worse outcomes for neonates with a culture proven infection compared to clinical definitions of infection. These findings further highlight the importance of including microbiological data from blood and cerebrospinal fluid in future research exploring pathogen-specific associations. For Danish researchers, the Danish Microbiology Database (MiBa) contains information on all identified pathogens in the Danish Departments of Clinical Microbiology since 2010.[45]

The ICD10 diagnoses of early-onset infection may still be useful for future epidemiological studies when combined with information on identified pathogens, given the potential for false negative bacterial test results in newborns.[12–14] However, the diagnostic validity remained poor even when probable infections also were considered to represent true infections. Only 52% of neonates with a diagnosis of sepsis and 38% with a diagnosis of meningitis met the criteria for either proven or probable infection. We restricted our population to neonates with at least 5 days of admission for sepsis and 14 days for meningitis to ensure that they could have received sufficient intravenous antibiotic treatment, as would be required if the clinicians suspected the infection. Future epidemiological studies may benefit from applying similar criteria based on the relevant national or institutional guidelines for duration of intravenous antibiotics of suspected neonatal infection. To further explore factors that may influence diagnostic accuracy, we also conducted stratified analyses by birth year, region, hospital type, and diagnosis type. However, none of these analyses showed any substantially higher PPVs within any strata.

No consensus definition of neonatal sepsis exists with a previous meta-analysis finding 128 different definitions from 80 randomized clinical trials.[1,7] We defined neonatal sepsis as a multiorgan disease, which therefore would result in clinical signs from at least two organ systems and distortion of at least one biomarker of infection. However, higher PPVs were obtained using more lenient definitions of infection.[7] The PPV for diagnoses of sepsis did increase to 75% when modifying the study criteria for probable sepsis to require only one clinical sign instead of two and CRP $\geq$10 mg/l rather than >35 mg/l. These criteria have previously been used in several other randomized controlled trials.[7] The PPV for diagnoses of meningitis also increased to 58% when WBC >15*10^6/l in the cerebrospinal fluid was the only required biochemical criteria for probable meningitis. However, we believe that these increases in PPVs also come with a higher likelihood of misclassifying neonates who were not truly infected (ie including more false positives in the gold standard). Nonetheless, which definition most accurately identifies neonates with early-onset infection remains uncertain, emphasizing the need for a consensus definition.

This study only examined ICD10 diagnoses of early-onset infection in neonates born after 35 weeks of gestation in Denmark. However, the absence of a consensus definition for neonatal sepsis and meningitis, as well as variability in clinical thresholds for initiating antibiotic treatment, likely contributes to diagnostic differences in other countries as well.[1,46] Our findings suggest that diagnoses of early-onset infection should not be used for international comparisons or collaborative studies aimed at monitoring disease development. In addition, although our estimates may not directly generalize to populations such as preterm neonates or late-onset infections, the findings suggest that studies in these groups should include validation of a subsample of infection diagnoses to assess the reliability of their estimates.

Study Limitations

We conducted a rigorous review of 564 medical records from neonates diagnosed with early-onset neonatal infection, extracting comprehensive information during the first week of life on microbiology, clinical signs, biomarkers, and treatment. However, some limitations should be considered.

The level of detail in the medical records varied considerably. It is likely that some clinical signs were undocumented by the clinicians, potentially leading to an underestimation of the PPVs when also using the definition for probable infection. In addition, we were unable to precisely specify the frequency and durations of the clinical states. The Danish regions use dedicated software to store biomarker data from blood and cerebrospinal fluid. Changes in software after the study period meant that information on biomarkers from some regions was only available if explicitly noted in the medical records (Southern Region, Zealand Region, and Capital Region). This may have further contributed to an underestimation of the PPVs. However, since the clinicians are expected to document any relevant information to support initiation of antibiotic treatment, it is likely that key biomarkers were most often noted. This is in accordance with the fact that no substantial differences were observed between the PPVs when stratifying by region.

In a subsample of 50 neonates, classification agreement between the primary and secondary investigators was almost perfect for proven infections (Cohen's kappa = 0.84) and substantial for probable infections (Cohen's kappa = 0.75).[47] Due to specific regulations for the Southern Region of Denmark, all records from this region were examined by a third investigator. Some discrepancy for the extraction of information from this region may therefore exist. However, it may again be stressed that the PPVs between regions did not vary significantly.

We included all neonates diagnosed with meningitis during the study period, whereas only a randomly selected subsample of neonates with sepsis was included. A complete validation of sepsis cases would have been preferable but was infeasible due to the high number of neonates with this diagnosis. The number of included neonates with sepsis was determined through sample size calculations to ensure sufficient statistical power.

Conclusion

We observed a poor accuracy of the ICD10 diagnoses of early-onset neonatal sepsis and meningitis in the Danish National Patient Register based on our pre-specified criteria. This highlights the importance of considering additional information, such as microbiological data from blood and cerebrospinal fluid, when using the diagnoses to study disease determinants and outcomes as well as disease surveillance. A consensus definition of neonatal sepsis is critically needed to improve guidance on how the diagnoses should be assigned in clinical practice.

Data Sharing Statement

Individual level data may not be shared in accordance with regulations from The Danish Health Authority.

Ethics and Consent

The data accessed were handled in accordance with the Danish data protection and privacy regulations.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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