Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI): an extension of the STROBE statement for neonatal infection research

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Neonatal infections are estimated to account for a quarter of the 2·8 million annual neonatal deaths, as well as approximately 3% of all disability-adjusted life-years. Despite this burden, few data are available on incidence, aetiology, and outcomes, particularly regarding impairment. We aimed to develop guidelines for improved scientific reporting of observational neonatal infection studies, to increase comparability and to strengthen research in this area. This checklist, Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE- NI), is an extension of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. STROBE-NI was developed following systematic reviews of published literature (1996–2015), compilation of more than 130 potential reporting recommendations, and circulation of a survey to relevant professionals worldwide, eliciting responses from 147 professionals from 37 countries. An international consensus meeting of 18 participants (with expertise in infectious diseases, neonatology, microbiology, epidemiology, and statistics) identified priority recommendations for reporting, additional to the STROBE statement. Implementation of these STROBE-NI recommendations, and linked checklist, aims to improve scientific reporting of neonatal infection studies, increasing data utility and allowing meta-analyses and pathogen-specific burden estimates to inform global policy and new interventions, including maternal vaccines.

Introduction

Progress in improving child survival has been one of the greatest successes in international development.[1] However, there is an unfinished agenda,[2] since the mortality reduction has been slowest for neonates. Almost half (44%) of all child deaths now occur in the neonatal period (0–27 days),[3] with a substantial burden of mortality in the first few days after birth.[4] The Every Newborn Action Plan sets out a United Nations-led platform, endorsed by all countries, to end preventable neonatal deaths, but requires data to implement and inform innovation.[2,5]

Estimates by WHO for 195 countries suggest that infection accounts for around 680 000 deaths—a quarter of all neonatal deaths yearly;[6] and half of all neonatal deaths in settings with high neonatal mortality.[2] The closely linked 2·6 million annual stillbirths have an as yet poorly quantified infection burden.[7] Significant neurodevelopmental impairment affects approximately a quarter of neonates following meningitis, but few data exist regarding impairment worldwide, particularly for common infection syndromes such as sepsis and pneumonia.[8,9]

An estimated 6·9 million neonates have possible serious bacterial infection annually in sub-Saharan Africa, south Asia, and Latin America.[8] Approximately 84% of neonatal deaths attributed to infections could be averted by increasing coverage of prevention and access to treatment, yet currently the gap is high, especially in the poorest countries.[10] Recent large clinical trials have assessed the safety and efficacy of improving access to treatment through outpatient care, in cases for which referral is not possible.[11–13]

Aetiology-specific data for neonatal infections are scarce, and challenging to combine. Hospital-based studies suggest that *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* spp, and group B streptococci might be the most common pathogens globally.[14] As yet, there are no community-based aetiological studies from Africa, and few from south Asia. There is an urgent need to improve data on aetiology (bacterial, viral, and fungal), incidence (especially in the first days following birth), antimicrobial sensitivity, and outcomes. These data are essential to understand the burden and risk factors, refine treatment algorithms, support potential interventions (eg, maternal vaccines for respiratory syncytial virus and group B streptococcus),[15–17] and mitigate antimicrobial resistance, which threatens current treatment strategies.[18–20]

Recording, reporting, and interpreting neonatal infection data poses specific challenges. More than 95% of neonatal deaths occur in countries without adequate birth and death certification to capture cause-specific mortality,[2,6] let alone pathogen-specific surveillance. Systematic clinical assessment, with investigations providing microbiological data, is also uncommon.[8] Most available neonatal infection data are from tertiary referral hospitals, with recruitment bias, by missing those not accessing higher levels of care, or any care.[21] In population-based studies, which are extremely few in high-burden settings,[22–24] even if women are recruited in

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See Online for appendix

pregnancy, the challenge remains that many neonates die within hours of birth before being assessed, meaning counting, investigations, and treatment are missed.[25] In a population-based Bangladeshi cohort, 62% of neonates who died were never clinically assessed, with 59% of deaths occurring within 48 h of birth.[22] Even when cases are captured in the numerator and denominator, case definitions are often inconsistent. Diagnosis is usually based on clinical expertise, or in settings with fewer health workers, on simplified clinical algorithms designed to be highly sensitive. For example, the most commonly used WHO algorithm to classify young infants with possible serious bacterial infection is very sensitive (85%) and fairly specific (75%).[26–28] Additionally, unlike childhood infections, gestational age has a major effect on incidence, aetiology, and outcomes of neonatal infections. Neonates of 25 and 35 weeks' gestation are both preterm, yet differentiation between the two is often missing in reported data, which is crucial for interpretation.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[29] and Consolidated Standards of Reporting Trials (CONSORT)[30] statements were developed to improve scientific reporting. Several extensions of these statements have been published with additional recommendations for specialised fields of research—for example, the Strengthening the Reporting of Molecular Epidemiology for Infectious Diseases (STROME-ID)[31] and the Outbreak Reports and Intervention Studies of Nosocomial Infection (ORION)[32] statement. These extensions build on the principles of STROBE and CONSORT but explicitly address additional, problematic methods or settings. There are reporting guidelines under development that are specific to child health trials (SPIRIT-C; CONSORT-C),[33] and for systematic reviews and meta-analyses (PRISMA-C; PRISMA-PC).[34] We aim to address the specific challenges in reporting neonatal infections, using the STROBE[29] model. If these recommendations are applied by upcoming epidemiological and interventional studies on neonatal infections, the value of new data will increase, avoiding research waste.[35]

Aims of STROBE-NI

The purpose of these guidelines is to promote transparency, clarity, and comparability of scientific reporting, specifically for neonatal infection research. We focus on observational studies (although many elements will be true for other study designs), and include detailed consideration of aetiological (bacterial, viral, and fungal) data. Through improved reporting, we aim to facilitate reliable comparison of emerging newborn infection data across settings worldwide, and the synthesis of robust evidence to inform public health interventions. Our objectives were to assess current reporting components for neonatal infection in the scientific literature, to list all potential reporting items, and to use an online survey and expert consensus process to develop the STROBE-NI checklist. This checklist is intended to guide authors, reviewers, publishers, and funders of neonatal infection studies. We focused on factors that are not included in STROBE or other extensions.

Development of the STROBE-NI checklist

The STROBE-NI checklist was developed following recommended methods.[36] The participants, processes, and outputs are shown in figure 1. We searched the scientific literature to identify highly cited publications on neonatal infection from different regions worldwide (1996–2015), and more recent (2011–15) articles from high impact journals (see appendix for literature search criteria). Additional searches were done for reporting guidelines relevant to neonatal infections.

Through these reviews we identified a list of 133 reporting items, which was developed into an online survey (appendix). Respondents were asked to comment and/or rate the importance of each item in the list by selecting either "unnecessary", "sometimes useful", "important for most studies", or "essential for all studies". Participants were also asked to identify definitions and classifications needing discussion and clarification. The survey was disseminated to relevant investigator groups, corresponding authors of reviewed papers, and professional infectious disease and paediatrics networks worldwide (figure 1). 147 experts replied, from 37 countries, with more than 41% from low-income or middle-income countries (appendix).

In June, 2015, a group of 18 international, multidisciplinary experts (epidemiologists, statisticians, microbiologists, paediatricians, neonatologists) met in London to examine the literature reviews, potential reporting items, and survey results, and to draft the structure and content of the recommendations. Recommendations were aligned with STROBE items in one draft checklist, as a topic-specific implementation[36] of the STROBE statement.

The draft checklist was reviewed and revised by the expert group, disseminated to survey participants, and members of networks such as the Enhancing the Quality and Transparency of Health Research (EQUATOR) network, for further review and feedback, resulting in a final STROBE-NI checklist (table).

STROBE-NI standards

The final STROBE-NI checklist is an extension of the 22-item STROBE checklist, with 28 additional elements relating to neonatal infection. The STROBE-NI checklist includes a suggested flow diagram for both the recruitment and follow-up of mothers and newborn babies, for which a template is provided in figure 2. Here, we describe the additional recommendations for STROBE-NI that are not already outlined in detail in STROBE or other extensions.

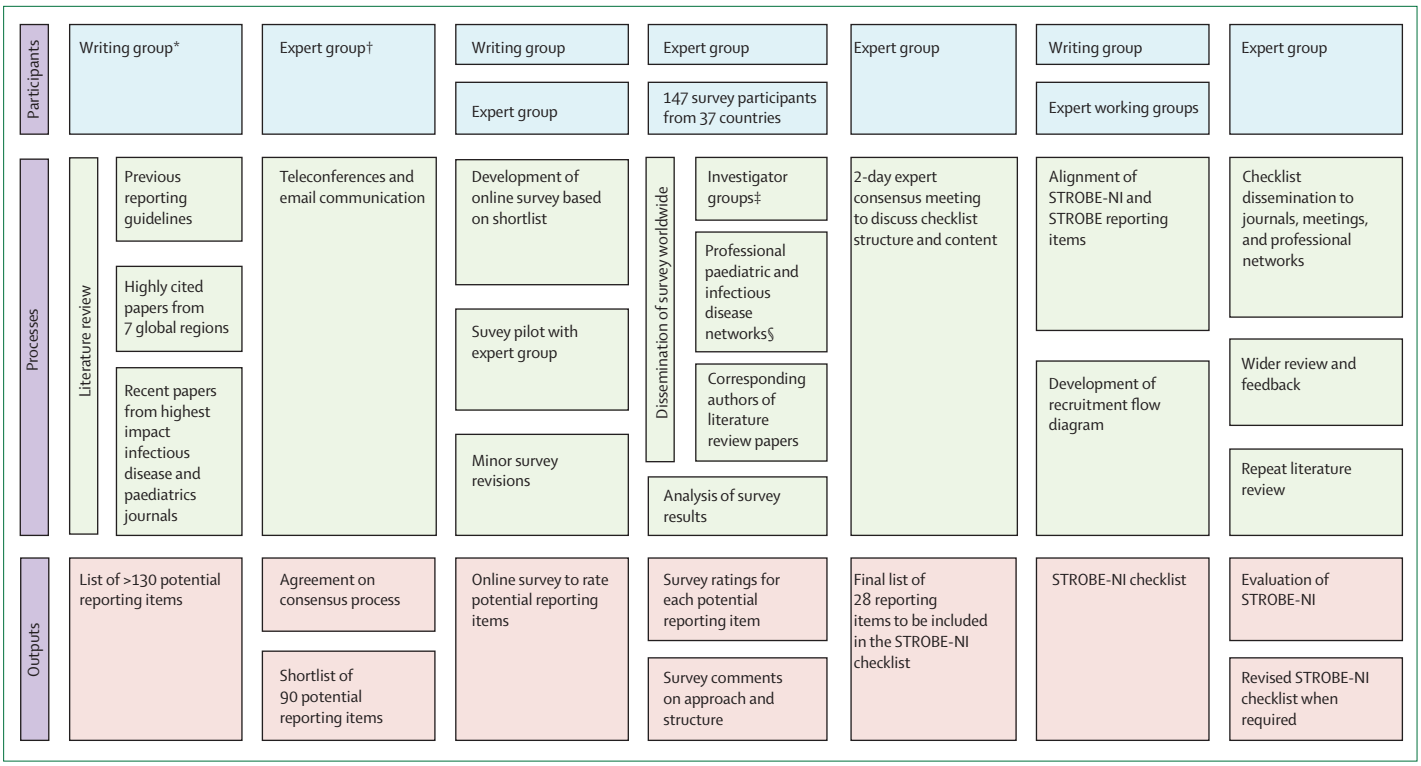

***Figure 1*: Development process for the STROBE-NI checklist, showing participants, processes, and outputs**

STROBE=Strengthening the Reporting of Observational Studies in Epidemiology. STROBE-NI=Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection. *Investigators EJAF, ACS, SV, MS, PTH, SKS, and JEL. †Investigators ACS, SV, MS, PTH, SKS, RA, AIA, ZAB, RB, KB, HC, SC, GLD, SAM, AS-tM, NM, JP, SQ, SJS, BJS, SNW, RDW, and JEL. ‡Possible Serious Bacterial Infection (pSBI) Investigator Group; African Neonatal Sepsis Trial (AFRINEST) investigators. §Infectious Disease Research Network; British Paediatric Allergy, Immunology and Infectious Diseases Group; Neonatal Infectious Disease Network; UK Infection in Critical Care Quality Improvement Group; Australian and New Zealand Neonatal Network; Global Antibiotic Resistance, Prescribing, and Efficacy Among Neonates and Children; NICHD Neonatal Research Network; NICHD Global Network for Women and Children's Health; All India Institute of Medical Sciences; Maternal, Adolescent, Reproductive and Child Health Centre.

Methods: study design

Clinical case definitions

Authors should describe the individual clinical signs used in clinical case definition algorithms (STROBE-NI 4.1), and state whether case ascertainment was through physician diagnosis or a clinical algorithm (eg, Young Infants Clinical Signs Study Group algorithm for possible serious bacterial infection).[26,27] Definitions of neonatal infection syndromes (pneumonia, meningitis, and sepsis) are important for consistency and comparability; however, they cannot be distinguished on clinical grounds alone. When reporting case definitions of specific syndromes, authors should state the microbiological and/or laboratory and/or radiological criteria for diagnosis (STROBE-NI 4.1), differentiating between probable and confirmed cases. For meningitis, the indications for lumbar puncture should be described (STROBE-NI 4.1). Case definitions should be aligned to international standards when available, and ideally be clinically validated.[26] Clinical algorithms might introduce case ascertainment bias, and potential limitations of case definitions should be discussed.

Authors should state the criteria used to differentiate between new infection episodes and relapses (STROBE-NI 4.2). For example, new episodes can be considered when clinical signs develop more than 7 days after stopping treatment, versus a relapse, with reoccurrence of clinical signs within 7 days of stopping treatment. This information is important for health-care-associated infections, which should be explicitly differentiated from community-acquired infections, with reference to an international standard definition (STROBE-NI 4.3).[37] If relevant, specific hospital-acquired infections such as ventilator-associated pneumonia and central-line-associated bloodstream infection should be defined, and presented separately.[37] Reporting whether the observed cases were part of an outbreak (see ORION statement[32]) is essential, as is the definition used for outbreaks (STROBE-NI 4.4).

Microbiological sampling

The microbiological sampling strategy for infections should be presented (STROBE-NI 4.5), such as samples being taken from all participants, or a subset meeting a case definition (eg, possible serious bacterial infection). This information is important given that the positive and negative predictive values of tests differ according to the

	Item number	STROBE items	STROBE-NI items
Title and abstract			
Introduction	1	(a) Indicate the study's design with a commonly used term in the title or abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	..
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	..
Objectives	3	State specific objectives, including any prespecified hypotheses	..
Methods			
Study design	4	Present key elements of study design early in the paper	STROBE-NI 4.1: clearly state case ascertainment methods (eg, physician diagnosis, clinical algorithm), documenting individual clinical signs used for diagnosis of possible serious bacterial infection. Give microbiological and/or laboratory and/or radiological criteria for other infectious syndromes (eg, meningitis, sepsis, pneumonia). Include indications for clinical investigations (eg, lumbar puncture) STROBE-NI 4.2: give criteria used to differentiate between new infection episodes and relapses STROBE-NI 4.3: for facility-based studies, indicate if the study is of community and/or hospital-acquired infections (HAI), defining HAI using an international standard and presenting specific HAI clinical syndromes separately STROBE-NI 4.4: state whether this is an outbreak study, and if so define an outbreak, with reference to an international standard STROBE-NI 4.5: describe sampling strategy (eg, clinical indication *vs* routine surveillance) and sampling details (eg, minimum volumes; timing in relation to antimicrobial administration) STROBE-NI 4.6: describe conventional and/or molecular microbiological methods used, with details (eg, automation, enrichment steps), and the use of controls STROBE-NI 4.7: list pathogens that are likely to be identified by microbiological methods used STROBE-NI 4.8: describe antimicrobial susceptibility tests and thresholds used, with reference to an international standard (eg, CLSI or EUCAST)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	STROBE-NI 5.1: describe the study context in terms of incidence of neonatal mortality, stillbirth, and preterm birth STROBE-NI 5.2: describe the population included (eg, facility births, referrals from home, referrals from another facility) STROBE-NI 5.3: for community-based studies, describe care-seeking and adherence and time to referral STROBE-NI 5.4: for facility-based studies, describe obstetric care (basic or comprehensive), including proportion of births by caesarean section. Report annual number of livebirths per facility and state proportion of births in the study area that occur in hospital (*vs* community) STROBE-NI 5.5: for facility-based studies, indicate if the facility is public or private, and give the number of health-care staff and their training. Indicate the level of neonatal care available (eg, ventilatory support, indwelling catheters) and investigations available (eg, biochemistry, radiology). Report antimicrobial guidelines used for the empiric management of neonatal sepsis STROBE-NI 5.6: state the laboratory location and capacity to process different sample types, and give quality control and assurance measures in place
Participants	6	(a) *Cohort study*—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—give the eligibility criteria, and the sources and methods of selection of participants (b) *Cohort study*—for matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—for matched studies, give matching criteria and the number of controls per case	STROBE-NI 6.1: state age of participants (eg, 0–27 days defines neonates; day 0 as day of birth). Disaggregate neonatal data from that of older infants and from stillbirths
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	STROBE-NI 7.1: state criteria used to define clinically significant organisms for each sample type
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	..
Bias	9	Describe any efforts to address potential sources of bias	..
Study size	10	Explain how the study size was arrived at	..

(Table continues on next page)

	Item number	STROBE items	STROBE-NI items
(Continued from previous page)			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	..
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study*—if applicable, explain how loss to follow-up was addressed *Case-control study*—if applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—if applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	..
Results			
Participants	13*	(a) Report numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	STROBE-NI 13.1: see figure 2 for suggested components of a flow diagram for neonatal infections
Descriptive data	14*	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) *Cohort study*—summarise follow-up time (eg, average and total amount)	STROBE-NI 14.1: describe maternal infections (clinical or on screening—eg, group B streptococcus or HIV) or risk factors for infection (eg, premature rupture of membranes, peripartum fever) STROBE-NI 14.2: describe key neonatal characteristics, including sex, postnatal and gestational age categories (range and median), birthweight categories (range and median), birth place, feeding (breastmilk or other), and comorbidities STROBE-NI 14.3: report data on occurrence of individual signs, according to case definitions STROBE-NI 14.4: give proportion of mothers and neonates with peripartum antibiotic exposure (with or without pre-admission exposure for neonates). Report details of antimicrobial drugs (or supportive care) given during the study
Outcome data	15*	*Cohort study*—report numbers of outcome events or summary measures over time *Case-control study*—report numbers in each exposure category, or summary measures of exposure *Cross-sectional study*—report numbers of outcome events or summary measures	STROBE-NI 15.1: report the number (and the proportion) of samples microbiologically tested (including lumbar punctures for meningitis cases); the number (and the proportion) that were positive (including thresholds for detection, where applicable); all isolates obtained (including clinically significant and non-significant); and antimicrobial susceptibilities of pathogens, where done STROBE-NI 15.2: report the number (and the proportion) of babies with microbiologically proven infection (and number of infections per baby), and include this in the flow chart (see figure 2) STROBE-NI 15.3: report infections by day, for days 0–6. State age categories, if used, defining early-onset and late-onset infection (eg, <72 h and ≥72 h, respectively) STROBE-NI 15.4: report deaths and any subanalyses by risk groups
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorised (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	STROBE-NI 16.1: for incidence, give risk per 1000 livebirths, or if alternative denominator used (eg, total births or bed days), define this clearly
Other analyses	17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses	..
Discussion			
Key results	18	Summarise key results with reference to study objectives	..
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	STROBE-NI 19.1: discuss sources of recruitment bias, particularly regarding the period of time shortly after birth. State source of denominator data and discuss possible related biases
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	..
Generalisability	21	Discuss the generalisability (external validity) of the study results	..

(Table continues on next page)

	Item number	STROBE items	STROBE-NI items
(Continued from previous page)			
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	..
Ethics	23	..	STROBE-NI 23.1: report any ethical considerations, including the recruitment of young mothers (minors), and the consent process for early recruitment of neonates after delivery. Provide details of research ethics approval or state why not required

STROBE=Strengthening the Reporting of Observational Studies in Epidemiology. STROBE-NI=Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection. CLSI=Clinical and Laboratory Standards Institute. EUCAST=European Committee on Antimicrobial Susceptibility Testing. *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

***Table*: The STROBE checklist and additional STROBE-NI items**

prevalence in those sampled. For instance, if few cases of possible serious bacterial infection have lumbar punctures, then cases of meningitis might not be captured. The number of participants from whom samples were taken and sample type should be provided, including sample volume ranges for blood cultures, or minimum sample volume, because small volumes reduce sensitivity. Authors should report whether samples were taken before antimicrobial administration (as antimicrobial exposure reduces sensitivity of testing; STROBE-NI 4.5).

Microbiological methods

Detailed reporting of laboratory methods is essential to assess implications and potential biases (STROBE-NI 4.6). To assess the extent of diagnostic investigation, a list of pathogens (or types of pathogen) being tested for, or likely to be identified by the methods used, should be available (including bacteria, viruses, and fungi; STROBE-NI 4.7). For diagnostic technologies using molecular methods, details of the assay should be given, describing any control samples used to determine clinical significance of detected organisms.[38–40] Authors should report methods for antimicrobial susceptibility testing according to an international standard (eg, Clinical and Laboratory Standards Institute), stating the susceptibilities tested and the criteria used to determine susceptibility to each antimicrobial drug (STROBE-NI 4.8). Methods of molecular analyses[41] should be explained (eg, for whole genome sequencing, details of mapping to reference genomes and quality assessment of sequences). Further details are in STROME-ID.[31]

Methods: setting

Context and denominator

If available, preterm, stillbirth, and neonatal mortality risks or rates at the study facility are helpful contextual information (STROBE-NI 5.1). These data could be presented as the annual number of deaths, preterm births, and stillbirths at the health facility, with livebirths (including the definition of livebirth used) or total births at the facility as the denominator.

When considering infection acquisition, stratification into "inborn" or "outborn" is not specific enough to be helpful, because multiple pathways to health-care presentation exist; "outborn" could reflect births at home or at another facility, and "inborn" does not differentiate between those admitted from birth, and those returning to the facility following discharge. Alternative categories are "admitted from birth at this facility", "referred from another facility", or "referred from home" (STROBE-NI 5.2). If specifying place of birth as a variable, similar categories of "born at this facility", "born at another facility", or "born at home" could be used.

Community studies

Community-based studies (ie, those that recruit participants from home or follow up a community cohort) should report the surveillance strategy, including whether active or passive, and the methods used for defining and enumerating the population. Passive surveillance can underestimate disease, especially where care seeking is low (varying from 10% to 100%),[21] and an estimate of this should be made if possible. For active surveillance, if clinical algorithms are used by community health workers visiting homes, this should be documented, including visitation schedules. Active surveillance increases case ascertainment, particularly on days when visits are made.[42] In view of variation in adherence to referral, details on referral (including time from first presentation to treatment) are necessary, as well as loss to follow-up (STROBE-NI 5.3). These details could be presented in a flow diagram (figure 2).

Facility-based studies

In facility-based studies (ie, those that recruit participants from a hospital or neonatal care unit), levels of neonatal and obstetric care differ greatly. Authors should describe the obstetric care available,[43] including the percentage of births that occur in a facility (*vs* the community) and the incidence of operative delivery (STROBE-NI 5.4). Details about the level of neonatal care in place are essential, including availability of basic neonatal care (eg, resuscitation, breastfeeding practices) and if there is

intensive neonatal care such as ventilation (eg, invasive, non-invasive, oxygen), indwelling catheters, intravenous fluids, staffing (eg, nurse-to-patient ratio), non-microbiological investigations (eg, biochemistry, radiology), and treatment (eg, antimicrobial drugs available; STROBE-NI 5.5). If relevant, specific clinical infection control measures in place (and level of adherence) can be important contextual information to understand potential routes of infection acquisition and transmission.

The microbiology laboratory should be described, including location, facilities for different sample types, and capacity for conventional or molecular microbiology, or both. Laboratory quality control and quality assurance measures should also be reported (STROBE-NI 5.6).

Methods: participants

Neonatal age groups

The neonatal period is defined as less than 28 days (ie, day 0 to 27·99) from birth. For babies born before 37 weeks' gestation, noting gestational age at birth is essential to allow age correction. Disaggregating neonatal data from infants and children is important because of differing risk factors, aetiologies, and outcomes (STROBE-NI 6.1).[44] Timing is crucial for neonatal infections because incidence rates for pathogens, such as group B streptococcus, vary by day.[45] The day of birth is best termed day 0, as used in demographic work and most epidemiological studies (STROBE-NI 6.1). Time limits vary as to when day 0 becomes day 1 (eg, at midnight, or 24 h after birth), and the method used should be stated.[4]

Methods: variables

Clinical significance of pathogens

Authors should be explicit about the clinical significance of the organisms detected, which can vary across settings (particularly organisms associated with indwelling devices—eg, coagulase-negative staphylococci)[46] and the rationale for determining clinical significance should be stated, including control data, if available.[38–40] Publishing comprehensive lists of detected organisms, by sample type (eg, cerebrospinal fluid, blood), categorised as clinically significant, probably significant, and clinically non-significant (the preferred term to "contaminant") are encouraged (STROBE-NI 7.1), since criteria for clinical significance can change over time.

Results: participants

Flow diagram

Figure 2 shows how the flow of eligibility, recruitment, sampling, and diagnosis can be mapped in neonatal infection studies, including mothers and neonates (STROBE-NI 13.1).

Results: descriptive data

Maternal infections, and risk factors for infection, are important to report because maternal infections can result in vertical transmission and early-onset neonatal infections, or stillbirth.[47,48] Results of antenatal screening tests (eg, for group B streptococcus, syphilis, HIV), when done, and risk factors at delivery (eg, prolonged rupture of membranes [>18 h], fever, maternal urinary tract infection; STROBE-NI 14.1) are important for identifying high-risk groups and informing interventions.[49]

Authors should describe neonatal characteristics, including sex, postnatal and gestational age categories (eg, <28 weeks; 28 to <32 weeks; 32 to <37 weeks; ≥37 weeks),[50] birthweight categories (eg, ≤1500 g; 1501–2500 g; >2500 g), place of birth, and mode of feeding, and state ranges and medians for each numeric variable (STROBE-NI 14.2). Comorbidities (eg, neonatal encephalopathy) should be reported, including any

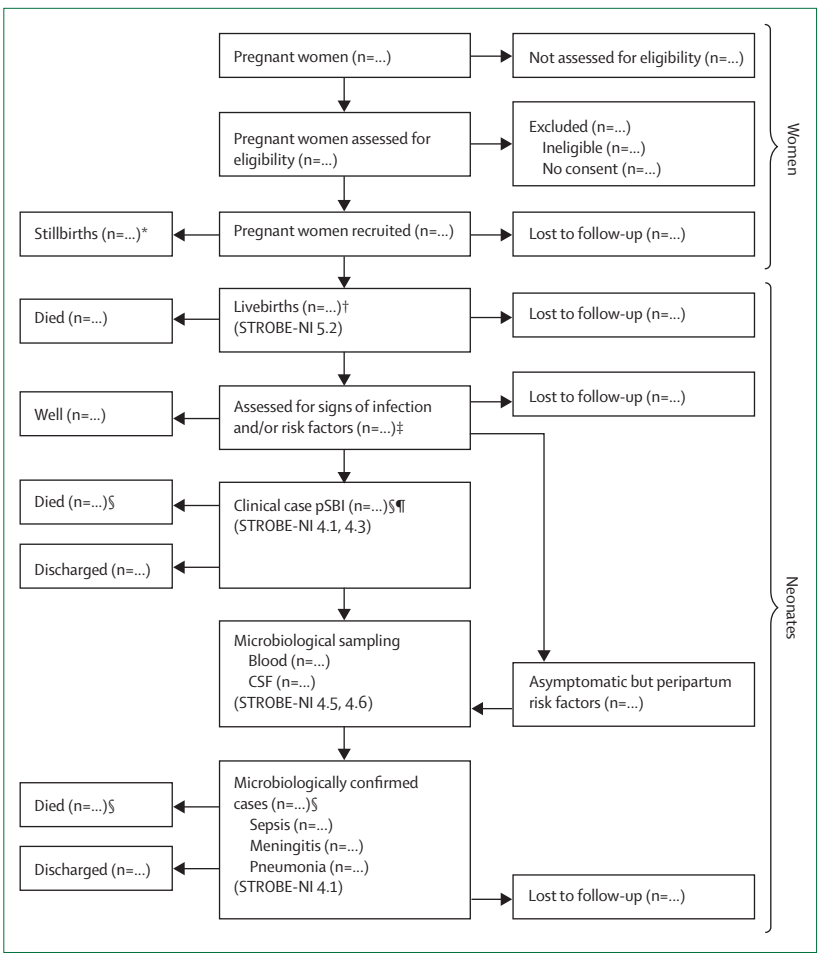

***Figure 2*: STROBE-NI recommended flow chart showing recruitment and participation in the study**
STROBE-NI=Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection. CSF=cerebrospinal fluid. pSBI=possible serious bacterial infection. *Give details of assessment, microbiological sampling if done. †If livebirths are assessed for eligibility (rather than pregnant women), give numbers of livebirths assessed for eligibility and then recruited after this box. ‡If neonates are assessed (eg, at admission for care), give the numbers of neonates assessed and recruited. Differentiate between neonates born at home, at this facility, or at another facility (STROBE-NI 5.2). §Give details by day if possible. ¶Give clinical algorithm used to define pSBI (STROBE-NI 4.1) and clinical signs for each neonate if possible (STROBE-NI 14.3).

Search strategy and selection criteria

We searched Scopus to identify the three leading research articles published (most citations per year) on neonatal infection, from seven regions worldwide (1996–2015; last search Feb 27, 2015), and PubMed for more recent research articles (2011–15; last search March 15, 2015) in paediatric and/or infectious disease journals with the highest impact factors (Thomson Reuters) in 2015. We used the search terms "neonat*" OR "newborn*" OR "newborn infant*" OR "young infant*" AND "infect*" OR "sepsis" OR "meningitis" OR "pneumonia" OR "tetanus" OR "omphalitis". There were no language restrictions. We excluded papers presenting data only on very high-risk neonatal populations (eg, extremely premature) or those focusing on HIV, tuberculosis, or congenital infections. Additional searches were done for reporting guidelines relevant to neonatal infections using the EQUATOR network website and PubMed.

For the **EQUATOR network** see http://www.equator-network.org

exclusion from analysis (STROBE-NI 14.2). Reporting of individual clinical signs is encouraged (STROBE-NI 14.3)[8] to allow comparison with other studies and this information can be helpful in refining diagnostic algorithms.[2]

Details of treatment given before and after enrolment are important (STROBE-NI 14.4). Serum antimicrobial testing has shown that parents under-report antimicrobial administration;[22] thus, it is preferable to report results of testing. Use of intrapartum antibiotic prophylaxis and its indication (eg, maternal risk factors *vs* positive screening for group B streptococcus)[51] should be reported to inform interpretation of culture results (STROBE-NI 14.4).

Results: outcome data

Microbiological results

Microbiological results should be reported in the context of participants recruited, and the number and type of samples taken (STROBE-NI 15.1–15.2). For example, the number of participants meeting clinical criteria for diagnostic lumbar puncture should be provided, as well as the cerebrospinal fluid results. The number and proportion of microbiologically proven clinical infections should be given, and incorporated within a flow diagram (figure 2; STROBE-NI 15.2).

Reporting all organisms detected (eg, as an appendix), including those considered clinically non-significant, is helpful. For molecular assays in particular, reporting thresholds for detection and the organisms detected in control samples supports clinical case interpretation.[38–40] Antimicrobial susceptibility data are essential to guide future antimicrobial policy development (STROBE-NI 15.1). It is helpful to provide raw antimicrobial susceptibility test result data (eg, minimum inhibitory concentrations), which can be analysed further in the future if international standards change.

Timing of infection

If categorisation into early-onset (eg, within 72 h of birth) and late-onset (eg, after 72 h of birth) disease is used, these terms should be clearly defined (STROBE-NI 15.3). Because of the changing aetiologies of neonatal disease, reporting infections by day for the first week after birth (days 0–6; STROBE-NI 15.3) is more informative than dichotomous categories, and might improve understanding of early-onset and late-onset disease.[45]

Mortality and long-term outcomes

Mortality and other serious clinical outcomes should be reported (STROBE-NI 15.4), ideally by day (figure 2). If sample size allows, stratification of mortality by potential risk factors including sex, birthweight categories, gestational age groups,[50] infection syndromes, individual pathogens, or antimicrobial resistance profiles, can highlight intervention opportunities for high-risk groups.

If authors are reporting other long-term outcomes, such as neurological impairment, an international standard approach should be used, including the timing of follow-up and assessment.

Results: main results

Incidence

For incidence, the selection and source of the denominator should be explained, as previously mentioned. For neonates the usual method is to calculate incidence risk per 1000 livebirths (STROBE-NI 16.1), because the time period (28 days) is short.

Discussion: limitations

Bias

The first 12–48 h after birth are critical, because the survival curve is steep,[4] and causes of infection differ later after birth. These aetiologies can be systematically underestimated if there is recruitment bias arising from lack of poor access to care, or death before accessing care (STROBE-NI 19.1).[44] Identification of the possible causes of recruitment and other biases in studies is therefore essential in the interpretation of findings.

For all denominators used, authors should state the source (eg, hospital data or census/registration data), commenting on possible bias (STROBE-NI 19.1).

Other information

Ethics

Because of ethical issues around recruitment, consent, and sampling in neonates, approaches taken must be reported, including processes for requesting consent from young mothers (minors; STROBE-NI 23.1).[52,53] If the timeframe for sample collection and obtaining consent is limited (eg, during delivery), a staged process of consent might be appropriate, to avoid exclusion of emergency cases (and reduce recruitment bias).[54]

Implications of STROBE-NI

The STROBE-NI checklist provides a tool for researchers, funders, reviewers, and publishers to improve neonatal infection data, which have specific, previously unaddressed, requirements for scientific reporting. Building on the STROBE[29] statement and its related extensions, the checklist mainly targets observational studies.[29] However, STROBE-NI checklist items should also be considered for randomised controlled trials, alongside other guideline extensions.[33,34] To our knowledge, there are no other reporting guidelines specific to neonatal health research.[34] Although neonatal infections are a priority starting point, future reiterations should also address other aspects of neonatal research, as well as maternal and stillbirth outcomes. Only recommendations for reporting acute outcomes of infection were included in this checklist. However, we recognise that other important long-term outcomes, such as neurological impairment, are increasingly being assessed, and are important to include.[55] Reporting guidance for impairment outcomes after neonatal infection as well as other common neonatal complications, such as preterm birth,[56] is an area for future development.

The STROBE-NI checklist guides minimum standards for high-quality reporting but is not exhaustive, and some research objectives or contexts might necessitate other details. For instance, new technologies, such as molecular investigations,[31,38] are likely to require additional descriptors. This list was designed to be applicable to a wide range of settings, including those with limited resources and a high burden of neonatal infection. To achieve this, we sought inputs from around the world through experts and our online survey, as well as systematic literature reviews.

Uptake of the STROBE-NI checklist depends on dissemination through global research networks and meetings, and use by journals, funders, and academics. Feedback and suggestions for improvement are welcomed, because the STROBE-NI checklist will be updated periodically. Going forward, we intend to present explanation and elaboration of this guidance (to build on that included in the appendix), develop abstract guidance for conference submissions, and assess the impact of STROBE-NI, as is recommended.[36]

The STROBE-NI checklist has been developed at a crucial point in time for emerging opportunities in neonatal infection research. It is a demonstration of a new commitment towards reducing the unacceptable burden of mortality and morbidity from neonatal infection, and more broadly, as part of the movement to end preventable maternal and newborn deaths, and stillbirths.[5,57–59]

Contributors

EJAF, ACS, SV, MS, PTH, and JEL coordinated the expert group and planned the expert meeting. EJAF, ACS, and SV did the literature reviews and compiled the initial list of potential reporting items. SV, ACS, EJAF, and JEL developed the online survey. ACS, SV, MS, PTH, SKS, RA, AIA, RB, KB, HC, SC, GLD, NM, JP, SQ, SNW, RDW, and JEL participated in the expert meeting and developed the STROBE-NI checklist, chaired by MS, SKS, RB, HC, SC, and JEL, and coordinated by EJAF. EJAF, ACS, and JEL wrote the first draft of the manuscript. ACS, SKS, and JEL developed the flow diagram with feedback from RDW, PTH, RA, and SJS. SV, MS, PTH, RA, AIA, ZAB, RB, HC, SC, GLD, SAM, AS-tM, NM, JP, SQ, SJS, and BJS edited and contributed to successive versions of the manuscript.

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Declaration of interests

SKS has received a grant from the Bill & Melinda Gates Foundation to run a multicountry study on neonatal infection in south Asia. SAM reports grants from the Bill & Melinda Gates Foundation, grants and personal fees from GSK, grants and personal fees from Pfizer, personal fees from MedImmune, and personal fees from Sanofi Pasteur, outside the submitted work. AS-tM and JP are salaried employees of the Bill & Melinda Gates Foundation. AS-tM was previously a salaried employee for Novartis Vaccines Research and Development (2012–13). NM reports membership of the steering groups of the UK Infection in Critical Care Quality Improvement Programme, the Royal College of Paediatrics and Child Health National Neonatal Audit Programme, the UK Neonatal Data Analysis Unit, the International Neonatal Benchmarking and Evaluation Programme (eNewborn), and the International Network for Evaluation of Outcomes in neonates (iNeo), all of which are involved in population-based reporting of neonatal infections. All other authors declare no competing interests.

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