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

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**ABSTRACT**

Neonatal infections are estimated to account for a quarter of the 2·8 million annual neonatal deaths, as well as approximately 3% of all DALYs. Despite this burden, data are limited on incidence, aetiology and outcomes, particularly regarding impairment. We aimed to develop guidelines for improved scientific reporting of observational and interventional neonatal infection studies, to increase comparability and to strengthen research in this area. This statement is an extension of the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) checklist. SPRING was developed following systematic reviews of published literature (1996-2015), compilation of over 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 SPRING 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.

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**Background**

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](http://www.everynewborn.org/)” 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 the World Health Organisation (WHO), for 195 countries, suggest that infection accounts for around 680 000 deaths – a quarter of all neonatal deaths annually;6 and half of all neonatal deaths in high neonatal mortality settings.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 impairment data are very limited worldwide, particularly for common infection syndromes such as sepsis and pneumonia.8,9

There are an estimated 6·9 million neonates with possible serious bacterial infection (pSBI) 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 where referral is not possible.11–13

Aetiology-specific data for neonatal infections are limited, and challenging to combine. Hospital-based studies suggest that *Staphylococcus aureus,* *Escherichia coli*, *Klebsiella* species and group B Streptococci (GBS) may be the most common pathogens globally.14 As yet there are no community-based aetiological studies from Africa, and few from South Asia, which together carry over 75% of the burden. Hence, there is an urgent need to improve data on incidence (especially in the first days following birth), aetiology (bacterial, viral and fungal), 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, are also limited.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 pregnancy, the challenge remains that many newborns 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 hours 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 young infant pSBI algorithm 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 week’s 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)31andthe 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 which are specific to child health trials (SPIRIT-C; CONSORT-C),33 and for systematic reviews and meta-analyses (PRISMA-C; PRISMA-PC).34 This paper aims to address the specific challenges in reporting neonatal infections, using the STROBE29 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 SPRING**

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 literature, to list all potential reporting items, and to use an online survey and expert consensus process to develop the ‘Strengthening Publications Reporting Infections in Newborns Globally (SPRING)’ checklist. The SPRING checklist is intended to guide authors, reviewers, publishers and funders of neonatal infection studies. We focussed on parameters that are not included in STROBE, or other extensions.

**Development of the SPRING checklist**

The SPRING checklist was developed using recommended methods.36 The participants, processes and outputs are illustrated in Figure 1. Literature searches were undertaken to identify highly cited neonatal infection publications from different regions worldwide (1996-2015), and more recent (2011-2015) articles from high impact journals (see appendix for literature search criteria). Additional searches were carried out 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 requiring 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/middle income counties (appendix).

In June 2015, a group of 18 international, multi-disciplinary 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 implementation36 of the STROBE statement. The structural relationship between SPRING and STROBE29 recommendations is illustrated in Figure 2.

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 SPRING Checklist (Table 1)

**SPRING Standards**

The final SPRING checklist is an extension of the 22 item STROBE list, with 28 additional parameters relating to neonatal infection. This includes a suggested flow diagram for both the recruitment and follow up of mothers and newborns, for which a template is provided in Figure 3. Below, we describe the additional recommendations for SPRING that are not already outlined in detail in STROBE, or other extensions. Recommendations for reporting study methods are outlined, such as clinical case definitions, microbiological sampling and methods, description of the study context with reference to both community and facility settings, and key clinical characteristics of participants. Guidelines for specific details on microbiological and clinical outcomes, including the clinical significance of pathogens, as well as maternal infections and antibiotic exposures are addressed. Finally, essential additional information concerning sources of recruitment bias and key ethical issues specific to this area of research are described.

**Methods: Study design**

***Clinical case definitions (SPRING 4.1 – 4.4)***

The individual clinical signs used in clinical case definition algorithms should be detailed, (SPRING 4·1), making clear whether case ascertainment was through physician diagnosis or a clinical algorithm (eg. Young Infants Clinical Signs Study Group algorithm for pSBI). Definitions of neonatal infection syndromes (pneumonia, meningitis and sepsis) are important for consistency and comparability, however, they cannot be distinguished on clinical grounds alone. Where authors are reporting case definitions of specific syndromes, microbiological and/or laboratory and/or radiological criteria for diagnosis should be stated (SPRING 4·1), differentiating between probable and confirmed cases. For meningitis, the indications for lumbar puncture should be described (SPRING 4·1). Case definitions should be aligned to international standards, when available and ideally be clinically validated.26 Clinical algorithms may 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 (SPRING 4·2). For example, new episodes may 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 is important for healthcare associated infections, and these should be explicitly differentiated from community-acquired infections, with reference to an international standard definition (SPRING 4·3).37 Where 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, and the definition used for outbreaks (SPRING 4·4).

***Microbiological sampling (SPRING 4.5)***

The microbiological sampling strategy for infections should be presented (SPRING 4·5), such as samples being taken from all participants, or a subset meeting a case-definition (eg pSBI). This is important given that the positive and negative predictive values of tests differ according to the prevalence in those sampled. For instance if few cases of pSBI have lumbar punctures, then cases of meningitis may not be captured. Numbers from whom samples were taken, and sample type, should be provided, including sample volume ranges for blood cultures, or minimum sample volume, as small volumes reduce sensitivity. It should be reported whether samples were taken prior to antimicrobial administration (which reduces sensitivity of testing) (SPRING 4·5).

***Microbiological methods (SPRING 4.6 – 4.8)***

Detailed reporting of laboratory methods is essential in order to assess implications and potential biases (SPRING 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) (SPRING 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 Antimicrobial susceptibility testing methodology should be reported according to an international standard (eg. Clinical and Laboratory Standards Institute) reporting the susceptibilities tested, and the criteria used to determine susceptibility to each antimicrobial (SPRING 4·8). For molecular analyses, methods41 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 (SPRING 5.1 – 5.2)***

Where possible, preterm, stillbirth, and neonatal mortality risks or rates at the study facility are helpful contextual information (SPRING 5·1). This could be presented as the annual number of deaths, preterm births and stillbirths at the health facility, with live births (including the live birth definition 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, as multiple pathways to healthcare presentation exist; ‘outborn’ may 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’ (SPRING 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 (SPRING 5.3)***

Community-based studies should report the surveillance strategy, including whether active or passive, and the methods used for defining and enumerating the population. Passive surveillance may 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 (SPRING 5·3). This could be presented in a flow diagram (Figure 3).

***Facility based studies (SPRING 5.4 – 5.6)***

Levels of neonatal and obstetric care differ greatly. The obstetric care available,43 including the percentage of births that occur in a facility (versus the community) and the incidence of operative delivery, should be described (SPRING 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. antimicrobials available) (SPRING 5·5). Where relevant, specific clinical infection control measures in place (and level of adherence), may 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 and/or molecular microbiology. Laboratory quality control and quality assurance measures should be reported (SPRING 5·6).

**Methods: Participants**

***Neonatal age groups (SPRING 6.1)***

The ‘neonatal’ period is defined as <28 days (i.e. 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 due to differing risk factors, aetiologies and outcomes (SPRING 6·1).44 Timing is crucial for neonatal infections as 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 (SPRING 6·1). Time limits vary as to when ‘day 0’ becomes ‘day 1’ (eg. at midnight, or 24h after birth), and the method used should be stated.4

**Methods: Variables**

***Clinical significance of pathogens (SPRING 7.1)***

Authors should be explicit about the clinical significance of the organisms detected. This may 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 (SPRING 7·1); as criteria for clinical significance may change over time.

**Results: Participants**

***Flow diagram (SPRING 13.1)***

Figure 3 illustrates how the flow of eligibility, recruitment, sampling and diagnosis can be mapped in neonatal infection studies, including mothers and neonates (SPRING 13·1).

**Results: Descriptive data *(SPRING 14.1 – 14.4)***

Maternal infections, and risk factors for infection, are important to report as maternal infections may result in vertical transmission and early onset neonatal infections, or stillbirth.47,48 Results of antenatal screening tests (eg. for GBS, syphilis, HIV) when done, and risk factors at delivery (eg. prolonged rupture of membranes (>18h) fever, maternal urinary tract infection) (SPRING 14·1), are important for identifying high risk groups and informing interventions.49

Neonatal characteristics, including sex, postnatal and gestational age categories (e.g. <28 weeks; 28 – <32 weeks; 32 – <37 weeks; ≥37 weeks)50, birth weight categories (e.g. <=1500 grams; 1501-2500 grams; >2500 grams), place of birth (see above) and mode of feeding should be described, with ranges and medians stated for each numeric variable (SPRING 14.2). Co-morbidities (eg. neonatal encephalopathy) should be reported, including any exclusion from analysis (SPRING 14·2). Reporting of individual clinical signs is encouraged (SPRING 14·3),8 allowing comparison with other studies and may be helpful in refining diagnostic algorithms.2

Details of treatment given before and after enrolment are important (SPRING 14·4). Serum antimicrobial testing has shown that parents under-report antimicrobial administration;22 and results of testing are preferable to report. Use of intrapartum antibiotic prophylaxis and its indication (eg. maternal risk factors versus positive GBS screening)51 should be reported to inform interpretation of culture results (SPRING 14·4).

**Results: Outcome data**

***Microbiological results (SPRING 15.1 – 15.2)***

Microbiological results should be reported in the context of participants recruited, and the number and type of samples taken (SPRING 15·1-2). For example, the number of those 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 3) (SPRING 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 (SPRING 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 (SPRING 15.3)***

Where categorisation into ‘early-onset’ (e.g. within 72 hours of birth) and ‘late-onset’ (e.g. after 72 hours of birth) disease is used, these terms should be clearly defined (SPRING 15·3). Due to the changing aetiologies of neonatal disease, reporting infections by day, for the first week after birth (days 0-6) (SPRING 15·3) is more informative than dichotomous categories, and may improve understanding of early and late onset disease.45

***Mortality (SPRING 15.4) and long-term outcomes***

Mortality and other serious clinical outcomes should be reported (SPRING 15·4), ideally by day (Figure 3). Sample size permitting, stratifying mortality by potential risk factors including sex, birthweight categories, gestational age groups,50 infection syndromes, individual pathogens or antimicrobial resistance profiles, may highlight intervention opportunities for high risk groups.

Where studies 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 (SPRING 16.1)***

For incidence, the selection and source of the denominator should be explained (see above). For neonates it is usual to calculate incidence risk per 1000 live births (SPRING 16·1), as the time period (28 days) is short.

**Discussion: Limitations**

***Bias (SPRING 19.1)***

The first 12-48 hours after birth are critical, as the survival curve is steep,4 and infectious aetiologies differ later after birth. These aetiologies may be systematically underestimated if there is recruitment bias arising from lack of access to care, or death before accessing care (SPRING 19·1).44 Identifying possible causes of recruitment and other biases in studies is therefore essential in interpreting findings.

For all denominators used, authors should state the source (eg. hospital data or census / registration data), commenting on possible bias (SPRING 19·1).

**Other information: *Ethics (SPRING 23.1)***

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) (SPRING 23·1).52,53

If the time frame for sample collection and obtaining consent is limited (eg. during delivery), a staged process of consent may be appropriate, to avoid exclusion of emergency cases (and reduce recruitment bias).54

**Implications of SPRING**

The SPRING 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 STROBE29 statement and its related extensions, the checklist primarily targets observational studies.29 However, SPRING 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 Whilst neonatal infections are a priority starting point, future re-iterations 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 SPRING checklist guides minimum standards for high quality reporting but is not exhaustive; and certain research objectives or contexts may 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 neonatal infection burden. 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 SPRING checklist depends on dissemination through global research networks and meetings, and use by journals, funders and academics. Feedback and suggestions for improvement would be welcomed, as the SPRING checklist will be updated periodically. Going forward, we intend to publish an ‘explanation and elaboration’ document, develop abstract guidance for conference submissions, and conduct further literature reviews and surveys to evaluate the impact of SPRING, as is recommended.36 The SPRING checklist has been developed at a critical 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

**Author contributions:**

EJAF, ACS, SV, MS, PTH and JEL coordinated the expert group and planned the expert meeting. EJAF, ACS and SV conducted 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, SS, RA, AIA, RB, KB, HC, SC, GLD, NM, JP, SQ, SW, RW and JEL participated in the expert meeting and developed the SPRING checklist, chaired by MS, SS, RB, HC, SC, and JEL, and coordinated by EJAF. EJAF, ACS and JEL wrote the first draft of the manuscript. ACS, SS and JEL developed the flow diagram with feedback from RW, PTH, RA and SJS. SV, MS, PTH, RA, AIA, ZAB, RB, HC, SC, GLD, SAM, NM, JP, SQ, SJS and BJS edited and contributed to successive versions of the paper.

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**Figures**

Figure 1: **Development process for the SPRING checklist, showing participants, process and outputs**

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c Possible Serious Bacterial Infection (pSBI) investigator group; African Neonatal Sepsis Trial (AFRINEST) investigators

d Infectious Disease Research Network (IDRN); British Paediatric Allergy and Immunology Group (BPAIIG); Neonatal Infectious Disease Network (neonIN); UK Infection in Critical Care Quality Improvement Group; Australian and New Zealand Neonatal Network; Global Antibiotic Resistance, Prescribing and Efficacy Among Neonates and Children (GARPEC); 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 (MARCH) Centre

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Figure 2: **Graphic showing structural relationship between STROBE28 and SPRING checklist items**

Figure 3: **Strengthening Publications Reporting Infections in Newborns Globally (SPRING) recommended flow chart showing recruitment and participation in the study**

 Give details by day where possible

\*Give clinical algorithm used to define pSBI (SPRING 4.1) and clinical signs for each neonate if possible (SPRING 14.3)

\*\* Give details of assessment, microbiological sampling if done.

†If live births are assessed for eligibility (rather than pregnant women), give numbers of live births assessed for eligibility and then recruited after this box.

††If neonates are assessed, for example 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.

Table 1: **Strengthening Publications Reporting Infections in Newborns Globally (SPRING) Checklist:**

**A topic-specific implementation of the STROBE statement**29

|  |  |  |
| --- | --- | --- |
| Section | Item No. |  Recommendation  |
| **TITLE AND ABSTRACT** |
|  | STROBE1(a) | Indicate the study's design with a commonly used term in the title or abstract |
|  | STROBE1(b) | Provide in the abstract an informative and balanced summary of what was done and what was found |
| **INTRODUCTION** |
| **Background** **/ rationale** | STROBE2 | Explain the scientific background and rationale for the investigation being reported |
| **Objectives** | STROBE3 | State specific objectives, including any pre-specified hypotheses |
| **METHODS** |
| **Study design** | STROBE4 | Present key elements of study design early in the paper |
|  | SPRING4.1 | 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) |
|  | SPRING4.2 | Give criteria used to differentiate between new infection episodes and relapses  |
|  | SPRING4.3 | 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 |
|  | SPRING4.4 | State whether this is an outbreak study, and if so define an outbreak, with reference to an international standard |
|  | SPRING4.5 | Describe sampling strategy (eg. clinical indication vs. routine surveillance) and sampling details, (eg. minimum volumes; timing in relation to antimicrobial administration) |
|  | SPRING4.6 | Describe conventional and/or molecular microbiological methods used, with details (eg. automation, enrichment steps), and the use of controls |
|  | SPRING4.7 | List pathogens that are likely to be identified by microbiological methods used, and criteria used to determine clinical significance  |
|  | SPRING4.8 | Describe antimicrobial susceptibility tests and thresholds used, with reference to an international standard (eg. CLSI or EUCAST) |
| **Setting** | STROBE5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
|  | SPRING5.1 | Describe the study context in terms of incidence of neonatal mortality, stillbirth and preterm birth.  |
|  | SPRING5.2 | Describe the population included eg. facility live births, referrals from home, referrals from another facility |
|  | SPRING5.3 | For community-based studies, describe care-seeking and adherence and time to referral |
|  | SPRING5.4 | For facility-based studies, describe obstetric care (basic or comprehensive), including proportion of births by caesarean section. Report annual number of live births per facility and state proportion of births in the study area that occur in hospital (vs. community) |
|  | SPRING5.5 | 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. |
|  | SPRING5.6 | State the laboratory location and capacity to process different sample types, and give quality control and assurance measures in place. |
| **Participants** | STROBE6(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 |
|  | STROBE6(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 |
|  | SPRING6.1 | 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** | STROBE7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
|  | SPRING7.1 | State criteria used to define clinically significant organisms for each sample type |
| **Data sourcesmeasurement** | STROBE8 | 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** | STROBE9 | Describe any efforts to address potential sources of bias |
| **Study size** | STROBE10 | Explain how the study size was arrived at |
| **Quantitative variables** | STROBE11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| **Statistical methods** | STROBE12(a) | Describe all statistical methods, including those used to control for confounding |
|  | STROBE12(b) | Describe any methods used to examine subgroups and interactions |
|  | STROBE12(c) | Explain how missing data were addressed |
|  | STROBE12(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 |
|  | STROBE12(e) | Describe any sensitivity analyses |
| **RESULTS** |
| **Participants** | STROBE13(a) | Report numbers of individuals at each stage of study—eg. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
|  | STROBE13(b) | Give reasons for non-participation at each stage |
|  | STROBE13(c) | Consider use of a flow diagram |
|  | SPRING13.1 | See Figure 3 for suggested components of a flow diagram for neonatal infections |
| **Descriptive data** | STROBE14(a) | Give characteristics of study participants (eg. demographic, clinical, social) and information on exposures and potential confounders |
|  | SPRING14.1 | Describe maternal infections (clinical or on screening, eg. GBS or HIV) or risk factors for infection (eg. PROM, peripartum fever).  |
|  | SPRING14.2 | Describe key neonatal characteristics, including sex, postnatal and gestational age categories (range and median), birth weight categories (range and median), birth place, feeding (breast milk or other) and comorbidities |
|  | SPRING14.3 | Report data on occurrence of individual signs (eg. fast breathing), according to case definitions |
|  | SPRING14.4 | Give proportion of mothers and neonates with peripartum antibiotic exposure (+/- pre-admission exposure for neonates). Report details of antimicrobials (or supportive care) given during the study |
|  | STROBE14(b) | Indicate number of participants with missing data for each variable of interest |
|  | STROBE14(c) | Cohort study—Summarise follow-up time (eg. average and total amount) |
| **Outcome data** | STROBE15 | 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 |
|  | SPRING15.1 | Report the number (+/- proportion) of samples microbiologically tested (including lumbar punctures for meningitis cases); the number (+/-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. |
|  | SPRING15.2 | Report number (+/- proportion) of babies with microbiologically proven infection (and number of infections per baby), and include this in the flow chart (see Figure 3). |
|  | SPRING15.3 | Report infections by day, for days 0-6. State age categories, if used, defining ‘early-onset’ and ‘late-onset’ infection (eg. <72 hours and ≥ 72 hours respectively).  |
|  | SPRING15.4 | Report deaths and any sub-analyses by risk groups  |
| **Main results** | STROBE16(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 |
|  | STROBE16(b) | Report category boundaries when continuous variables were categorized |
|  | STROBE16(c) | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
|  | SPRING16.1 | For incidence, give risk per 1000 live births, or if alternative denominator used (eg. total births or bed days), define this clearly |
| **Other analyses** | STROBE17 | Report other analyses done—eg. analyses of subgroups and interactions, and sensitivity analyses |
| **DISCUSSION** |
| **Key results** | STROBE18 | Summarise key results with reference to study objectives |
| **Limitations** | STROBE19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
|  | SPRING19.1 | 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** | STROBE20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| **Generalisability** | STROBE21 | Discuss the generalisability (external validity) of the study results |
| **OTHER INFORMATION** |
| **Funding** | STROBE22 | 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** | SPRING 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. |