STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship

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To cite: Tacconelli E, Cataldo MA, Paul M, et al. STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship. BMJ Open 2016;6:e010134. doi:10.1136/bmjopen-2015-010134

Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2015-010134).

Received 30 September 2015
Revised 3 December 2015
Accepted 18 December 2015

ABSTRACT

Objectives: To explore the accuracy of application of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) tool in epidemiological studies focused on the evaluation of the role of antibiotics in selecting resistance, and to derive and test an extension of STROBE to improve the suitability of the tool in evaluating the quality of reporting in these area.

Methods: A three-step study was performed. First, a systematic review of the literature analysing the association between antimicrobial exposure and acquisition of methicillin-resistant Staphylococcus aureus and/or multidrug-resistant Acinetobacter baumannii was performed. Second, articles were reviewed according to the STROBE checklist for epidemiological studies. Third, a set of potential new items focused on antimicrobial-resistance quality indicators was derived through an expert two-round RAND-modified Delphi procedure and tested on the articles selected through the literature review.

Results: The literature search identified 78 studies. Overall, the quality of reporting appeared to be poor in most areas. Five STROBE items, comprising statistical analysis and study objectives, were satisfactory in <25% of the studies. Informative abstract, reporting of bias, control of confounding, generalisability and description of study size were missing in more than half the articles. A set of 21 new items was developed and tested. The new items focused particularly on the study setting, antimicrobial usage indicators, and patients epidemiological and clinical characteristics. The performance of the new items in included studies was very low (<25%).

Conclusions: Our paper reveals that reporting in epidemiological papers analysing the association between antimicrobial usage and development of resistance is poor. The implementation of the newly developed STROBE for antimicrobial stewardship (AMS) tool should enhance appropriate study design and reporting, and therefore contribute to the improvement of evidence to be used for AMS programme development and assessment.

INTRODUCTION

The rate of infections caused by antimicrobial-resistant microorganisms is seen increasingly by the public and healthcare inspection organisations as an indicator of quality of healthcare and patient safety.1 Several studies have explored risk factors associated with infection or colonisation due to antimicrobial-resistant microorganisms.2 3 Among them, antimicrobial exposure is a well-known risk factor for
studies in Epidemiology

several de

sequential antibiotic therapy) and heterogeneity in

biotics, knowledge of carrier status, combination and

for confounding factors (ie, duration and dosage of anti-

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infections are the retrospective design, poor controlling

for confounding factors (ie, duration and dosage of anti-

iotics, knowledge of carrier status, combination and

sequential antibiotic therapy) and heterogeneity in

several definitions (ie, definition of infection and of

antimicrobial-resistant microorganisms, time-at-risk

period for previous antimicrobial exposure, selection of

control group). A further limitation affects external

validity, since prevalence of resistance changes in differ-

ten locations and in time. In an era of increasing anti-

microbial resistance, reducing these flaws and increasing

appropriate reporting is critical to the application of

findings to AMS programmes.

The 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) was an initiative to

improve the quality of reporting evidence.14 It aimed to

provide useful guidance by establishing a checklist con-

sisting of 22 items for the transparent and complete

publication of observational studies, facilitating their

critical evaluation.14 Recently, an extension of the

STROBE statement (STROME-ID) established recom-

mendations to support good scientific reporting of

molecular epidemiological studies.15 However, the pecu-

liarity of the epidemiology of antimicrobial-resistant

infections being strongly connected to patients' charac-

teristics as well as to different settings (hospital,

community and healthcare centres) as well as surveil-

 lance methods of antibiotic usage (ie, defined daily

dose or packets or prescriptions) cannot be properly

covered through the items currently included in

STROBE.

Therefore, we performed a study with two main

objectives: (1) to explore the accuracy of application of

STROBE in epidemiological studies focused on the link

between antibiotics usage and development of resist-

ance; and (2) to derive and test an extension of

STROBE that could improve the suitability of the tool

in evaluating the quality of reporting of epidemiological

studies in this area. Studies addressing MRSA and the

MDR-Acinetobacter baumannii group were selected for

the frequency with which they have been used

worldwide as indicators of healthcare associated

infections.2 16

STUDY DESIGN

Methods

There were three-steps to the study design. First, to

explore the STROBE application, we searched the litera-

ture (1976–2013) for articles analysing the association

between antimicrobial exposure, and acquisition of

MRSA and/or MDR-A. baumannii. Second, all the arti-

cles were reviewed according to the STROBE checklist.14

Third, a set of potential new items focused on

antimicrobial-resistance quality indicators for proper

reporting was derived through a two-round RAND-modi-

fied Delphi procedure, involving experts in the field of

antimicrobial prescribing.17 The extension of STROBE

for AMS (STROBE-AMS) was then tested on the articles

selected in the first study step.

Selection of articles

Published human studies concerning the role of previ-

ous antimicrobial therapy as a risk factor for developing

MRSA and MDR-A. baumannii colonisation or infection

in hospitalised patients were identified through compu-

terised literature searches using MEDLINE (National

Library of Medicine, Bethesda, Maryland, USA) and

EMBASE (Excerpta Medica Database), and by reviewing

the references of the retrieved articles. Index search
terms included the following Medical Subject Headings:

‘risk factors’, ‘resistance’, ‘antimicrobial therapy’,

‘Acinetobacter’, ‘outbreak’, ‘Staphylococcus aureus’ and

‘methicillin-resistant’. The search was carried out with

no language restriction and followed PRISMA

(Preferred Reporting Items for Systematic reviews and

Meta-Analyses) guidelines. Studies were considered eli-

gible if they included adult patients (>16 years old) and

presented data pertaining to the relationship between

antimicrobial use and the development of MRSA or

MDR-A. baumannii colonisation or infection. Authors

were contacted for missing information.

Data extraction

Data extraction was performed by four independent

researchers in two centres. This process involved infec-

tious disease specialists as well as epidemiologists. In

case of disagreement among the reviewers, a senior

reviewer was consulted. Reviews, letters, editorials and

case reports were excluded. Data extraction included

also the impact factor (IF) of the journal (2013 Journal

Citation Report, Thomson Institute for Scientific

Information), which is a measure of average citation

frequency for all the articles over a given period of time.
**Reporting assessment**

The assessment of the quality of reporting was performed according to the STROBE statement. Data from each study were entered into standardised forms, verified for consistency and accuracy, and then entered into a computerised database. Entries for each item of the STROBE statement were categorised as ‘Yes’, if they were completely in agreement with the STROBE statement explanation and elaboration documentation, ‘No’, if this was not satisfied, and ‘Partly’, if evident only in part of the text. Absolute and relative frequencies were used to describe the results of these judgments of quality reporting according to the STROBE statement.

**New items development**

The new items development was carried out through a two-round Delphi approach. A list of experts in the field of antimicrobial prescribing was collated from the network of the European Society of Infectious Diseases and Clinical Microbiology (ESCMID) and the Impact of Specific Antibiotic Therapies on the prevalence of hUman host ResisteNt bacteria (SATURN) Project on antimicrobial usage and selection of resistance in hospitalised patients (EU-7th FP7-241796). To develop a first set of quality indicators, the literature was reviewed to define the major limitations of current research on the association between antimicrobial usage and antimicrobial resistance, and a first set of indicators, developed from the authors, was sent out in December 2013. Respondents were asked to rate each new item against two continuous 1–9 integer scales and provide their comments. The second round was performed in May 2014, according to the same indications. Ethic consent was not required because no patient data were used and the study was based on literature review.

**Test of the new items**

The new developed items were then applied to the papers selected for the systematic review. The same reporting assessment used for the STROBE evaluation was applied.

**Statistical analysis**

Scores were analysed using a non-parametric test (Fischer’s test). Analysis was performed with STATA V.12.1 (Stata Corporation, Texas, USA).

| Level of satisfaction | STROBE statement number | Section |
|-----------------------|-------------------------|---------|
| <25% of studies       | 3. State specific objectives, including any prespecified hypotheses. | Introduction |
|                       | 9. Describe any efforts to address potential sources of bias | Methods |
|                       | 10. Explain how the study size was arrived at | |
|                       | 11. Explain how quantitative variables were handled | |
| ≥25% to <50% of studies | 1a. Indicate the study design with a commonly used term in the title or the abstract | Title and Abstract |
|                       | 1b. Provide an informative and balanced summary in the abstract | Discussion |
|                       | 19. Discuss limitations of the study, taking into account sources of potential bias or imprecision | |
| ≥50% to <75% of studies | 2. Explain the scientific background and rationale for the investigation being reported. | Introduction |
|                       | 4. Present key elements of study design early in the paper | Methods |
|                       | 7. Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers | |
| ≥75% of studies       | 8. For each variable of interest, give sources of data and details of methods of assessment | |
|                       | 13. Report the numbers of individuals at each stage and reason for non-participation | Results |
|                       | 16. Give unadjusted estimates and, if applicable, confounder-adjusted estimates. | |
|                       | Make clear which confounders were adjusted for and why they were included | |
|                       | 5. Describe the setting, locations and relevant dates | Methods |
|                       | 6. Description of participants—eligibility criteria, sources and methods | |
|                       | 12. Describe all statistical methods, including those used to control for confounding. | |
|                       | Explain how missing data, lost to follow up and sensitivity analyses were addressed | |
|                       | 14. Give the characteristics of study participants | Results |
|                       | 15. Report outcome data | |
|                       | 18. Summarise key results with reference to study objectives | Discussion |
|                       | 20. Give a cautious overall interpretation of results | |

Bold typeface indicates main variables included in the STROBE tool.

MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

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**Table 1** STROBE item checklist for 78 epidemiological studies analysing antimicrobial usage and development of colonisation/infections due to MRSA and MDR-Acinetobacter baumannii

| Level of satisfaction | STROBE statement number | Section |
|-----------------------|-------------------------|---------|
| <25% of studies       | 3. State specific objectives, including any prespecified hypotheses. | Introduction |
|                       | 9. Describe any efforts to address potential sources of bias | Methods |
|                       | 10. Explain how the study size was arrived at | |
|                       | 11. Explain how quantitative variables were handled | |
| ≥25% to <50% of studies | 1a. Indicate the study design with a commonly used term in the title or the abstract | Title and Abstract |
|                       | 1b. Provide an informative and balanced summary in the abstract | Discussion |
| ≥50% to <75% of studies | 2. Explain the scientific background and rationale for the investigation being reported. | Introduction |
|                       | 4. Present key elements of study design early in the paper | Methods |
|                       | 7. Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers | |
| ≥75% of studies       | 8. For each variable of interest, give sources of data and details of methods of assessment | |
|                       | 13. Report the numbers of individuals at each stage and reason for non-participation | Results |
|                       | 16. Give unadjusted estimates and, if applicable, confounder-adjusted estimates. | |
|                       | Make clear which confounders were adjusted for and why they were included | |
|                       | 5. Describe the setting, locations and relevant dates | Methods |
|                       | 6. Description of participants—eligibility criteria, sources and methods | |
|                       | 12. Describe all statistical methods, including those used to control for confounding. | |
|                       | Explain how missing data, lost to follow up and sensitivity analyses were addressed | |
|                       | 14. Give the characteristics of study participants | Results |
|                       | 15. Report outcome data | |
|                       | 18. Summarise key results with reference to study objectives | Discussion |
|                       | 20. Give a cautious overall interpretation of results | |

Bold typeface indicates main variables included in the STROBE tool.

MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

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**References**

Tacconelli E, et al. BMJ Open 2016;6:e010134. doi:10.1136/bmjopen-2015-010134
RESULTS
Identification of relevant articles
The search identified 1008 potentially relevant studies; 311 were excluded because they were reviews, case reports or letters; 233 were excluded because they did not investigate previous antibiotic therapy. Among the remaining 464, 386 articles were excluded because they did not analyse the relationship between antibiotic usage and development of resistance, were duplicates, or their authors could not provide missing information. Overall, 78 studies (57 on MRSA and 21 on MDR-Acinetobacter) fulfilled inclusion criteria for the association between antimicrobial usage and antimicrobial resistance: 39 (51%) case-control, 28 (35%) cohort and 11 (14%) cross-sectional studies. The list of reviewed articles and the flow chart are reported in online supplementary annex 1—figure 1 and table 1.

Reporting assessment
The results of the assessment of quality of reporting through the STROBE statement of these 78 studies are shown in table 1. Overall, the quality of reporting appeared to be poor in most areas. Best performing areas of the STROBE tool were seven items including the description of setting, participants and generic review of statistical methods that were well satisfied in >75% of the studies. However, five items, comprising statistical details for the analysis of quantitative variables, subgroup analysis, sample size calculation, addressing potential sources of biases and, most notably, the description of main study objectives, were satisfactory in <25% of the studies.

Table 2 describes the association between the value of the IF and the grade of satisfaction of the STROBE statement’s items. Informative abstract, explanation of objectives, reporting of bias, statistical methods, control of confounding, generalisability, definition of quantitative variables, giving of estimates and description of study size, were missing or incomplete in more than half the articles published in 13 journals with IF greater than four. The cut-off of four was selected based on the IF median distribution. There was no association between type of journal (general medicine vs clinical infectious diseases and microbiology-dedicated journal) and year of study publication (before and after 2007, when the STROBE tool was introduced).

Development of new items
In the first round, 16 new items were sent to the experts. No indicators were discarded between rounds and five new items were added. In the second round, participants were provided with the frequency of distribution of scores and qualitative comments. The final set included 21 new variables, presented in table 3. The main new items referred to the description of the study setting and participants. In particular, the following four areas were graded as the most relevant for studies reporting on antimicrobial usage and resistance development: definition of infection and/or colonisation, and evidence of robustness of the new definition (if not a validated reference); definition of setting (epidemic or endemic); definition of antibiotic usage at patient’s level including type, dosage, duration, route of administration and combinations; description of antimicrobial formulary at the hospital level and measurement of antibiotic usage (defined as daily dosage, packet daily dosage, treatments, units); definition of how antibiotic consumption data were obtained (pharmacy, patients’ charts, etc) and if it was actually used or purchased/dispensed. The remaining three items focused on infection control measures applied at the study location: description of resistance, cross-resistance and molecular resistance...
Table 3  New checklist items proposed to be included in the STROBE statement for deepening the assessment of epidemiological studies analysing the impact of antimicrobial usage on the development of antimicrobial-resistant infections

| Item | Item number | STROBE recommendation | STROBE-AMS new items |
|------|-------------|-----------------------|----------------------|
| Introduction | 2 | Explain the scientific background and rationale for the investigation being reported | 2.1 Report previous clinical in vivo and in vitro studies |
| Background/rationale | 2 | | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | |
| Methods | 5 | Describe the setting, locations, relevant dates, including periods of recruitment, exposure, follow-up and data collection | 5.1 Describe if setting is epidemic or endemic (high, low, medium) for the study outcome |
| Setting | 5.1 | Describe if setting is epidemic or endemic (high, low, medium) for the study outcome | 5.2 Specify type of hospital or unit and characteristics of population served by the healthcare setting |
| | 5.2 | Specify type of hospital or unit and characteristics of population served by the healthcare setting | 5.3 Describe antimicrobial formulary in use at the study location related to the analysed antibiotics |
| | 5.3 | Describe antimicrobial formulary in use at the study location related to the analysed antibiotics | 5.4 Describe infection control measures dedicated to the target resistant bacteria applied at the study location |
| | 5.4 | Describe infection control measures dedicated to the target resistant bacteria applied at the study location | |
| Participants | 6 | (a) Cohort study—Give the eligibility criteria, the sources and methods of selection of participants. Describe methods of follow-up | 6.1 Define unit analysed (person, department or other) |
| | 6.1 | Define unit analysed (person, department or other) | 6.2 Provide reasons (epidemiological and clinical) for choosing matching criteria |
| | (b) Case–control study—Give the eligibility criteria, the sources, methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | | |
| | | Cross-sectional study—Give the eligibility criteria, the sources and methods of selection of participants | |
| | | | (b) Cohort study—For matched studies, give matching criteria, the number of exposed and unexposed |
| | | Case–control study—For matched studies, give matching criteria and the number of controls per case | |
| | | | | 7.1 Specify antimicrobial usage according to: type, dosage, duration and route of administration |
| | | | 7.2 Provide information using defined daily dosages (DDDs) and, in addition, other definitions closer to local reality (packages, prescriptions). Provide justification for the measurement presented |
| | | | 7.3 Address antimicrobial combinations |
| | | | 7.4 Explain rationale for grouping of antimicrobials |
| | | | 7.5 Define time at risk for antimicrobial exposure and for resistance development |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers. Give diagnostic criteria, if applicable | 7.6 Include description of potential confounders (other than epidemiological variables) |
| | | | 7.7 Provide definition of resistance, multidrug resistance, including pattern of co-resistance; whether studies performed to identify location or resistance eg, plasmid, chromosome, integron, transposon |
mechanisms, for example, plasmids, chromosomes, integrons, transposons; and statistical methods including controlling for confounders, rationale for grouping of antimicrobials and time at risk for antimicrobial exposure. Among the confounders, items reporting on previous stay in long term care facilities, nursing home and other hospitals, were added.

Test of new items
The performance of reviewed articles to the new items was very poor. Overall, the new items were satisfied in <25% of the papers reviewed (item 5.3, 6.2, 7.1–4, 8, 11, 17 and 21).

DISCUSSION
With increasing reporting of antibiotic-resistant infections worldwide, epidemiological investigations on risk factors for resistance require rather special attention regarding designing and reporting in order to maximise their ability to inform AMS programmes. Our paper reveals that current reporting in epidemiological studies focusing on the association between antibiotic usage and development of resistance is very poor. Although some items including the description of setting and generic review of statistical methods were well satisfied in >75% of the studies, more than half the 22 domains included in the STROBE checklist were not satisfied in the majority of studies analysing the role of antibiotics in selecting MRSA and MDR-

| Item number | STROBE recommendation | STROBE-AMS new items |
|-------------|-----------------------|----------------------|
| 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 |
| 11          | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why |
| 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) |
| 17          | Report other analyses performed—eg, analyses of subgroups and interactions, and sensitivity analyses |
| 19          | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| 21          | Discuss the generalisability (external validity) of the study results |
| 22          | Give the source of funding, the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

Bold typeface indicates main variables included in the STROBE tool. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; STROBE-AMS, STROBE for antimicrobial stewardship.
We would advocate that, for observational trials meta-analyses need to comply with the PRISMA guidelines. The new items developed by a group of experts through a Delphi approach, which combined evidence and expert opinion, mainly focuses on the methods section and includes specific epidemiological items (ie, definition of the epidemiological setting in terms of endemicity or epidemicity) as well as a set definitions for antimicrobial usage (ie, local formulation, antibiotic measurements, presence or absence of any AMS, etc). To further underline the innovation of the items and the importance of introducing the new STROBE-AMS, our results showed that the new items were not reported in more than two-thirds of 78 already published studies.

Interestingly, although a significant correlation was observed between the IF of the journal and satisfactory compliance with the STROBE statement criteria, there were very important areas such as an informative abstract, explanation of objectives, reporting of statistical methods and generalisability, that were missing or incomplete in >50% of articles published even in higher quality journals with IF factors >4. This result underlines the need for involvement of major scientific journals on clinical infectious diseases in a re-evaluation process concerning the review process of such papers. Indeed, RCTs are not accepted for publication in high-ranked journals if they do not comply with the CONSORT guidelines (Consolidated Standards for Reporting Trials). Similarly, systematic reviews and meta-analyses need to comply with the PRISMA guidelines.

We would advocate that, for observational trials on antibiotic-resistant infections, where there is a greater potential for bias, this adaptation of the STROBE tool must be an essential review requirement, significantly contributing to the global efforts to combat the spread of antimicrobial-resistant microorganisms with improvement of the quality of evidence of the reports. Implicit in this requirement is that the studies will have had to consider these checklists at the design stage as well.

Our study has limitations. The analysis of STROBE application in the field of antimicrobial-resistant microorganisms was limited to epidemiological studies on MRSA and MDR-A. baumannii. These microorganisms were selected as their occurrence is very common, the majority of published epidemiological studies are focused on these bacteria, and their prevention and control are important potential indicators of the success, or otherwise, of healthcare associated interventions. The testing of the new items was performed on the same group of articles tested for satisfying the STROBE. However, we believe that, since the postdevelopment test was performed only for observational reports, no specific bias was introduced. Generalisability of our study applies therefore only to epidemiological studies exploring the association between previous antibiotic therapy and development of infection and/or colonisation due to antimicrobial-resistant strains.

Our study has shown, through an expert’s Delphi approach, that the current version of the STROBE tool does not describe all the components considered essential to define the association between antibiotic usage and resistance. That these studies should be conducted and reported effectively has become an imperative, given the global threat imposed by antimicrobial-resistant microorganisms, for future effective therapies. Increasing proper reporting will reduce heterogeneity between papers, and assist in the evaluation of the evidence through systematic reviews and peer reviewing for journal and grant proposals. The implementation of the STROBE-AMS will also impact on other aspects of antimicrobial-resistant research, including study design, extraction of data and generalisability of results. We do believe that the introduction of STROBE-AMS will increase the quality of available evidence to policymakers, relevant healthcare workers and the research community, and ultimately ensure that there are sustained improvements to AMS throughout the world.

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Funding The study was partially funded through the DZIF (Deutsches Zentrum für Infektion Forschung; German Center for Infectious Diseases Research) funding for the Clinical Trial Unit for healthcare-associated infection and the DRIVE-AB study (IMI 115618).

Disclaimer The funding source had no role in the analysis of data and results reporting.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.
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