22nd ECCMID London, United Kingdom 31 March – 3 April 2012

Educational Workshop

EW16: Improving the quality of investigator-initiated studies in infectious diseases

Arranged with the ESCMID Study Group for Antibiotic Policies (ESGAP) and the ESCMID Study Group for Nosocomial Infections (ESGNI)

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ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Stone - Appropriate and inappropriate use of publication guidelines for transparent reporting of observational, intervention and outbreak studies

Appropriate and inappropriate use of publication guidelines for transparent reporting of observational, intervention and outbreak studies

Using the short "ORION" and "STROBE" Abstract" for conference and journal abstract submission & review

Dr Sheldon Stone, Royal Free Campus, University College London Medical School, UK
Professor Barry Cookson, HPA and LSHTM
On behalf of ORION group

ECCMID 2012
Guidelines for submission of abstracts

ESCMID strongly support the improvements of reporting of study results. For this reason, all Authors submitting randomised clinical trial (RCT), infection control interventional study, outbreak report of nosocomial infections, and observational study in epidemiology are kindly requested to consult the following abstract checklists (please click on the respective link to download the document) for reporting their research results:

CONSORT (RCT)
STROBE (observational study in epidemiology)
ORION (outbreak report or interventional study)

EQUATOR NETWORK
www.equator-network.org

Too often, good research evidence is undermined by poor quality reporting.

The EQUATOR Network is an international initiative that seeks to improve reliability and value of medical research literature by promoting transparent and accurate reporting of research studies.

The ORION statement:

Guidelines for transparent reporting of
***O**utbreak **R**eports & **I**ntervention studies **O**f **N**osocomial **I**nfection*

A CONSORT equivalent for Infection Control Studies

Funded by Health Technology Assessement Board

Stone et al Lancet Infect Dis 2007; J Antimicrob Chemother 2007
www.idrn.org/orion.php

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Evidence Base for Infection Control Interventions

Davey et al Cochrane 2005;Cooper et al BMJ 2004

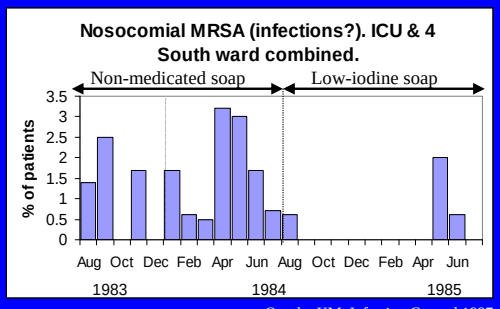
- Cochrane review of interventions to change antibiotic prescription & evaluate HCAI outcomes (2005) & HTA (2003) review isolation practices in MRSA show limited evidence of some effect but inadequate reporting & major flaws in design & statistical analysis
- Lack of details eg on interventions & timings
- Failure to assess & adjust for confounders/biases
- Aggregation of outcomes (misses trends)
- Analysis fails to account for dependencies of infectious outcomes
- Quality of infection control research must improve to provide robust evidence for policy & practice

To summarise the problem…..

Cooper B et al BMJ 2004, HTA 20003, Davey et al Cochrane 2005;Ramsay et al JAC 2003

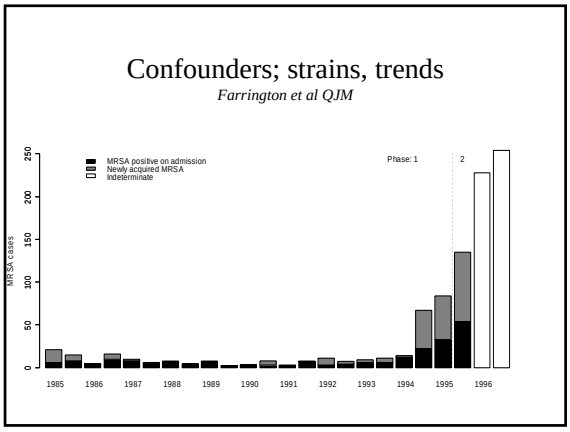
- Studies conclude interventions cause Δ MRSA or antibiotic use or *Clostridium difficile*
- Validity of conclusions threatened by **confounders & biases**, unaccounted for in studies, which provide plausible alternative explanations of outcome and by **inappropriate statistics** e.g. aggregation of data (misses time trends) & assumption that infection outcomes are independent (Chi-Sq; OR)

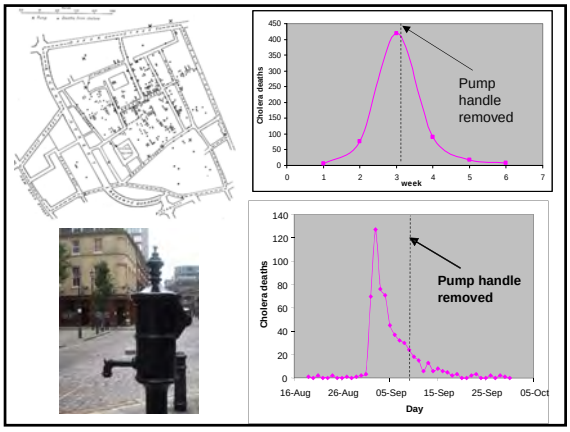
The sort of problems: regression to mean, statistical analysis

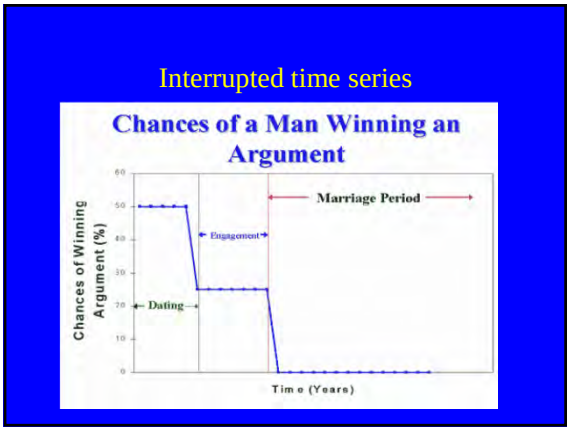


Onesko KM, Infection Control 1987

Stone - Appropriate and inappropriate use of publication guidelines for transparent reporting of observational, intervention and outbreak studies







AIM OF ORION Statement

CONSORT equivalent for infection control studies

- Improve standards research & publication
- Transparency of reporting
- Readers relate studies to their situation.
- Facilitate synthesis of evidence
- Framework for reviewers & editors to assess papers
- Criteria research grant assessment panels

- Designed especially for Interrupted Time Series (with or without controls groups) and outbreak reports.

Key issues addressed by ORION

Transparency: Why was the study done? (hypothesis)
What sort of study? (design)
Exactly what was done, to whom, when?

Analysis: Disaggregated data
Account for dependencies
Confounders

Inference: How do findings relate to hypothesis?
What else influenced the findings?
Do findings generalise ?

Components of ORION

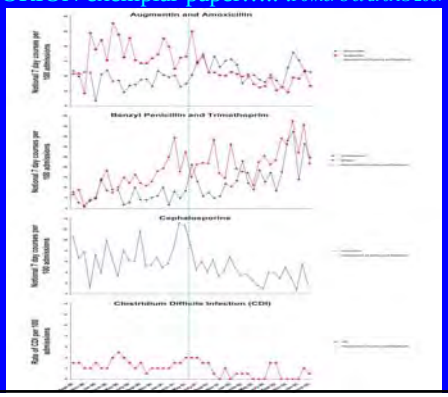
Stone et al Lancet ID 2007;JAC 2007;www.idrn.org/orion.php

- adapted CONSORT statement to the wide variety settings interventions, designs & statistical issues infection control studies & outbreak reports
- Consultation with professional societies
- Independent academic review in two journals

- 22 item checklist
  Title
  Abstract
  Introduction
  Methods
  Results
  Discussion
- Summary table
  Population
  Clinical setting
  Precise nature & timing of all interventions
- Graphical summary results

Stone - Appropriate and inappropriate use of publication guidelines for transparent reporting of observational, intervention and outbreak studies

ORION exemplar paper….. .*Fowler S et al JAC 2007*



CONSORT journal & conference abstract checklist

Hopewell et al PLOS Med 2008

- CONSORT for ABStRACTS : for submission & review of conference & journal abstracts of RCTs (same flaws as full articles)
- ORION and then STROBE suit
- STROBE
- Used for SHEA Conference 2011 & ECCMID 2012

AIMS ABSTRACT CHECKLISTS

1. Help investigators write a high quality conference/journal abstract
2. Provide referees with a framework to help referee a conference abstract
3. Help HCWs and researchers select the best papers/conference presentations for continuing professional development..
   what article to read?
   what conference oral/poster session to go to?

SUBMISSION & REVIEWER'S ORION ABSTRACT CHECKLIST FOR INTERVENTION STUDIES & OUTBREAK REPORTS (see handouts)

Title	1.Clear statement that this is an intervention study or outbreak report.
Background	2.Rationale for study with clear hypothesis for intervention studies or objective for outbreak reports
Methods-	3.Clear statement of intervention study design[1] or case and outbreak definition for outbreak report.
	4.Brief description of participants, setting and of intervention or outbreak control measures (with start & stop dates)
	5. Clearly defined outcomes & denominators at regular time intervals[2], not as totals for each phase *(can be put in results instead)*
	6. Statistical analysis accounts for any dependencies in the data (can be in results instead) *(analysis may not be appropriate for OR)*

ABSTRACT CHECKLIST (cont)

Methods (cont)	7. Which potential confounders or biases were considered, recorded or adjusted for[3] *(can be in results instead)*
	8. Where relevant: details of culture, typing, environmental sampling, & risk factors for acquisition, root cause analysis or organisational risk assessment.
Results-	9. For main outcomes: estimated effect size & its precision (usually 95% CI) (A graphical summary is often appropriate eg for most time series).
Conclusions	10. For intervention studies: consider in relation to original hypothesis, accounting for potential confounders & biases. For outbreak reports: consider clinical significance of observations & hypothesis to explain them.

STROBE (see hand outs)

http://www.strobe-statement.org/

- STrengthening the Reporting of OBservational studies in Epidemiology
- Cohort, Case control & Cross sectional studies
- Abstract checklist with same aims as CONSORT and ORION abstract checklists

Similarities ORION, CONSORT and STROBE

- Design study clearly stated
- Objective/Hypothesis explicit
- Eligibility criteria/case definition for setting and participants
- Clearly defined primary outcome
- Statistical issues addressed- ----dependencies (ORION)
  --disaggregation data (ORION)
  --confounding (STROBE)
- Estimate size effect & precision

Differences ORION, CONSORT and STROBE

- **Title:** intervention study or outbreak report (O), mention RCT (C) mention design (S)
- Description intervention (O and C)
- Details randomisation, allocation, blinding (C)
- Results- graphical summary (O)
- Conclusions- relate to hypothesis/objective (O) v general interpretation (S,C)
- All are works in progress

Where do we go from here?

- Interactive use (following presentations now)
- Similar workshops other conferences and in training to familiarise people
- Evaluate effects of having them on abstract submission site ECMID 2011 v 2012
- Continue to use in conferences & evaluate longitudinal changes?
- Elaboration document for ORION and STROBE
- Carrots---best STROBE/ORION/CONSORT consistent abstract?

Conclusion:

- Only appropriate to use publication guidelines & inappropriate not to
- Ensure transparency & validity of inference
- This is the present and future reality--Equator network ..mentioned by all journals
- Should our own journals now use these guidelines for abstracts initially and then full articles?
- Maybe you will have views after interactive use of them in this workshop?

Thank you

Comments & suggestions to
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The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection

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Lancet Infect Dis 2007; 7: 282–88

See **Reflection and Reaction** page 244

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For more information on the **STROBE initiative** see http://www.strobe-statement.org
For more information on **isolation policies in the hospital management of MRSA** see http://www.hta.nhsweb.nhs.uk

The quality of research in hospital epidemiology (infection control) must be improved to be robust enough to influence policy and practice. In order to raise the standards of research and publication, a CONSORT equivalent for these largely quasi-experimental studies has been prepared by the authors of two relevant systematic reviews, following consultation with learned societies, editors of journals, and researchers. The ORION (Outbreak Reports and Intervention Studies Of Nosocomial infection) statement consists of a 22 item checklist, and a summary table. The emphasis is on transparency to improve the quality of reporting and on the use of appropriate statistical techniques. The statement has been endorsed by a number of professional special interest groups and societies. Like CONSORT, ORION should be considered a "work in progress", which requires ongoing dialogue for successful promotion and dissemination. The statement is therefore offered for further public discussion. Journals and research councils are strongly recommended to incorporate it into their submission and reviewing processes. Feedback to the authors is encouraged and the statement will be revised in 2 years.

Introduction

The move towards evidence-based medicine has gained momentum this past decade. The publication of the CONSORT (Consolidated Standards of Reporting Trials) statement in 1996,[1] its revision in 2001,[2] and extension in 2004,[3] which sought to improve the quality of reports of randomised controlled trials (RCTs), has contributed to this. Through its insistence on complete transparency of reporting, the statement has enabled editors and readers to understand exactly why and how an individual RCT was designed, conducted, and analysed, and to assess the threats to the validity of its results.

The recent publication of the TREND statement (Transparent Reporting of Evaluations of Nonrandomised Designs) sought to do for public-health interventions—most of which are described in non-randomised studies—what CONSORT has achieved for the RCT.[4] The TREND statement adapted the CONSORT statement, its checklist of descriptors, and its flow diagram, but with revisions relevant to non-randomised designs and some important enhancements relevant to RCTs evaluating public-health interventions. Transparency was key to improving the quality of reporting so that information critical to synthesis of research was not missing.[5] The current STROBE initiative (Strengthening the Reporting of Observational studies in Epidemiology) seeks to do the same for epidemiological research, especially for cohort, case control, and cross-sectional studies (http://www.strobe-statement.org).

Hospital interventions to control the rising levels of antimicrobial resistance and healthcare-associated (nosocomial) infections form a large body of non-randomised studies. Systematic reviews of isolation policies in the hospital management of meticillin-resistant *Staphylococcus aureus* (MRSA)[6,7] and of interventions to improve antibiotic prescribing to hospital inpatients[8,9] revealed major methodological weaknesses and inadequate reporting in published research. These included lack of details on study design, as others have noted,[10] the timing and nature of interventions, failure to consider threats to validity of inference in the form of potential confounders and biases, and inappropriate statistical analyses. Studies were largely quasi-experimental and often basic information such as the number of isolation beds, criteria to diagnose infection, culture and typing of organisms, or the timing of interventions were missing. Guidelines for the publication of future outbreak reports and intervention studies were produced,[6] informed by theoretical considerations,[11] but although available on-line (http://www.hta.nhsweb.nhs.uk), these refer primarily to MRSA and are not as user-friendly as the revised CONSORT statement with its 22 item checklist and flow diagram. Moreover, the CONSORT, TREND, and STROBE statements do not provide items or descriptors easily translatable into the wide variety of interventions, settings, designs, and statistical issues relating to infectious diseases.

The authors of the two systematic reviews of isolation[6] and antibiotic prescribing[8] therefore modified previous guidelines[6] for the publication of MRSA outbreak reports and intervention studies to make them relevant to nosocomial organisms in general and to take account of issues pertinent to evaluation of interventions to change hospital antibiotic prescribing.[8,9] The resultant ORION (Outbreak Reports and Intervention Studies Of Nosocomial infection) statement is written in the spirit of the CONSORT and TREND statements, taking into account the variety of interventions, settings, designs, and statistical issues pertinent to health-care associated infections, with team members reaching consensus agreement through repeated email correspondence and

telephone conversations. The statement was then put out to consultation with learned societies, editors of journals, and many researchers, acknowledged below, whose responses have been taken into account in the revised statement. The statement is designed especially for quasi-experimental (ie, non-randomised) study designs commonly used in hospital epidemiology: interrupted time series with and without control groups, and outbreak reports.

The interrupted time series is the predominant study design for infectious disease epidemiology, especially in the hospital setting. Outcome measures are not independent, which introduces specific threats to the validity of inferences, which have had to be addressed. Much research into nosocomial infections blurs the distinction between formal studies and outbreak reports, planned and unplanned comparisons. The guidelines attempt to address this problem by emphasising precision and thoroughness in reporting: as well as the usual what was done and when it was done for such quasi-experimental research, it is also important to know why interventions and particular comparisons were made. As in the TREND statement, "transparency is key" and the ORION items and descriptors "type of paper", "design", and "dates" have been added to ensure this, since even such basic details are often lacking in the hospital infection literature.[6–9]

Our aims in producing these guidelines are to raise the standards of research and publication in hospital epidemiology, to facilitate synthesis of evidence and promote transparency of reporting, to enable readers to relate studies to their own experience, and to assess the degree to which results can be generalised to other settings. The guidelines are aimed at researchers, editors, reviewers, and grant assessment panels. It is intended that the guidelines facilitate well-designed interventional studies to help choose which methods are effective in reducing antimicrobial resistance or health-care associated infections.

ORION components

ORION consists of a 22 item checklist (table). A summary table is strongly recommended for description of the population, clinical setting, and the precise nature and timing of all interventions and outcomes (panel), and a graphical summary of the main results is recommended when outcomes are not independent. For intervention studies, such as cross-over studies, but also for interrupted time series where the primary outcome is a patient outcome, such as infection, and where there are exclusions, we recommend a flow chart to track participants through each stage of the study.

The items and descriptors in the table are largely self-explanatory. We restrict further detailed comment in this paper to those items and descriptors concerning the difference between outbreak reports and intervention studies, the rationale and aim of studies, the description of interventions, the documentation of potential threats to validity of inference from biases and confounders, and the choice of appropriate statistical techniques to minimise threats to statistical conclusion validity. We also make brief comments on economic evaluation, the adverse effects of interventions, and the relation between ORION and CONSORT in the design, analysis, and reporting of RCTs in infection control.

Outbreak reports and intervention studies

The hospital infection literature frequently blurs the distinction between outbreak reports (and the subsequent interventions adopted to control the outbreak) and planned studies of the effectiveness of interventions. Because many important biases may be in operation and several interventions are often made simultaneously, outbreak reports are of limited value for assessing the effectiveness of interventions.[16] They can, however, be important for generating hypotheses or describing new phenomena. The objective of an outbreak report should therefore be stated in the introduction, examples being to report a new epidemic strain,[17] to quantify or describe the resources used to control the outbreak,[17,18] or to describe obstacles to the outbreak control encountered.[17] The essential components of an outbreak investigation and report have been listed elsewhere.[19] We recommend that these be adhered to and have incorporated them into our guidelines.

Aim and rationale of studies

The aim of an intervention study should be stated in the introduction and its design should be referred to in the abstract and title. It should be stated whether a study is prospective (ie, looking forward, and typically using data collected for the purpose of the study) or retrospective (using historical data collected for purposes other than the study), or whether it is ambidirectional (using both prospectively and retrospectively collected data).

When reporting studies evaluating interventions, authors have often failed to explicitly document the reasons behind the decision to intervene at a certain point in time.[6] This is important, since studies where interventions are introduced because of unusual levels of infection are likely to be vulnerable to regression to the mean artefacts and must be interpreted with caution.[20] It should therefore be made clear whether any part of the study data prompted the decision to intervene. Similarly, the reasons for choosing comparisons between certain groups or time periods should be clearly stated. When this choice could be influenced by knowledge of some part of the outcome data, the validity of inferences about the intervention is again threatened (for example, by reporting bias if the successful interventions are more likely to be reported than the unsuccessful). Measures taken to prevent such influence should therefore be reported. These problems with unplanned interventions and comparisons most commonly affect retrospective studies, but prospective studies can

	Item number	Descriptor
Title and abstract	1	Description of paper as outbreak report or intervention study. Design of intervention study (eg, interrupted time series with or without control group, cross over study). Brief description of intervention and main outcomes.
Introduction		
Background	2	Scientific and/or local clinical background and rationale. Description of organism as epidemic, endemic, or epidemic becoming endemic.
Type of paper	3	Description of paper as intervention study or an outbreak report. If an outbreak report, report the number of outbreaks.
Dates	4	Start and finish dates of the study or report.
Objectives	5	Objectives for outbreak reports. Hypotheses for intervention studies.
Methods		
Design	6	Study design. Use of Effective Practice and Organisation of Care Group classification[12] recommended (controlled before and after study or interrupted time series). Whether study was retrospective, prospective, or ambidirectional. Whether decision to report or intervene was prompted by any outcome data. Whether study was formally implemented with predefined protocol and endpoints.
Participants	7	Number of patients admitted during the study or outbreak. Summaries of distributions of age and lengths of stays. If possible, proportion admitted from other wards, hospitals, nursing homes, or from abroad. Where relevant, potential risk factors for acquiring the organism. Eligibility criteria for study. Case definitions for outbreak report.
Setting	8	Description of the unit, ward, or hospital and, if a hospital, the units included. Number of beds, the presence and staffing levels of an infection control team.
Interventions	9	Definition of phases by major change in specific infection control practice (with start and stop dates). A summary table is strongly recommended (see panel) with precise details of interventions, how and when administered in each phase.
Culturing and typing	10	Details of culture media, use of selective antibiotics and local and/or reference typing. Where relevant, details of environmental sampling.
Infection-related outcomes	11	Clearly defined primary and secondary outcomes (eg, incidence of infection, colonisation, bacteraemia) at regular time intervals (eg, daily, weekly, monthly) rather than as totals for each phase, with at least three data points per phase[12] and, for many two phase studies, 12 or more monthly data points per phase.[13] Denominators (eg, numbers of admissions or discharges, patient bed days). If possible, prevalence of organism and incidence of colonisation on admission at same time intervals. Criteria for infection, colonisation on admission, and directly attributable mortality. All cause mortality. For short studies or outbreak reports, use of charts with duration of patient stay and dates organism detected may be useful (see text).
Economic outcomes	12	If a formal economic study done, definition of outcomes to be reported, description of resources used in interventions, with costs broken down to basic units, stating important assumptions.
Potential threats to internal validity	13	Which potential confounders were considered, recorded or adjusted for (eg, changes in length of stay, case mix, bed occupancy, staffing levels, hand-hygiene compliance, antibiotic use, strain type, processing of isolates, seasonality). Description of measures to avoid bias including blinding and standardisation of outcome assessment and provision of care.
Sample size	14	Details of power calculations, where appropriate.
Statistical methods	15	Description of statistical methods to compare groups or phases. Methods for any subgroup or adjusted analyses, distinguishing between planned and unplanned (exploratory) analysis. Unless outcomes are independent, statistical approaches able to account for dependencies in the outcome data should be used, adjusting, where necessary, for potential confounders. For outbreak reports statistical analysis may be inappropriate.
Results		
Recruitment	16	For relevant designs, such as cross over studies,[14] or where there are exclusions of groups of patients, the dates defining the periods of recruitment and follow-up, with a flow diagram describing participant flow in each phase.
Outcomes and estimation	17	For the main outcomes, the estimated effect size and its precision (usually using confidence intervals). A graphical summary of the outcome data is often appropriate for dependent data (such as most time series).
Ancillary analyses	18	Any subgroup analyses should be reported and it should be stated whether or not it was planned (ie, specified in the protocol) and adjusted for possible confounders.
Harms	19	Prespecified categories of adverse events and occurrences of these in each intervention group. This might include drug side-effects, crude or disease-specific mortality in antibiotic policy studies, or opportunity costs in isolation studies.
Discussion		
Interpretation	20	For intervention studies an assessment of evidence for/against hypotheses, accounting for potential threats to validity of inference including regression to mean effects and reporting bias. For outbreak reports, consider clinical significance of observations and hypotheses generated to explain them.
Generalisability	21	External validity of the findings of the intervention study—ie, to what degree can results be expected to generalise to different target populations or settings. Feasibility of maintaining an intervention long term.
Overall evidence	22	General interpretation of results in context of current evidence.

Table: **ORION checklist of items to include when reporting an outbreak or intervention study of a nosocomial organism**

also be vulnerable if the study protocol contains insufficient detail about the implementation of interventions or the analysis. The extent to which different aspects of the study are specified by the protocol should therefore be clearly reported. Such aspects include the nature and timing of interventions, the groups to be compared, the start and

endpoints of the study, and the analysis plan, including details of subgroup analyses. Deviations from the protocol should also be reported.

Summary table

Details on participants, setting, and interventions are often insufficient and we recommend that a summary table be used to describe the populations, clinical settings, and the precise nature and timing of all interventions (see panel for an example), defining each phase of the study by a major change in specific infection control practice. The patient isolation, screening, and eradication policies and other interventions (for example, antibiotic restriction, hand-hygiene education or feedback, ward closures, feedback of surveillance, or outcome data) should all be specified and clearly described in each phase. We have found it possible to do so in table form[6,15] in a way that we would suggest makes for both clarity and brevity, and we have written a companion paper that illustrates how to report an intervention study in an ORION compliant way[15] to help readers to understand the statement in operation.

Description of interventions

We recommend avoiding the use of terms such as contact or strict isolation, barrier nursing, enteric or skin precautions to describe isolation interventions, since these may not be universally understood to have the same meaning. Even when accompanied by a reference to, for example, national guidelines, these may not be easily accessible or relevant, especially internationally. We therefore recommend the use of more descriptive terms such as isolation ward, cohort (on a general ward) with designated staff, cohort without designated staff, single room, use of aprons or gowns and gloves only, or no measures taken. Similarly, we recommend avoiding descriptions of interventions such as "according to UK National Working Party Guidelines". This provides insufficient detail—for example, the most recent UK guidelines[21] have in-built flexibility that requires further detail to be given in reporting an outbreak or intervention study. Terms such as "search and destroy" or "Scutari"[22] similarly lack clarity, although they remain useful concepts in general discussion. A glossary, as published elsewhere,[6] may be helpful to avoid confusion but we recommend precise description of isolation, eradication, screening, antibiotic, hand-hygiene, and other policies as detailed in the webappendix. Again, the companion paper[15] gives an example of this in practice.

Documentation of potential confounders and biases

Attention should be paid to describing, minimising, and adjusting for plausible threats to the validity of inference from biases and confounders.[6,7] Measures taken to prevent bias should be considered in the study design, and reported in detail. Potential bias in studies with comparison groups should be sought in the usual way[1] with attention paid to method of allocation and possible selection bias. Blinding may be as relevant to non-RCT designs as to RCTs and, even when impossible to blind

***Panel:* Example of summary table of population, clinical setting, nature, and timing of interventions[15]**

Setting
Three acute care of elderly wards (78 beds) in 1200-bed tertiary hospital with 0·3 whole time equivalent infection control doctor and 4·5 whole time equivalent infection control nurses.

Dates
Sept 1, 1999–March 31, 2003

Population characteristics
6129 unselected acute consecutive elderly medical admissions (80 years plus). Monthly length of stay 11·93–13·53 days. Endemic *Clostridium difficile* infection (CDI) and E-MRSA 15 & 16. No inter-hospital transfers.

Major infection control changes during the study
Change from "cephalosporin restrictive" antibiotic policy with feedback every 2–3 months (phase 1: Sept 1, 1999–Jun 30, 2001; 21 months) to "narrow-spectrum" antibiotic policy with feedback as before and provision of laminated pocket-sized card with policy written on it (phase 2: July 1, 2001–March 31, 2003; 21 months).

Antibiotic policy
Phase 1: cephalosporin restrictive policy (see below for details)
Phase 2: narrow-spectrum (see reference 15) policy, written on portable pocket-sized laminated card

Feedback
Phase 1 and 2: 2–3 monthly feedback of antibiotic use in notional 7-day courses per 100 admissions per month and of monthly numbers of CDI and new MRSA cases.

Isolation policy CDI
Both phases: all proven cases isolated in side rooms. Aprons and gloves worn for contact.

Isolation policy MRSA
Both phases: all cases colonisation or infection isolated in side rooms or four-bedded cohort on one ward. Aprons and gloves worn for contact.

Cephalosporin restrictive antibiotic policy details (phase 1)
Community-acquired pneumonia: amoxicillin; urinary tract infection: trimethpoprim; cellulitis: flucloxacillin and benzylpenicillin; community-acquired aspiration pneumonia: benzylpenicillin and metronidazole. Ceftriaxone reserved for (1) severe community-acquired pneumonia; (2) hospital-acquired aspiration pneumonia; (3) urinary tract infection with renal failure. Gentamicin: urinary tract infection with shock, septicaemia with no apparent focus infection, and intra-abdominal sepsis (with ampicillin and metronidazole); erythromycin: penicillin allergy.

(Continues on next page)

See **Online** for webappendix

(Continued from previous page)

Isolation details (both phases)
Ten side rooms available on the three wards. One four-bedded MRSA cohort on one ward. All other beds configured in four-bedded bays. Wall-mounted liquid soap and alcohol handrub dispenser and sink in each side room. One sink for each four-bedded bay with liquid soap and, from January 2002, one wall-mounted alcohol handrub dispenser per four-bedded bay.

MRSA screening policy (both phases)
Admission screening (nose, perineum, wounds, and devices) of admissions from nursing homes, of those with a past history of MRSA, (both groups admitted to side room). Patients screened during admission if they had been in the same bay with a new case of MRSA.

MRSA eradication policy (both phases)
Intranasal mupirocin and chlorhexidine body washes and shampoo for patient with no wounds. Clearance defined as three consecutive negative weekly swabs.

Definition CDI (both phases)
An episode of diarrhoea a sample of which was positive for toxin (1). No culture or typing performed.

Definition of new MRSA acquisition (both phases)
Cases found on screening or clinical specimens taken more than 48 h after admission. No routine typing performed but E-MRSA 15 & 16 endemic.

the care provider or patient, it may be possible to blind the outcome assessor. When blinding is not possible, this should be stated. Possible confounders or effect modifiers should be acknowledged and, where possible, quantified and adjusted for in the analysis. Such factors may include changes to length of stay, case mix, bed occupancy, staffing levels or workloads, and seasonal effects. Similarly, changes in antibiotic use, hand-hygiene, and ward closures—unless part of the intervention under investigation—are all potential confounders.

Variations in laboratory practices may also affect both the ability to make valid inferences about an intervention and the ability to generalise results to other settings. The fact that variants of the same pathogen species may have very different properties poses further challenges for reporting and interpreting results and for generalising findings. This consideration led to the inclusion of pathogen typing as a separate item on the checklist. For longer studies, changes in the properties of the pathogens may be important, and where information is available these should be described.

When accurate data on potential confounders are unavailable, descriptive summaries should still be provided—for example, whether or not there were believed to be changes in patient characteristics, processing of isolates, antibiotic or screening policies, etc.

Appropriate statistical analysis

Threats to statistical conclusion validity should be minimised in intervention studies by seeking advice from a statistician with epidemiological expertise (and ideally knowledge of special issues relating to infectious diseases) before conducting the study. Typically, statistical approaches assuming independence of outcomes relating to infection or colonisation will be inappropriate, since for a communicable disease the risk to one patient will depend on the status of other patients. Incorrect use of approaches that assume independence (which include the chi-squared test, Fisher's Exact test, linear regression, etc) can lead to false inferences.

All outcome data should be clearly described in the methods, as should the statistical methods. These might include survival analysis or time series methods for interrupted time series. Unless it is reasonable to assume outcomes to be independent, analysis of aggregated data should be avoided when disaggregated data are available. In general, for interrupted time series designs the outcome data (which may include both infection-related outcomes and indirect or behavioural outcomes such as antibiotic use or hand-hygiene compliance) should be presented as time series rather than averages in the pre- and post-interventions phase, because the latter do not provide information about trends over time, and regression to mean effects may operate.[6,8,9,20] Before and after studies should either have a contemporary control (no intervention) group or there should be sufficient observations for analysis as an interrupted time series.[8,9] The absolute minimum number of data points is three before and three after the intervention.[12] Uncontrolled before and after studies with fewer data points than this are unacceptable. A general pragmatic recommendation is for at least 12 monthly data points before and 12 monthly points after the intervention, although more data points and longer study periods provide even stronger evidence because trends, seasonal effects, and natural stochastic variability can be better identified.[13] Unnecessary aggregation of data such as reporting yearly or 6-monthly rather than monthly or weekly loses information, weakens the evidence, and should be avoided. Graphical summaries of the main outcomes are often useful for presenting time series data in a condensed and informative manner.

For short studies or outbreak reports, charts showing the duration of individual patient stays and dates of detection of organisms, including data on exposed patients who did not acquire the organism are often informative. Formal statistical analysis is not required for outbreak reports and may sometimes be inappropriate, an exception to this being appropriate analysis of a case control study done within the outbreak report.

Economics

"Economic outcomes" have been included, although they are not obligatory. They do not appear in

CONSORT but are often highly relevant to complex interventions,[23] such as infection control interventions, and systematic review has established a lack of robust economic evaluation in this field.[6–9] To be useful, however, economic evaluations should attempt to adopt an approach that is comprehensive in so far as it documents and measures all resources used (such as hours or minutes of physician or nurse time, number of extra agarose plates) and costs these resources using cost vectors that are available and transparent to other researchers. Such resources should be precisely described (eg, minutes or hours of nurse or physician time, number of extra swabs, etc) to help with generalisability. Moreover, any change in practice consumes resources that could have been used for other purposes and therefore has an opportunity cost.[24] Care should be taken when attributing the costs to ensure that the attribution is appropriate. If no economic analysis was done, this should be clearly stated. Advice should be sought before conducting the study from a health economist with, ideally, knowledge of the special issues[25,26] relating to nosocomial infection.

Harms

All potential harms should be specified beforehand.[27] These might include measures of clinical outcome such as mortality (all-cause mortality should be routinely reported), re-admissions, or length of stay. Such measures may need to be monitored after interventions intended to reduce antibiotic prescribing in order to provide evidence about unintended adverse effects, as might the use of empirical antibiotic treatment that is later shown not to match the sensitivity of the isolated organism. There may often be no explicit evidence directly linking recommended policies with clinical outcomes[24] and this may be especially true for local antibiotic policies.[28] In certain studies, different unintended adverse effects, such as operations cancelled or isolation beds that could have been used for other purposes, or the adverse effects of isolation, will require pre-specification and assessment.

ORION and RCTs in infection control

The statement does not address issues specific to the conduct, description, and analysis of RCTs (including those with cluster-randomisation) because the CONSORT statement already covers these. However when cluster RCTs are used to evaluate infection control interventions, ORION may be useful to identify potential confounders and to ensure sufficient detail is reported to maximise transparency and enable assessments of external validity to be made. Examples are those items or, more often, descriptors relating to culture and typing, participants, interventions, infection-related outcomes, and harms. Similarly, for cohort or case control studies STROBE should apply, although ORION may be helpful in similar respects.

Dissemination, enforcement, feedback, revision, and evaluation

CONSORT and TREND consider themselves "work in progress". We regard ORION in the same light, realising that such guidelines require dissemination, endorsement, enforcement, feedback, revision, and evaluation.[29] Dissemination of ORION by joint publication, conference presentations and workshops, and open access to its own website (http://www.idrn.org/orion.php) is being allied to MSc or post-graduate diploma teaching in infectious diseases, infection control, and pharmacy. The statement has been endorsed by the Association of Medical Microbiologists, who have placed it on their website, and welcomed by the Infection Control Nurses' Association Research and Development Group. The British Society for Antimicrobial Chemotherapy has placed it on their website (http://www.bsac.org.uk), intends to incorporate it into their grant assessment process, and their journal intends to trial its incorporation into its instructions to authors and reviewers. We strongly recommend that other journals and research councils follow suit. Feedback directly through the website and through postgraduate teaching will be stored for a revision meeting in 2 years. Evaluation will be through an electronic search strategy for citations of ORION in relevant published studies and, following precedent with CONSORT,[30] a controlled before and after study comparing adopter with non-adopter journals in the first 5 years of its publication.

For more information on **the ORION website** see http://www.idrn.org/orion.php

For more information on **the British Society for Antimicrobial Chemotherapy** see http://www.bsac.org.uk

Conflicts of interest

SS has received research grant contributions and expenses for conference attendance from GOJO industries, manufacturers of Purell Hand-Rub. PGD has received sponsorship for speaking at meetings from Aventis, Pfizer, and Wyeth, and research funding from GlaxoSmithKline, Pfizer, and Boehringer Ingelheim. He is also a member of the Johnson & Johnson Global Anti-infectives Advisory Board. All other authors have no conflicts of interest to declare.

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ORION SUBMISSION AND REVIEWER'S ABSTRACT CHECKLIST FOR INTERVENTION STUDIES* AND OUTBREAK REPORTS

* carried out either to reduce infection or to improve compliance with infection control measures such as hand hygiene, antibiotic prescription or care bundle implementation

1. Title- Clear statement that this is an intervention study or outbreak report.
2. Background- Rationale for study with clear hypothesis for intervention studies or objective for outbreak reports
Methods- 3. Clear statement of intervention study design[1] or case definition for outbreak report.
4. Brief description of participants, setting and of intervention or outbreak control measures (with start & stop dates)
5. Clearly defined outcomes & denominators at regular time intervals[2] , not as totals for each phase (can be put in results instead)
6. Statistical analysis accounts for any dependencies in the data (can be in results instead) (statistical analysis may not be appropriate for outbreak reports).
7. Which potential confounders or biases were considered, recorded or adjusted for [3] can be in results instead)
8. Where relevant: details of culture, typing, environmental sampling, and risk factors for acquisition, root cause analysis or organisational risk assessment.
Results- 9. For the main outcomes: estimated effect size & its precision (usually using 95% C.I.) (A graphical summary is often appropriate for dependent data -such as most time series).
Conclusions- **10.** For intervention studies: consider in relation to original hypothesis, accounting for potential confounders & biases. For outbreak reports: consider clinical significance of observations & hypothesis to explain them.

[1] e.g. Interrupted Time Series, Cluster or other Randomised Controlled Trial, Cross over, Controlled Before and After intervention, Uncontrolled Before and After Intervention (see explanatory document and www.ccg.cochrane.org/en/newPage1.html for standard terminology.

[2] at least 3 time points per phase and for many two phase studies 12 or more monthly data points.

[3] e.g. changes in length of stay, case mix, bed occupancy, staffing levels, hand-hygiene compliance, antibiotic use, strain type, processing of isolates, seasonality, other interventions, incomplete blinding, fidelity to intervention, non standardised outcome assessment.

CONSORT abstract checklist

Item	Description
Title	Identification of the study as randomised
Authors*	Contact details for the corresponding author
Trial design	Description of the trial design (e.g. Parallel, cluster non-inferiority)
Methods	
Participants	Eligibility criteria for participants and the settings where the data were collected
Interventions	Interventions intended for each group
Objective	Specific objective or hypothesis
Outcome	Clearly defined primary outcome for this report
Randomisation	How participants were allocated to interventions
Blinding (masking)	Whether or not participants, care givers, and these assessing the outcomes were blinded to group assignment
Results	
Numbers randomised	Number of participants randomised to each group
Recruitment	Trial status
Numbers analysed	Number of participants analysed in each group
Outcome	For the primary outcome a result for each group and the estimated effect size and its precision
Harms	Important adverse events or side-effects
Conclusion	General interpretation of the results
Trial registration	Registration number and name of trial register
Funding	Source of funding

**For conference abstracts.*

Table. Items to include when reporting randomised trials in journal or conference abstracts.

STROBE Statement—Items to be included when reporting observational studies in a conference abstract

Item	Recommendation
Title	Indicate the study's design with a commonly used term in the title (e.g cohort, case-control, cross sectional)
Authors	Contact details for the corresponding author
Study design	Description of the study design (e.g cohort, case-control, cross sectional)
Objective	Specific objectives or hypothesis
Methods	
Setting	Description of setting, follow-up dates or dates at which the outcome events occurred or at which the outcomes were present, as well as any points or ranges on other time scales for the outcomes (e.g., prevalence at age 18, 1998-2007).
Participants	*Cohort study*—Give the most important eligibility criteria, and the most important sources and methods of selection of participants. Describe briefly the methods of follow-up *Case-control study*—Give the major eligibility criteria, and the major sources and methods of case ascertainment and control selection *Cross-sectional study*—Give the eligibility criteria, and the major sources and methods of selection of participants
	Cohort study—For matched studies, give matching and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	Clearly define primary outcome for this report.
Statistical methods	Describe statistical methods, including those used to control for confounding
Results	
Participants	Report Number of participants at the beginning and end of the study
Main results	Report estimates of associations. If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Report appropriate measures of variability and uncertainty (e.g., odds ratios with confidence intervals
Conclusions	General interpretation of study results

Assessment of risk factors for a bad outcome in infectious diseases

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Vice Dean and Head of the School of Medicine, Sackler Faculty of Medicine, Tel-Aviv University, Israel;

Senior Editor, Journal of Antimicrobial Chemotherapy

What is the purpose of the study?

- To describe the effect of an intervention (especially if it cannot be tested in a RCT).
- To understand why patients come to a bad end (especially risk factors that can be altered).
- To compare the outcome and risk factors for a bad outcome between different groups of patients, or different pathogens (futile treatment? Pathogens that are not associated with fatal outcome?)

Who are the patients (i.e. what is the denominator?)

- The whole population?
- People in the catchment area?
- Patients with an infection?
- Patients with a specific pathogen?

Outcome (nominator)

- Failure of treatment?
- Really bad outcomes: composite of severe complications, on respirator, admittance to the ICU, slow recovery, death?
- Infection related deaths?
- All-cause mortality?
  - Thirty days (a fixed period of time) and not in-hospital or ICU.*

*Paul M et al. Antimicrob Agents Chemother 2010; 54(11):4851-63.

Prospective or retrospective?

- Prospective is always preferred but many times impossible.
- There are questions that cannot be answered in a retrospective design.

For both designs, write a protocol before the work starts.

Sample size

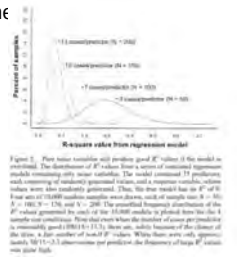
Outcomes were equivalent between patients treated with ertapenem and group 2 carbapenems (mortality rates 6% and 18%, p=0.18).

Calculations of sample size (1)

- Usually the final conclusion will be based on a multivariate analysis.
- Start with a simple bi-variate calculation:
  - What is the main exposure factor you're interested in?
  - What is the minimum effect size that matters?
  - If you have no chance of reaching this sample size, you probably should not do the study
- Formal calculations for multivariate analysis (e.g. SAS PROC POWER, logistic regression with binary response)

Calculations of sample size (2)

Rule of thumb: 7-10 patients with the least common outcome (e.g. failure if most patients were counted as success) for each factor you intend to enter into the



Which risk-factors to collect

- Primary and secondary outcomes
- Factors that reflect severity of infection:
  - Aggregate, e.g.: APACHE, SOPHA
  - Single risk factors*, e.g.: source of infection, pathogen, septic shock, creatinine
- Factors that reflect underlying conditions*, e.g.: age, functional capacity, congestive heart failure, on respirator, prior antibiotic treatment.
- Management: empiric and definitive inappropriate antibiotic treatment, fluids.

*Leibovici L et al. J Intern Med 1998;244(5):379-86.

Correcting for indication bias:
propensity scores

- Propensity scores estimate the predicted probability (propensity) of use of a given drug or procedure in a particular subject, based on his or her characteristics when the treatment is chosen.
- Patients that were given the intervention are compared to these that were not by comparing variables known at the start of treatment.
- The variables that differ are combined into a score (usually using logistic regression analysis) and the score used to compare like to like.

Three ways to use propensity scores:

- Matching: excellent internal validity, problems with external validity.
- Stratification.
- Used as a variable in the model predicting outcome.

Journal of Clinical Epidemiology 59 (2006) 437–447

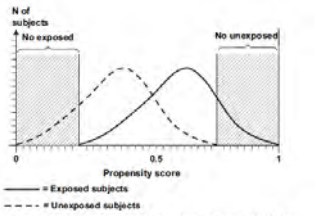


Fig. 1. Nonoverlap of the propensity score distributions among exposed and unexposed subjects. In this example, subjects with low propensity scores are never exposed, and subjects with high propensity scores are always exposed.

Limitations of propensity scores:

- We are not sure that variables of interest were really captured.
- Edges with no overlap.
- One score.

Propensity scores: suggested references

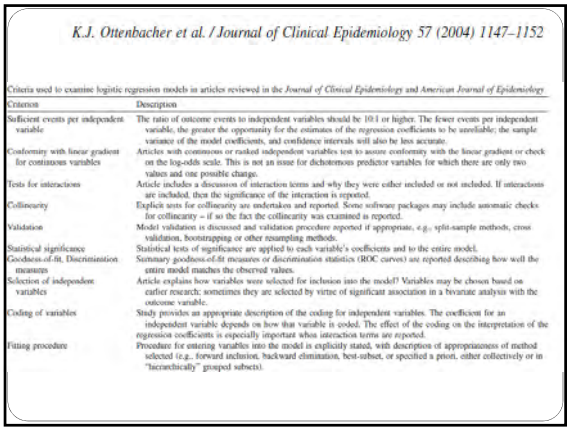
- Biondi-Zoccai G et al. Contemporary Clinical Trials 32 (2011) 731–740.
- Kuss O et al. J Clin Epidemiol. 2011 Oct;64(10):1076-84.
- Austin PC. Circ Cardiovasc Qual Outcomes. 2008 Sep;1(1):62-7.

Analysis:

- Choice of variables: depends on purpose whether you want to maximize external or internal validity.
- Causal pathway.

Causal pathway: an example

- We tested the hypothesis that appropriate empirical treatment given within 12 hours reduces fatality rate of bacteremia.
- Fatality rate in inappropriate treatment group = 36% (277/767).
- Fatality rate in appropriate treatment group = 29% (73/252).
- On a logistic regression analysis, septic shock, age, pneumonia as source of bacteremia, congestive heart failure and acute renal failure emerged as independent predictors of a fatal outcome, but not appropriateness of treatment.



K.J. Ottenbacher et al. / Journal of Clinical Epidemiology 57 (2004) 1147–1152

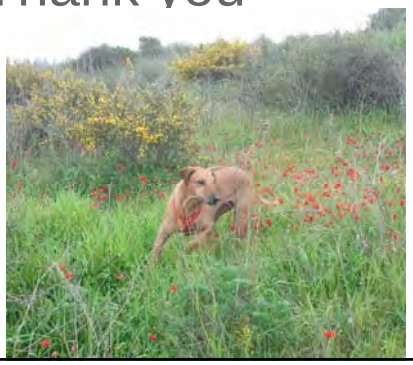
Criteria used to examine logistic regression models in articles reviewed in the *Journal of Clinical Epidemiology* and *American Journal of Epidemiology*

Criterion	Description
Sufficient events per independent variable	The ratio of outcome events to independent variables should be 10:1 or higher. The fewer events per independent variable, the greater the opportunity for the estimates of the regression coefficients to be unreliable; the sample variance of the model coefficients, and confidence intervals will also be less accurate.
Conformity with linear gradient for continuous variables	Articles with continuous or ranked independent variables test to assure conformity with the linear gradient or check on the log-odds scale. This is not an issue for dichotomous predictor variables for which there are only two values and one possible change.
Tests for interactions	Article includes a discussion of interaction terms and why they were either included or not included. If interactions are included, then the significance of the interaction is reported.
Collinearity	Explicit tests for collinearity are undertaken and reported. Some software packages may include automatic checks for collinearity – if so the fact the collinearity was examined is reported.
Validation	Model validation is discussed and validation procedure reported if appropriate, e.g., split-sample methods, cross validation, bootstrapping or other resampling methods.
Statistical significance	Statistical tests of significance are applied to each variable's coefficients and to the entire model.
Goodness-of-fit, Discrimination measures	Summary goodness-of-fit measures or discrimination statistics (ROC curves) are reported describing how well the entire model matches the observed values.
Selection of independent variables	Article explains how variables were selected for inclusion into the model? Variables may be chosen based on earlier research; sometimes they are selected by virtue of significant association in a bivariate analysis with the outcome variable.
Coding of variables	Study provides an appropriate description of the coding for independent variables. The coefficient for an independent variable depends on how that variable is coded. The effect of the coding on the interpretation of the regression coefficients is especially important when interaction terms are reported.
Fitting procedure	Procedure for entering variables into the model is explicitly stated, with description of appropriateness of method selected (e.g., forward inclusion, backward elimination, best-subset, or specified a priori, either collectively or in "hierarchically" grouped subsets).

Summary:

- Be clear as to your purpose.
- Write a protocol.
- Address ethical issues.
- Define your population and outcome.
- Do a sample size analysis.
- Define the variables of interest.
- Consider the use of a propensity score to try and correct for indication bias.
- Take the causal pathway into account.
- Make an explicit decision on the ways to include variables into your model.
- Perform correct multivariable analysis.
- Be modest in your conclusions.

Thank you



Applying the ORION statement to antimicrobial stewardship intervention studies: worked example

Endemic *Clostridium difficile* case study

Background

Ninewells Hospital is an 855 bed University hospital. In 2008 the average incidence of *C. difficile* infection was 1.5 cases per 1000 patients per month with no significant increase over 3 years. A time series analysis of the relationship between antibiotic use and the prevalence of *C. difficile* infection was completed in 2008.[1] The number of cases of *C. difficile* infection in 1 month was dependent on the average number of cases of *C. difficile* infection in the previous 2 months. The models with data from the whole hospital showed a statistically significant relationship between the number of hospital-acquired *C. difficile* infections and consumption of piperacillin/tazobactam, ciprofloxacin, cefuroxime and co-amoxiclav. The model for hospital-acquired *C. difficile* infections explained 61% of the variance in *C. difficile* infections.

The Scottish Government is about to introduce a new target for reduction of the rate of *C. difficile* infection among patients aged 65 and over by at least 30% by 31 March 2011.[2]

Baseline data

Current infection control policies (Table 1), use of key antibiotics in the previous year (Table 2), prevalence of *C difficile* infections (Figure 1), antibiotic policy for empiric treatment (Figure 2) and surgical antibiotic prophylaxis (Figure 3) are provided.

Medical and surgical awards account for 80% of the hospital antibiotic use and cases of hospital acquired *C. difficile* infection.

Activities

1. Plan an intervention to reduce *C. difficile* infection by at least 30% in medical and surgical wards

Table 1: Population, antibiotic policy, audit and feedback and infection control policy in Phase 1 (pre-intervention)

Setting: Nine adult medical wards and six adult surgical wards in a 855 bed University hospital			
Dates: April 2004 to October 2008			
Population characteristics: **Medical:** all admissions through the Acute Medical Admissions Unit. **Surgical:** all admissions to six surgical wards Endemic *C. difficile* infection at an average of 1.5 cases per 1000 patients per month in the pre-intervention period with no significant increase during the pre-intervention period, Figure 1 [1] Few inter-hospital transfers from two other hospitals in Tayside with no change during the study period. No inter-hospital transfers from other regions			
	Antibiotic policy	**Audit and Feedback**	**Infection Control Policy**
Phase 1: 36 months (1 October 2006 to 30 September 2008)	Policy for use of ALERT antibiotics introduced in August 2000, implemented by advice from clinical pharmacists [3]. (i) Carbapenems: imipenem and meropenem (ii) Glycopeptides: teicoplanin and vancomycin (iii) Intravenous (iv) amphotericin (iv) Ciprofloxacin (iv) (v) Linezolid (iv and oral) (vi) Piperacillin–tazobactam (Tazocin) (vii) Third-generation cephalosporins: ceftriaxone, cefotaxime and ceftazidime	Quarterly reports on ALERT antibiotic use by Clinical Group introduced in 2003. Reports expanded to include all antibiotics in April 2007. Quarterly reports on *C difficile* infections to clinical groups throughout Phase 1. Quarterly Infection Control reports with balanced scorecard to Clinical Groups and NHS Tayside Board from 2006	Policy for isolation of any patient with diarrhoea and any patient with confirmed *C difficile* infection in single rooms with aprons and gloves worn for contact throughout Phase 1. Weekly hand hygiene audits in study wards introduced from 2005 conducted by ward staff as part of the Safer Patients Initiative. Supplemented with bi-monthly audits by Infection Control practitioners as part of the National Hand Hygiene Campaign from January 2007 [4]. Annual environmental infection control audits by Infection Control practitioners

Table 2 Antibiotic usage in DDDs per month in 2007 for Surgery, Medicine, Specialist Services, Musculoskeletal/A&E and Critical Care

Antibiotic	Mean monthly DDDs for 2007
Cefuroxime	759
Ciprofloxacin	2704
Clarithromycin	2539
Co-amoxiclav	4618
Flucloxacillin	3563
Gentamicin	210
Levofloxacin	180
Meropenem	182
Metronidazole	1559
Moxifloxacin	421
Piperacillin tazobactam	314
Vancomycin	356

Figure 1: Cases of *C. difficile* infection in 2006-8

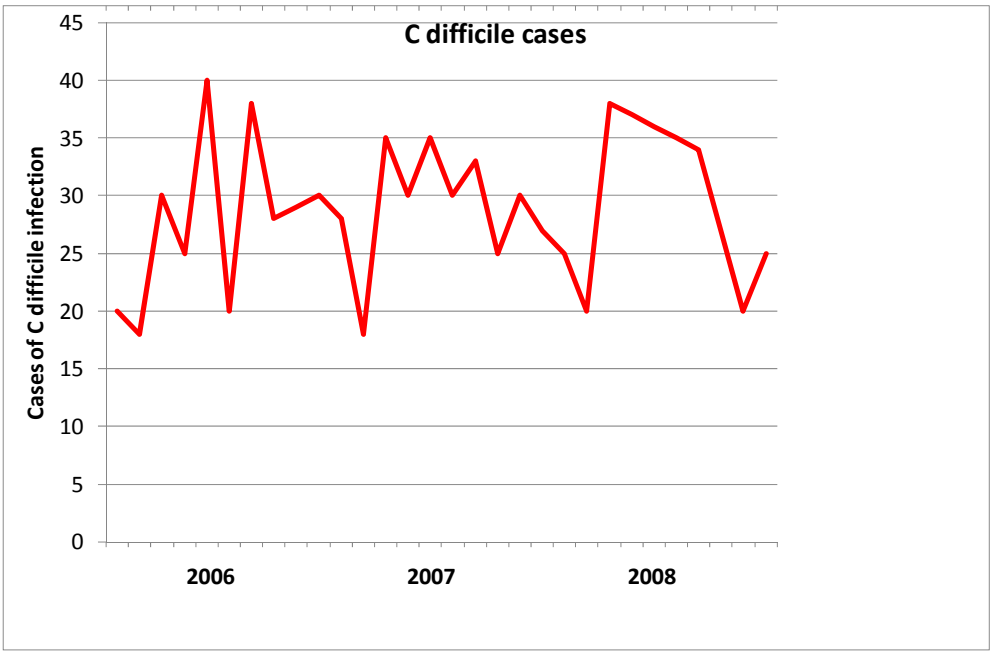
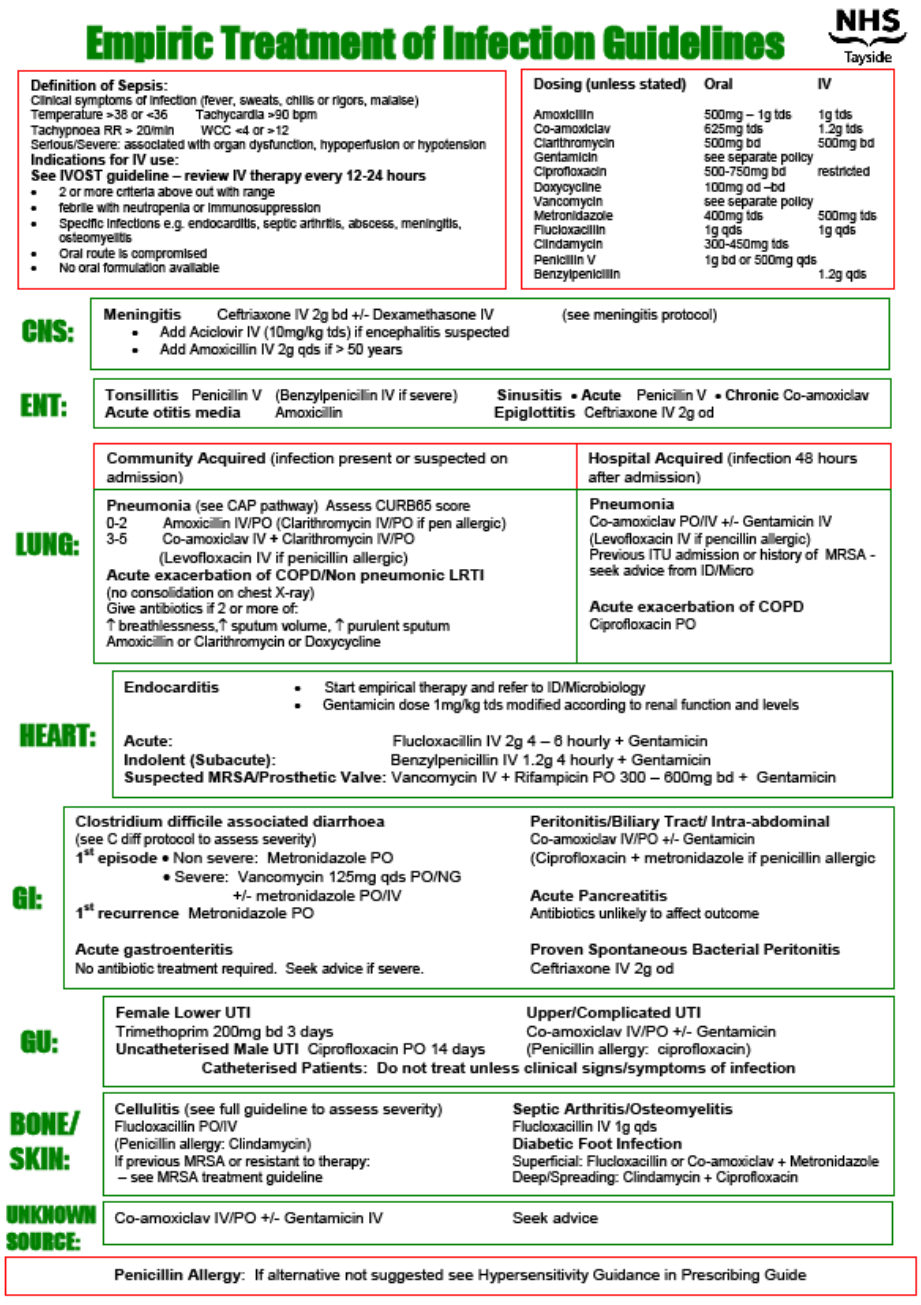


Figure 2: NHS Tayside Treatment Policy 2008 (pre-intervention)



Empiric Treatment of Infection Guidelines

NHS Tayside

Definition of Sepsis:
Clinical symptoms of infection (fever, sweats, chills or rigors, malaise)
Temperature >38 or <36 Tachycardia >90 bpm
Tachypnoea RR > 20/min WCC <4 or >12
Serious/Severe: associated with organ dysfunction, hypoperfusion or hypotension
Indications for IV use:
See IVOST guideline – review IV therapy every 12-24 hours
- 2 or more criteria above out with range
- febrile with neutropenia or immunosuppression
- Specific infections e.g. endocarditis, septic arthritis, abscess, meningitis, osteomyelitis
- Oral route is compromised
- No oral formulation available

Dosing (unless stated)	Oral	IV
Amoxicillin	500mg – 1g tds	1g tds
Co-amoxiclav	625mg tds	1.2g tds
Clarithromycin	500mg bd	500mg bd
Gentamicin	see separate policy	
Ciprofloxacin	500-750mg bd	restricted
Doxycycline	100mg od –bd	
Vancomycin	see separate policy	
Metronidazole	400mg tds	500mg tds
Flucloxacillin	1g qds	1g qds
Clindamycin	300-450mg tds	
Penicillin V	1g bd or 500mg qds	
Benzylpenicillin		1.2g qds

CNS:
Meningitis Ceftriaxone IV 2g bd +/- Dexamethasone IV (see meningitis protocol)
- Add Aciclovir IV (10mg/kg tds) if encephalitis suspected
- Add Amoxicillin IV 2g qds if > 50 years

ENT:
Tonsillitis Penicillin V (Benzylpenicillin IV if severe) **Sinusitis** • **Acute** Penicillin V • **Chronic** Co-amoxiclav
Acute otitis media Amoxicillin **Epiglottitis** Ceftriaxone IV 2g od

LUNG:

Community Acquired (infection present or suspected on admission)	**Hospital Acquired** (infection 48 hours after admission)
Pneumonia (see CAP pathway) Assess CURB65 score 0-2 Amoxicillin IV/PO (Clarithromycin IV/PO if pen allergic) 3-5 Co-amoxiclav IV + Clarithromycin IV/PO (Levofloxacin IV if penicillin allergic) **Acute exacerbation of COPD/Non pneumonic LRTI** (no consolidation on chest X-ray) Give antibiotics if 2 or more of: ↑ breathlessness,↑ sputum volume, ↑ purulent sputum Amoxicillin or Clarithromycin or Doxycycline	**Pneumonia** Co-amoxiclav PO/IV +/- Gentamicin IV (Levofloxacin IV if pencillin allergic) Previous ITU admission or history of MRSA - seek advice from ID/Micro **Acute exacerbation of COPD** Ciprofloxacin PO

HEART:
Endocarditis
- Start empirical therapy and refer to ID/Microbiology
- Gentamicin dose 1mg/kg tds modified according to renal function and levels

Acute: Flucloxacillin IV 2g 4 – 6 hourly + Gentamicin
Indolent (Subacute): Benzylpenicillin IV 1.2g 4 hourly + Gentamicin
Suspected MRSA/Prosthetic Valve: Vancomycin IV + Rifampicin PO 300 – 600mg bd + Gentamicin

GI:

Clostridium difficile associated diarrhoea (see C diff protocol to assess severity) **1st episode** • Non severe: Metronidazole PO • Severe: Vancomycin 125mg qds PO/NG +/- metronidazole PO/IV **1st recurrence** Metronidazole PO	**Peritonitis/Biliary Tract/ Intra-abdominal** Co-amoxiclav IV/PO +/- Gentamicin (Ciprofloxacin + metronidazole if penicillin allergic **Acute Pancreatitis** Antibiotics unlikely to affect outcome
Acute gastroenteritis No antibiotic treatment required. Seek advice if severe.	**Proven Spontaneous Bacterial Peritonitis** Ceftriaxone IV 2g od

GU:

Female Lower UTI Trimethoprim 200mg bd 3 days **Uncatheterised Male UTI** Ciprofloxacin PO 14 days	**Upper/Complicated UTI** Co-amoxiclav IV/PO +/- Gentamicin (Penicillin allergy: ciprofloxacin)
Catheterised Patients: Do not treat unless clinical signs/symptoms of infection	

BONE/ SKIN:

Cellulitis (see full guideline to assess severity) Flucloxacillin PO/IV (Penicillin allergy: Clindamycin) If previous MRSA or resistant to therapy: – see MRSA treatment guideline	**Septic Arthritis/Osteomyelitis** Flucloxacillin IV 1g qds **Diabetic Foot Infection** Superficial: Flucloxacillin or Co-amoxiclav + Metronidazole Deep/Spreading: Clindamycin + Ciprofloxacin

UNKNOWN SOURCE:
Co-amoxiclav IV/PO +/- Gentamicin IV Seek advice

Penicillin Allergy: If alternative not suggested see Hypersensitivity Guidance in Prescribing Guide

Figure 3: NHS Tayside Antibiotic Prophylaxis Policy 2008 (pre-intervention)

ANTIBIOTIC PROPHYLAXIS

IN GENERAL SURGERY (Ref: SIGN Publication 45, July 2000)

NB. Prophylaxis should be given at induction by the IV route. Additional doses may be required during prolonged procedures to maintain adequate blood antibiotic concentrations.

For further details, consult individual unit policies and guidelines.

Note: The use of antibiotic sprays or the application of antibiotic solutions to surgical wounds ***is not recommended.***

(a)	Abdominal surgery (i) Biliary surgery (Open) (ii) Gastric/small bowel (iii) Emergency appendicectomy (iv) Colorectal surgery	Co-amoxiclav 1.2g slow IV bolus injection with further dose *only* if prolonged surgery beyond > 4 hours. If penicillin hypersensitivity: gentamicin 4mg/kg IV bolus + metronidazole 1g ivi.
	Note: Laparoscopic cholecystectomy:	Not recommended.
(b)	Vascular surgery	As for Abdominal surgery. If patients are known MRSA +ve consider gentamicin 4mg/kg prophylaxis.
(c)	Abdominal or vaginal hysterectomy	See Guidelines for Antibiotic Prophylaxis in Major Gynaecological Surgery.
(d)	Orthopaedic surgery (e.g. total hip replacement)	Cefuroxime 1.5g slow IV bolus then further 750mg dose after 4 hours if surgery prolonged beyond 4 hours. If patients are known MRSA +ve consider gentamicin 4mg/kg prophylaxis.
(e)	Breast surgery	Single slow IV bolus of co-amoxiclav 1.2g or clarithromycin 250mg ivi.
(f)	Head and neck surgery (especially following deep X-ray therapy)	Flucloxacillin 1g by slow IV bolus injection + metronidazole 1g suppository.
(g)	Endoscopic urological surgery	Gentamicin 4mg/kg by IV bolus injection.

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1) 400 Protracted Outbreak of Postarthroscopy Infections Associated with Flash Sterilization of Instruments

Bert Lopansri, MD , Intermountain Medical Center, Salt Lake City, UT et al

Background: Infections following arthroscopic knee surgeries are rare. In June 2007 an increased number of postarthroscopy surgical site infections (SSIs) was reported at a community hospital (Facility A).

Objective: To identify and correct factors involved in the outbreak of postarthroscopy SSIs.

Methods: The case definition was septic arthritis requiring surgical washout and intravenous antibiotic within 30 days after arthroscopic procedure. Cases were identified by review of the SSI database. Infection control personnel interviewed operating room (OR) staff and observed OR practices related to arthroscopic procedure.

Results: 16 infections following arthroscopy were identified between Jan 1, 2006 and October 10, 2007, with 14 cases meeting the case definition. Seven different organisms were isolated with methicillin-susceptible *Staphylococcus aureus* being the most frequent organism. All but one infection was attributed to a single surgeon (Surgeon A). Surgeon A performed 552 arthroscopic procedures with 13 (2.4%) SSIs. In contrast, 1662 arthroscopic procedures were performed at Facility A by 8 other surgeons with one SSI (0.06%). The relative risk (RR) of developing SSI following arthroscopy performed by Surgeon A compared to other surgeons was 40.0, $p<0.0001$. Surgeon A performed 848 arthroscopic surgeries at an academic institution (Facility B) from 2001 – 2005, with SSIs occurring in 3 patients (0.3%). The RR of post-arthroscopy SSI occurring when Surgeon A performed arthroscopy at Facility A compared to Facility B was 6.7, $p=0.001$. At Facility A arthroscopes were cleaned in the OR suite and sterilized using flash steam sterilization between procedures. The arthroscope, surgical instruments and other supplies were placed in a single tray for sterilization, which was performed by surgical technicians who had not been trained in disinfection and sterilization procedures. No other surgeon at Facility A used flash sterilization to sterilize arthroscopes. Flash sterilization was not used at Facility B, where arthroscopes were decontaminated, cleaned and sterilized in the central processing area and transported to the OR in a sterile package. Following the investigation, several corrective actions were taken. Additional arthroscopes were purchased, flash sterilization was discontinued and all arthroscopes were processed in central processing by trained personnel. SSIs returned to baseline at Facility A.

Conclusions: We report a protracted outbreak of postarthroscopy SSIs associated with routine use of flash sterilization. Epidemiologic investigation implicated Surgeon A when operating at Facility A. Review of operating room procedures pointed to flash sterilization as the cause whereas review of performance-based measures led to the premature conclusion that Surgeon A was the source of the outbreak. Flash sterilization is not an appropriate method for routine sterilization

ORION SUBMISSION AND REVIEWER'S ABSTRACT CHECKLIST FOR INTERVENTION STUDIES* AND OUTBREAK REPORTS

* carried out either to reduce infection or to improve compliance with infection control measures such as hand hygiene, antibiotic prescription or care bundle implementation

1. Title- Clear statement that this is an intervention study or outbreak report.
2. Background- Rationale for study with clear hypothesis for intervention studies or objective for outbreak reports
Methods- 3. Clear statement of intervention study design[1] or case definition for outbreak report.
4. Brief description of participants, setting and of intervention or outbreak control measures (with start & stop dates)
5. Clearly defined outcomes & denominators at regular time intervals[2], not as totals for each phase (can be put in results instead)
6. Statistical analysis accounts for any dependencies in the data (can be in results instead) (statistical analysis may not be appropriate for outbreak reports).
7. Which potential confounders or biases were considered, recorded or adjusted for [3] can be in results instead)
8. Where relevant: details of culture, typing, environmental sampling, and risk factors for acquisition, root cause analysis or organisational risk assessment.
Results- 9. For the main outcomes: estimated effect size & its precision (usually using 95% C.I.) (A graphical summary is often appropriate for dependent data -such as most time series).
Conclusions- **10.** For intervention studies: consider in relation to original hypothesis, accounting for potential confounders & biases. For outbreak reports: consider clinical significance of observations & hypothesis to explain them.

[1] e.g. Interrupted Time Series, Cluster or other Randomised Controlled Trial, Cross over, Controlled Before and After intervention, Uncontrolled Before and After Intervention (see explanatory document and www.ccg.cochrane.org/en/newPage1.html for standard terminology.

[2] at least 3 time points per phase and for many two phase studies 12 or more monthly data points.

[3] e.g. changes in length of stay, case mix, bed occupancy, staffing levels, hand-hygiene compliance, antibiotic use, strain type, processing of isolates, seasonality, other interventions, incomplete blinding, fidelity to intervention, non standardised outcome assessment.

2) **Outbreak of Colistin Resistant Enterobacteriaceae at Detroit Medical Center**

Dror Marchaim, MD , Detroit Medical Center, Wayne State University, Detroit, MI
et al

Background: Carbapenem resistant enterobacteriaceae (CRE) have spread in Southeastern Michigan. Colistin is used extensively to treat these organisms in the Detroit Medical Center (DMC). We describe a cluster of colistin-resistant CRE infections that occurred at DMC and an attached long-term acute care facility (LTAC).

Objective: To conduct a comprehensive epidemiologic investigation of colistin-resistant CRE strains outbreak at DMC, including risk factors and outcomes assessment.

Methods: A cluster of 5 cases of colistin-resistant *Klebsiella* spp. emerged at DMC. Epidemiologic data were collected and transmission opportunities were analyzed. A transmission opportunity (TOP) was defined as two case patients staying on the same ward at the same time. Data regarding the usage of colistin were obtained from pharmacy records. Colistin defined daily doses (DDDs) were based on the assumption of a daily dose of colistin being 3 million units/day (90 mg base activity). Resistance to colistin was defined as MIC > 4. Cases were defined as patients with colistin-resistant CRE and controls were defined as patients with colistin-susceptible CRE isolated from 09/2008 to 09/2009.

Results: The first case of colistin-resistant CRE occurred in 07-27-2009, followed by 4 additional cases occurring between 08-16 and 08-22, 2009. Four of the cases were *Klebsiella pneumoniae* (2 from urine and 2 from wounds) and one case was of *K. oxytoca* bacteremia. The strains were isolated in 2 hospitals and one LTAC (attached to one of the affected hospitals). All cases, at a certain point, had stayed at a single involved hospital, or in the LTAC attached to it. The mean TOPs between cases was 2.3±0.5, and each case had at least one TOP with one of the other cases. When comparing the five colistn-resistant CRE cases to the 60 colistin-susceptible CRE controls, the MIC to imipenem for cases was significantly higher for cases ($p<0.001$). The mean age of case patients was 77±6 years, significantly older compared to controls (62±8 years, $p=0.05$). The mortality rate and length of stay were higher among cases than controls, though these differences did not reach statistical significance (40% and 26%; and 33±23 and 30±23 days, respectively). Colistin utilization during the quarter of the year immediately prior to cluster emergence (04-01 to 06-30, 2009), did not differ from the previous quarter (01-01 to 03-31, 2009), with a mean DDD/1,000 patient days of 20.7±3.4 for the entire 6 months studied.

Conclusions: This is the first report to our knowledge of a colistin-resistant CRE outbreak in the U.S. Geonotyping studies are ongoing. Although raw colistin exposure was not associated with the outbreak, further data regarding colistin dose and dosing intervals are needed to optimize killing and to prevent the emergence of resistance. This outbreak was controlled through implementation of strict infection control practices and effective communication at the 2 hospitals and LTAC.

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3) Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two-centre study

Cepeda et al, ***Lancet*** **2005; 365: 295–304**

Summary
Background Hospital-acquired infection due to meticillin-resistant *Staphylococcus aureus* (MRSA) is common within intensive-care units. Single room or cohort isolation of infected or colonised patients is used to reduce spread, but its benefit over and above other contact precautions is not known. We aimed to assess the effectiveness of moving versus not moving infected or colonised patients in intensive-care units to prevent transmission of MRSA.

Methods We undertook a prospective 1-year study in the intensive-care units of two teaching hospitals. Admission and weekly screens were used to ascertain the incidence of MRSA colonisation. In the middle 6 months, MRSA-positive patients were not moved to a single room or cohort nursed unless they were carrying other multiresistant or notifiable pathogens. Standard precautions were practised throughout. Hand hygiene was encouraged and compliance audited.

Findings Patients' characteristics and MRSA acquisition rates were similar in the periods when patients were moved and not moved. The crude (unadjusted) Cox proportional-hazards model showed no evidence of increased transmission during the non-move phase (0·73 [95% CI 0·49–1·10], p=0·94 one-sided). There were no changes in transmission of any particular strain of MRSA nor in handwashing frequency between management phases.

Interpretation Moving MRSA-positive patients into single rooms or cohorted bays does not reduce crossinfection. Because transfer and isolation of critically ill patients in single rooms carries potential risks, our findings suggest that re-evaluation of isolation policies is required in intensive-care units where MRSA is endemic, and that more effective means of preventing spread of MRSA in such settings need to be found.

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4) National One Week Audit of MRSA Admission Screening: current practice, MRSA prevalence and screening yield in 144 English hospital trusts.

Christopher Fuller, Julie Robotham, Joanne Savage, Susan Hopkins, Barry Cookson, Sheldon Stone.
(Details of corresponding author sent in separate sheet to ECCMID)

Submitted to ECCMID 14-11-2011. Abstract number 2410

OBJECTIVES

Routine MRSA screening of all hospital admissions is mandated by the Department of Health (DH) & is standard practice in English NHS acute hospitals. Research was requested by the DH to describe (1) policy implementation (2) current practice, (3) MRSA prevalence on one day (4) the extra yield of universal screening vs selective screening (5) effectiveness and cost effectiveness. This paper reports on the first 4 objectives.

METHODS

Surveys were sent to infection control teams in all 167 English NHS acute hospital trusts for completion between 9 &15th May 2011. Data requested: (1) number of patients admitted & screened that week (2) MRSA screening practice & patient management (3) number of MRSA +ve patients on a given day (4) clinical details & presence of 6 checklist risk factors for MRSA carriage (in all newly identified MRSA +ve and a random sample of 5-10 MRSA –ve patients screened that week).

RESULTS

Response : 144/167 (86.2%) trusts responded. Risk factor information received for 760 new MRSA+ves & 951 MRSA-ves. Proportion patients screened: 61% (emergency admissions), 81% (electives), 47% (day-cases) Proportion of MRSA screens positive on admission: 2.1% (emergencies), 0.9% (elective), 0.7% (day-case). Only half of these were newly identified cases.

Number needed to screen to identify one new positive: 102 (emergencies) 180 (elective) 186 (day-case). Screening practice & management: Mean time to MRSA+ve result 2.87 days (sd 1.33). 33% patients discharged before result available, 67% isolated after result known & 80% decolonised.

MRSA prevalence: 3.3% of inpatients had MRSA on audit day, 10% currently treated for MRSA infection. Risk factors: 60.3% of new +ves and 51% of negatives were checklist positive for one or more risk-factor. In an average trust, screening only checklist +ve patients would reduce screens from in from 858 to 478 a week, identifying 82% of positives. Screening only those in High risk specialties would reduce the number of screens to 94 a week, but identify only 10% of +ves.

CONCLUSIONS

Uptake of admission screening was low (especially for emergency and day-case admissions) as was the yield of MRSA+ve patients. The use of checklist activated screening would reduce the number of MRSA admission screens by 50% but identify 82% of all +ves. Screening high risk specialties only would reduce screens by c90% but identify only 10% of +ves. Health Economic modelling will use this data to determine the most cost effective screening policy.

STROBE Statement—Items to be included when reporting observational studies in a conference abstract

Item	Recommendation
Title	Indicate the study's design with a commonly used term in the title (e.g cohort, case-control, cross sectional)
Authors	Contact details for the corresponding author (Note above abstract is pre acceptance)
Study design	Description of the study design (e.g cohort, case-control, cross sectional)
Objective	Specific objectives or hypothesis
Methods	
Setting	Description of setting, follow-up dates or dates at which the outcome events occurred or at which the outcomes were present, as well as any points or ranges on other time scales for the outcomes (e.g., prevalence at age 18, 1998-2007).
Participants	*Cohort study*—Give the most important eligibility criteria, and the most important sources and methods of selection of participants. Describe briefly the methods of follow-up *Case-control study*—Give the major eligibility criteria, and the major sources and methods of case ascertainment and control selection *Cross-sectional study*—Give the eligibility criteria, and the major sources and methods of selection of participants
	Cohort study—For matched studies, give matching and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	Clearly define primary outcome for this report.
Statistical methods	Describe statistical methods, including those used to control for confounding
Results	
Participants	Report Number of participants at the beginning and end of the study
Main results	Report estimates of associations. If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Report appropriate measures of variability and uncertainty (e.g., odds ratios with confidence intervals
Conclusions	General interpretation of study results

Note: even if we do not get through all of these we will place the answers on the www site

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