How to design and assess intervention studies to improve healthcare and prescribing interventions

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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

Aims of Workshop

(i) Identify strengths & weaknesses in reporting of infection control and antimicrobial stewardship intervention studies when you design such studies

for your hospital

for grant applications

as a referee for grants and journals

(ii) Inform the ORION team as to the use of the workshop material as educational tools on the www to help you teach others to learn how to use “ORION”

Structure

1) Sheldon will deliver a lecture ~20m
2) We will provide the ORION checklist, an ORION compliant and one non-compliant paper

   One workshop group(s) will to use the checklist to analyse one paper and another the other (40m)

   – Nominate a rapporteur to complete the checklist and a chair
3) Discuss findings going around the rapporteurs (20m)
4) Discuss whether these materials should be on the www as a resource? (vote: comments!: 5m)

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…..

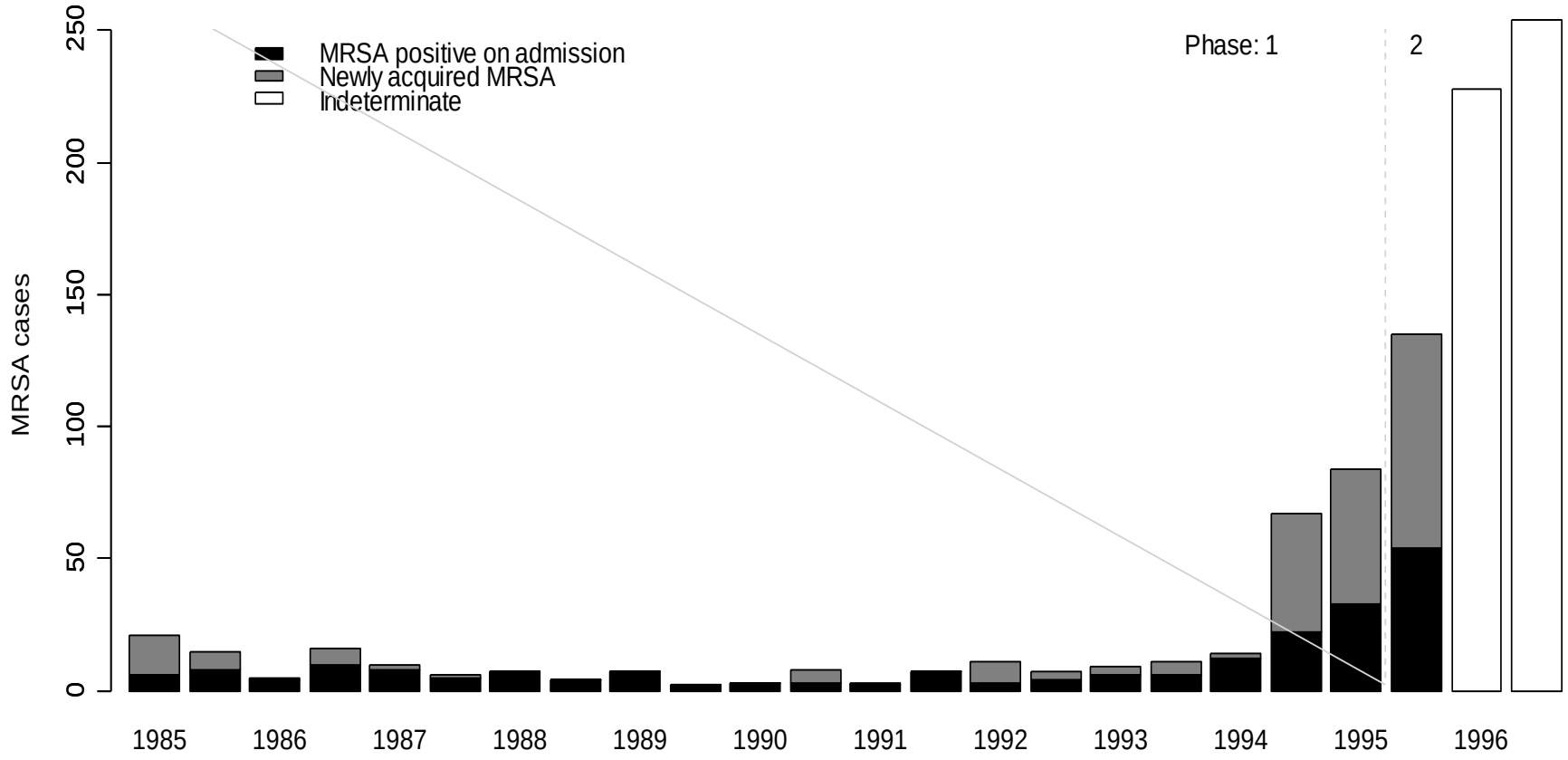
Cooper B et al BMJ 2004, HTA 20003, Davey et al Cochrane 2005;Ramsay et al JAC 2003

- Studies conclude interventions cause Δ MRSA or antibiotic use or *Clostridium difficile*

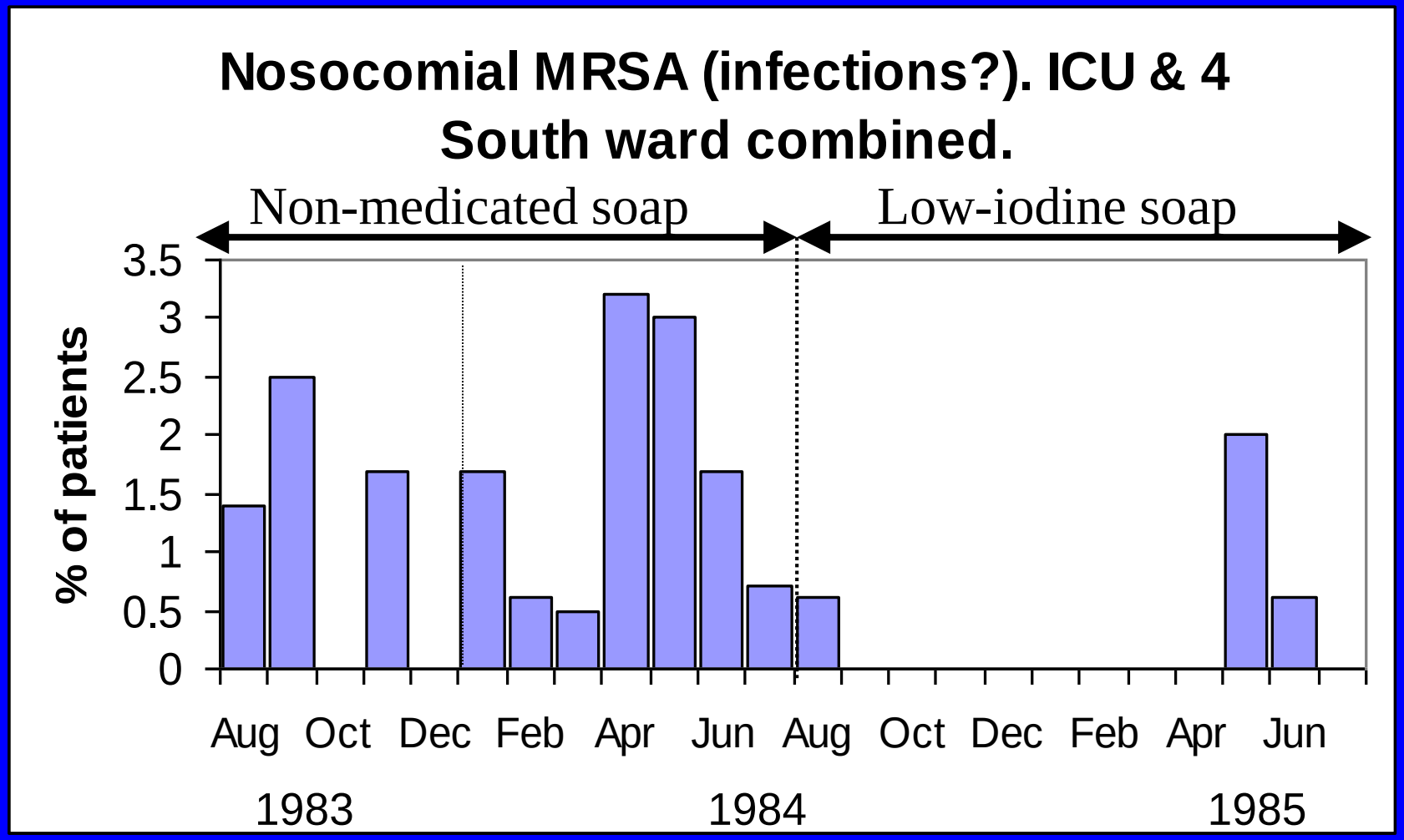
- Validity of conclusions threatened by **confounders & biases**, unaccounted for in studies, which provide plausible alternative explanations of outcome and by **inappropriate statistics** eg aggregation of data (misses time trends) & assumption that infection outcomes are independent (Chi-Sq; OR)

Confounders; strains, trends

Farrington et al QJM

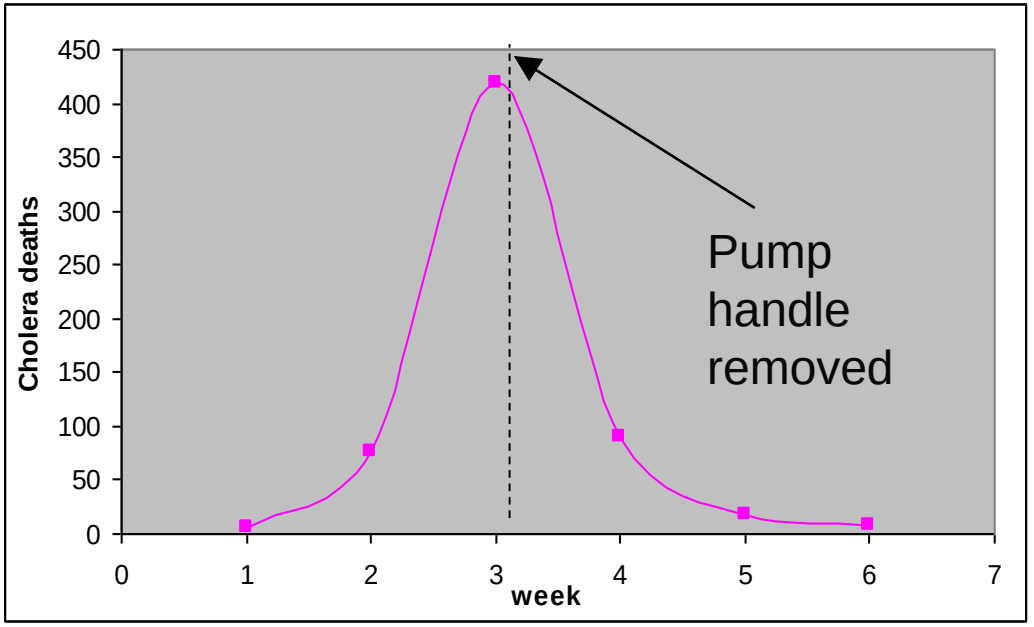


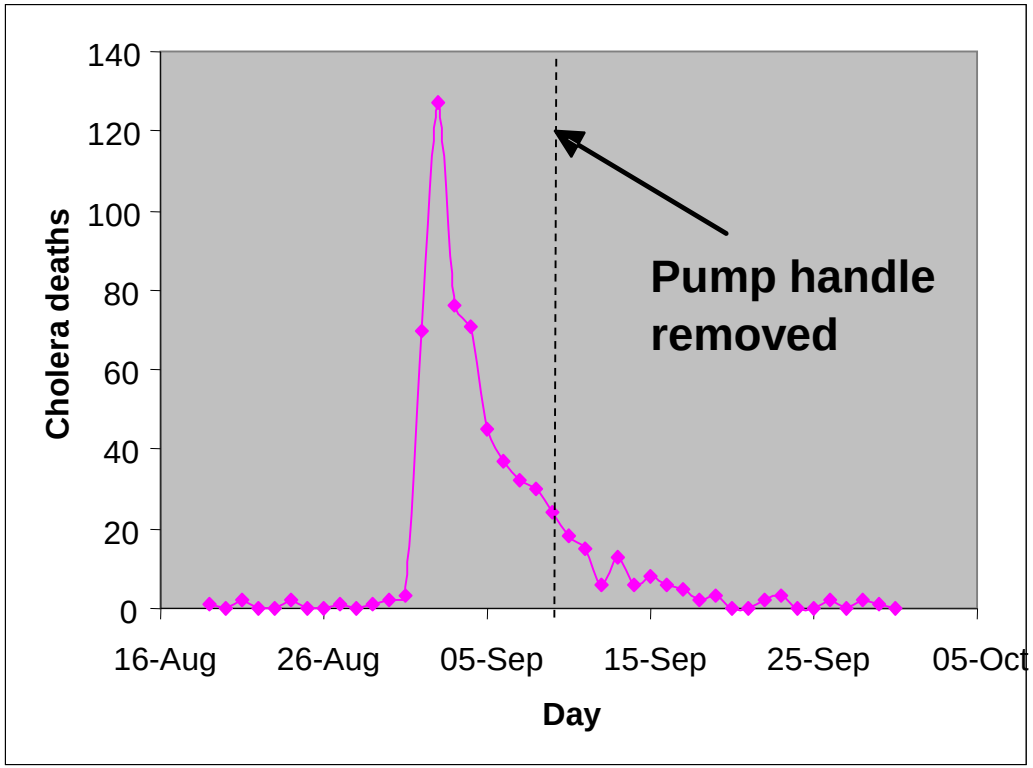
The sort of problems: regression to mean, statistical analysis



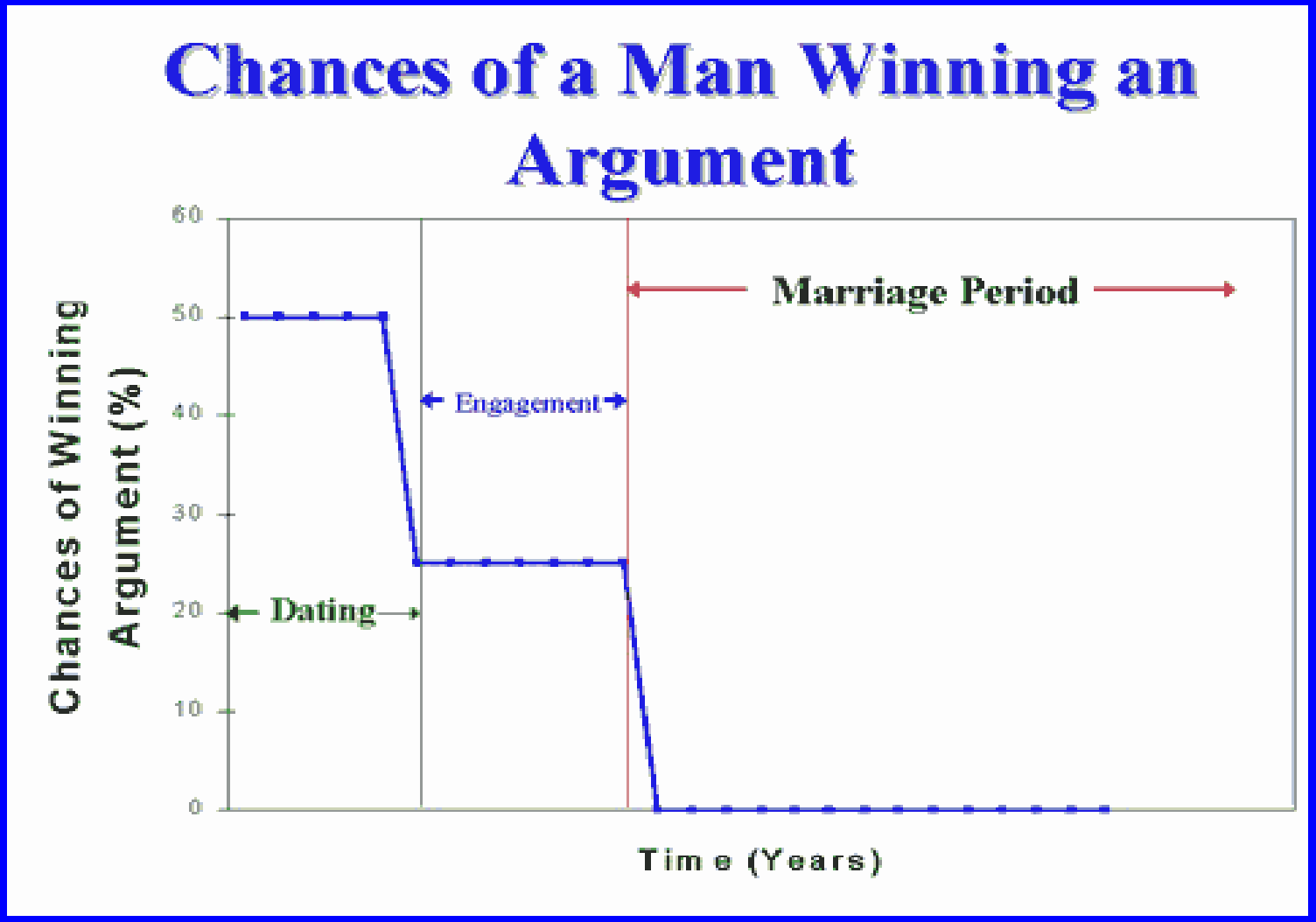
Onesko KM, Infection Control 1987

50 0 50 100 150 200 Yards
× Pump • Deaths from cholera
OXFORD STREET
REGENT STREET
CONDUIT STREET
ST MARLBOROUGH ST
BROAD STREET
GOLDEN SQUARE
BREWER STREET
SAVILLE ROW
NEW BOND STREET
REGENTS QUADRANT
PICCADILLY


Cholera deaths
450
400
350
300
250
200
150
100
50
0
0 1 2 3 4 5 6 7
week
Pump handle removed


Cholera deaths
140
120
100
80
60
40
20
0
16-Aug 26-Aug 05-Sep 15-Sep 25-Sep 05-Oct
Day
Pump handle removed

Interrupted time series



Improving the evidence base

CONSORT JAMA 1996, Lancet 1991;
TRENDS Am J Pub Health 2004;Cooper et al HTA 2003;
www.strobe-statment.org)

- HTA MRSA Review: guidelines for MRSA outbreak reports & intervention studies
- CONSORT to improve quality reporting RCTs: why & how designed, conducted & analysed..what the results mean
- TRENDS adapted CONSORT to meet non-RCT designs in Public Health Interventions
- STROBE adapted it for observational studies in epidemiology (cohort, case control, cross sectional)
- Transparency was key so that information critical to synthesis of research not missing

Limitations of MRSA reporting guidelines, CONSORT,TREND & STROBE for Infection Control Studies

- MRSA reporting guidelines exclude other nosocomial organisms & interventions to change antibiotic use
- On line but not as user friendly as CONSORT
- Neither CONSORT, TREND nor STROBE items & descriptors relevant to wide variety interventions, settings, designs & statistical issues relevant to infections

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 ?

Methods: from CONSORT to ORION

- HTA/Cochrane groups modified MRSA reporting guidelines to apply to nosocomial organisms in general & include antibiotic interventions
- adapted CONSORT statement to the wide variety settings interventions, designs & statistical issues infection control studies
- Consultation learned societies, editors, academics (incl USA), HPA & BSAC websites
- Independent critical academic review
- Endorsed/Welcomed by AMM, ICNA R&D, on BSAC & AMM sites & journals

- New Eng Journal Medicine

"we are willing to take the ORION statement into consideration in our review process….endeavors such as yours, CONSORT, STARD are helpful to the scientific Community …"

Components of ORION

Stone et al Lancet ID 2007;JAC 2007

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

ORION Checklist: Introduction

	Item No	Descriptor
Title & Abstract	1	**Description of paper as outbreak report or intervention study.** **Design of intervention study** (eg ITS +/- controls; cross over study etc). Brief description of intervention.
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 outbreak report. If an outbreak report, report the number of outbreaks.
Dates	4	Start and finish dates of the study or report stated.
Objectives	5	**Objectives for outbreak reports.** **Hypotheses for intervention studies.**

ORION Checklist: Methods 1

Methods Design	6	**Study design**. **Use of EPOC classification recommended (CBA, ITS)** Whether study was retrospective, prospective or ambidirectional **Whether decision to report or intervene was prompted by any outcome data** Whether formally implemented study with pre-defined protocol and endpoints.
Participants	7	Numbers of patients admitted during the study or outbreak. Mean ages & LOS. Eligibility criteria for intervention study. Case definitions for outbreak report
Setting	8	Description of the unit, ward or hospital and.if a hospital, the units involved. Number of beds, the presence and staffing of an Infection Control Team.
Intervention	9	**Definition of phases by a major change in specific infection control practice. Start & stop dates. A summary table is strongly recommended with precise details of interventions, how & when administered in each phase.**
Typing	10	Details of culture media, use of selective antibiotics & local and /or reference typing. Where relevant details of environmental sampling

Setting: 1300-1600 bed teaching hospital. ICT with 5 full time infection control nurses from Oct 1992.MRSA initially epidemic, later endemic	**Dates:** 1989-1997	**Population characteristics**: Number of patients during study: 506012. Mean age of MRSA patients (SD): 68 (23) years.

Major infection control changes during the study: Carer hand-hygiene education and feedback; patient isolation; screening; MRSA eradication; antibiotic use**;** automatic readmission alerts, disinfection, sterilization, air control & building construction.

	Isolation	**Screening**	**Eradication**	**Other measures**
Phase 1 48 months (Jan 1989 - Dec 1992)	None	None	None	No MRSA control measures
Phase 2 24 months (Jan 1993 - Dec 1994)	1.Single room. 2. Cohorting on closed and open bays in special circumstance (e.g. unit specific outbreaks).	1.Admission screens for previous MRSA patients. 2.Contacts screened. 3.Treated MRSA patients: weekly for 4 weeks, then monthly.	Mupirocin and chlorhexidine. Mupirocin used for almost all patients, irrespective of MRSA carriage*.	1.CDC guidelines 1983 2.Computer alerts for readmitted MRSA patients (July 1994 on).
Phase 3 36 months (Jan 1995 - Dec 1997)	As phase 2	As phase 2	As phase 2 until September 1997.	As phase 2 + staff hand-hygiene education & feedback programme

Isolation details: From 1993 single rooms may not have been used when there was nasal carriage only and lack of available rooms.). Contact for overflow with nasal carriage only. 60 single rooms available for acute services patients (without negative pressure).

Screening details. Screening sites: nose, lesion, groin, infected sites. Patients in "septic" orthopaedic ward screened on admission from July 1994.

Eradication Details: From phase 2 most patients received ≥1 nasal mupirocin courses, irrespective of MRSA carriage*. After September 1997 mupirocin was limited to those with known nasal carriage and without chronic skin lesions and indwelling devices. Criteria for eradication: 2 negative sets of cultures ≥24 hrs apart.

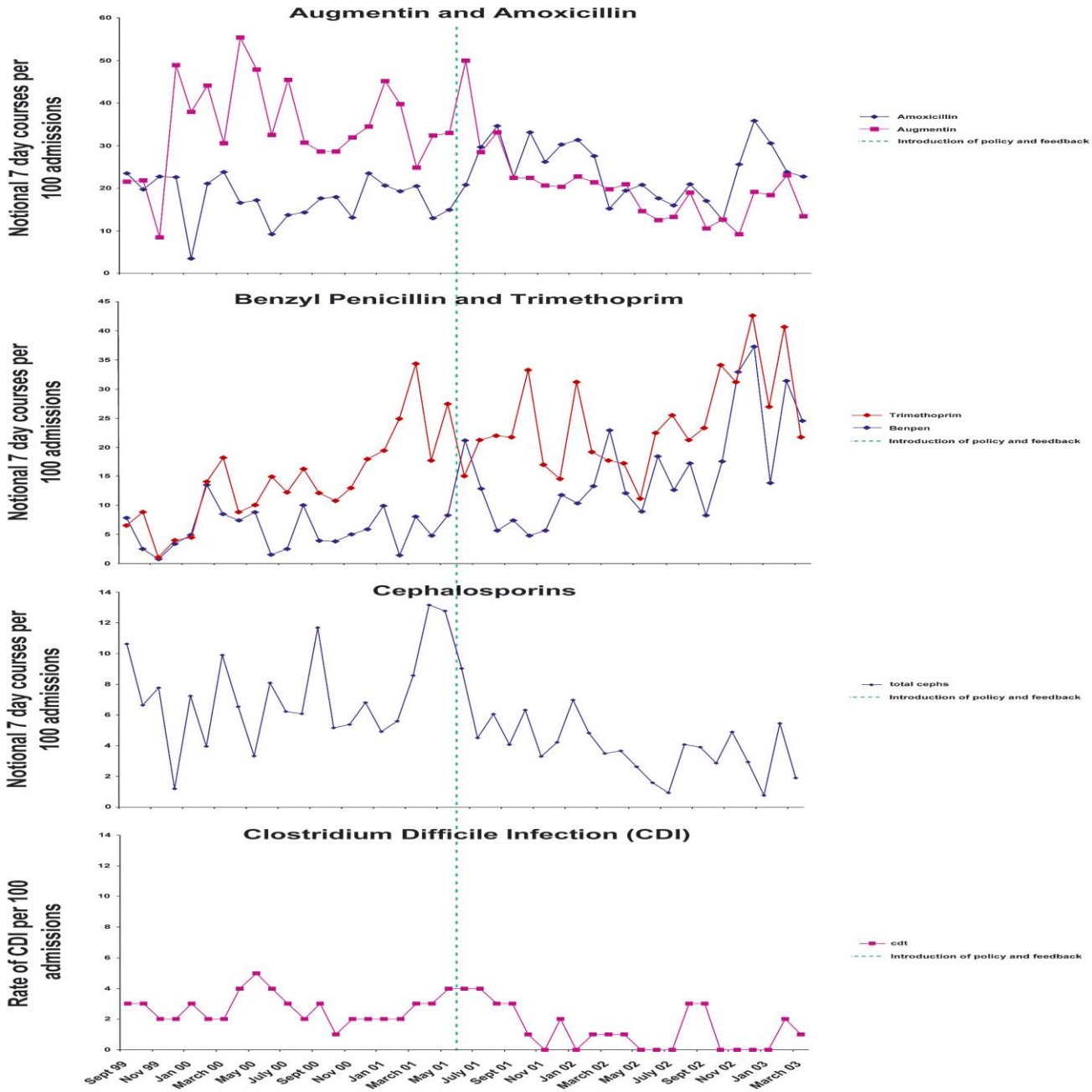
ORION Checklist: Methods 2

Infection related outcomes	11	**Clearly defined primary & secondary outcomes (eg incidence infection, colonisation) at regular time intervals (eg weekly, monthly,yearly) not as totals for each phase of a study, with at least 3 time points per phase and for many 2 phase studies, 12 or more monthly data points per phase.** **No place for the uncontrolled before and after study with only two time points.** Denominators (eg numbers admissions or discharges, patient bed days) Criteria for outcome measures. For short studies use of charts with duration patient stay & dates organism detected may be useful.
Economic outcomes	12	If a formal economic study done, definition of outcomes to be reported, description of resources used in intervention, costs broken down to basic units and important assumptions stated.
Potential Threats to Validity	13	**Which potential confounders were considered, recorded or adjusted for** (eg changes in length of stay, case mix, occupancy, staffing levels, hand-hygiene, antibiotic use, strain, processing isolates) Description of measures to avoid bias including blinding, standardisation outcome assessment & delivery care

ORION Checklist: Results

Results Recruitment	16	For relevant designs, the dates for each period recruitment & follow up. A flow diagram may help describe patient flows in each phase (eg cross over study)
Outcomes & estimation	17	For the main outcomes, the estimated effect size and its precision **A graphical summary is appropriate for dependent data (most ITS)**
Ancillary analyses	18	Report subgroup analyses and adjust for possible confounders.
Harms	19	Pre-specified categories of adverse events & occurences of these in each group or phase.

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



ORION Checklist :Discussion

Discussion Interpretation	20	**For intervention studies, an assessment of evidence for/against hypothesis** accounting for potential **threats to validity of inference** including regression to mean effects and reporting bias For outbreak reports consider clinical significance of observations & hypotheses generated to explain them
Generalisability	21	External validity of the findings of the outbreak report or intervention study
Overall evidence	22	General interpretation of results in context of current evidence.

Summary

- High quality infection control research needed to provide a robust evidence base for policy & practice
- Concensus statement to raise the standards of research & publication .. widespread consultation…..critical academic review
- Checklist of 22 items
- Summary table for population, setting, nature & timing of interventions,
- Graphical summary of results
- Emphasis on transparency to improve quality of reporting & the use of appropriate statistical techniques
- Statement has been endorsed by a number of specialist societies & groups & grant awarding bodies
- CONSORT like programme for dissemination, enforcement, evaluation & revision to include mainjournals (AJIC, ICHE, JHI,JAC, BJIC)
- Grant Awarding bodies to collaborate in adapting for grant application process for relevant studies
- Web site, MSc Courses, Workshops

ORION in Practice…IFIC workshop

- Take the checklist and the blank form
- Split into two groups with a rapporteur
- Each group cluster reads and reviews one paper, using the checklist (45 mins)
- Rapporteurs report as we go through slides
- We give our answers
- Good luck!

ORION in Practice

Stone et al Age Ageing 1998

- Title: brief description intervention & outcomes but not design or state intervention study β
- Background: rationale and local background; endemic/epidemic description α
- Dates: start and finish but not exact β
- Objectives: no hypothesis β
- Design: no description of design, whether retro or prospective, nor of prior knowledge any outcome data β
- Participants: number, length of stay. No eligibility criteria β
- Setting: description unit, number beds, but not ICT β
- Interventions: no table,exact timing of isolation unit relative to other interventions in text but not immediately clear, number isolation beds β
- Culture & Typing: details for both C difficile and MRSA α
- Infection related outcomes: defined but not clear which primary or secondary ie C diff, MRSA, antibiotic use; 3 data points per phase, but aggregated, denominators given, criteria for C diff but less clear for MRSA β
- Economic: mentions bed occupancy in winter but no formal definitions or evaluation β

ORION in Practice 2

Stone et al Age Ageing 1998

- Potential Threats to Validity: none formally considered or recorded β
- Sample size: not mentioned but may not be relevant β
- Statistical methods: described but inappropriate use Chi sq for C diff & MRSA and no analysis of antibiotic use. Aggregation data. β
- Recruitment: not relevant
- Outcomes & estimation: no graphical summary, and no estimation size effect β
- Ancillary analyses: not pre-specified, comparison MRSA rates in rest of hospital reported but not analysed. β
- Adverse events: not mentioned, except perhaps empty beds in winter. β
- Discussion: no assessement against hypothesis, no mention potential threats to validity esp regression to mean β
- Generalisability: well covered α
- Overall evidence: in context α

ORION in Practice

Cepeda et al Lancet 2005

- Title/Abstract : brief description intervention & outcomes. Clearly an intervention study. ITS X-over design not explicit β
- Background α: rationale explicit; endemic local background
- Dates α:clear start date, timing of X overs
- Objectives α : hypothesis that isolation reduced transmission
- Design: Prospective. Prespecified protocol. No explicit description β
- Participants α : Eligibility criteria (ITU>48 hrs) Number, length of stay, severity scores, sex, diagnostic group.
- Setting : description ICUs, number beds, layout. No ICT details β.
- Interventions α : Phases defined by major change in infection control practice. No summary table but text very clear. Isolation & screening details but not eradication. Clear description other interventions.
- Culture & Typing α : details culture, phage and PFGE typing.
- Infection related outcomes α : MRSA acquisition. Daily time points. Clear definitions acquisition, colonisation on admission, prevalence.
- Economic: not relevant
- Potential Threats to Validity α : Patient data, hand-hygiene, apron compliance, antibiotic use, daily staffing levels, staff carriage, environmental contamination. Lab staff blind to phases.

ORION in Practice 2

Cepeda et al Lancet 2005

- Sample size α : pre-study power calculations done
- Statistical methods α :Pre-defined. Cox proportional model adjusting for patient and ward level confounders. Adjusted for colonisation pressure (dependency)
- Recruitment α : flow diagram provided
- Outcomes & estimation α : graphical summary daily ITS hazard ratios with 95% CI
- Ancillary analyses α : pre-specified, effect of confounders
- Adverse events β : no specific pre-specified mention but MRSA deaths recorded and no change
- Discussion α : Evidence assessed against hypothesis. Potential threats to validity addressed.
- Generalisability α : external validity well covered
- Overall evidence α : results interpreted in in context current evidence

Co-authors & Collaborating Institutions

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- Chris Kibbler *Microbiology*
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- Jenny Roberts *Health Economics*
- Graham Medley *Modelling*
- GeorgiaDuckworth *Public Health*
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