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Isolation measures in the hospital management of methicillin resistant Staphylococcus aureus (MRSA): systematic review of the literature


Abstract

**Objective** To evaluate the evidence for the effectiveness of isolation measures in reducing the incidence of methicillin resistant Staphylococcus aureus (MRSA) colonisation and infection in hospital inpatients.

**Design** Systematic review of published articles.

**Data sources** Medline, Embase, CINAHL, Cochrane Library, System for Information on Grey Literature in Europe (SIGLE), and citation lists (1966-2000).

**Review methods** Articles reporting MRSA related outcomes and describing an isolation policy were selected. No quality restrictions were imposed on studies using isolation wards or nurse cohorting. Other studies were included if they were prospective or employed planned comparisons of retrospective data.

**Results** 46 studies were accepted; 18 used isolation wards, nine used nurse cohorting, and 19 used other isolation policies. Most were interrupted time series, with few planned formal prospective studies. All but one reported multiple interventions. Consideration of potential confounders, measures to prevent bias, and appropriate statistical analysis were mostly lacking. No conclusions could be drawn in a third of studies. Most others provided evidence consistent with a reduction of MRSA acquisition. Six long interrupted time series provided the strongest evidence. Four of these provided evidence that intensive control measures including patient isolation were effective in controlling MRSA. In two others, isolation wards failed to prevent endemic MRSA.

**Conclusion** Major methodological weaknesses and inadequate reporting in published research mean that many plausible alternative explanations for reductions in MRSA acquisition associated with interventions cannot be excluded. No well designed studies exist that allow the role of isolation measures alone to be assessed. None the less, there is evidence that concerted efforts that include isolation can reduce MRSA even in endemic settings. Current isolation measures recommended in national guidelines should continue to be applied until further research establishes otherwise.

Introduction

The incidence of hospital acquired methicillin resistant Staphylococcus aureus (MRSA) continues to rise globally. Attempts to control this spread have relied principally on three measures: hand hygiene among healthcare workers, restriction of antibiotics, and the detection and isolation of infected or colonised patients. We consider the detection and isolation of infected or colonised patients, which is central to most national guidelines.

Most transmission of MRSA from patient to patient is thought to be mediated by transiently colonised healthcare workers, although airborne dispersal and transmission through contacts with contaminated surfaces may also be important. Isolation measures for patients are intended to interrupt such transmission. The most intensive forms of isolating patients are isolation wards (designated for the treatment of known or suspected carriers of MRSA) and nurse cohorting (the physical segregation of MRSA patients in one part of a ward, with nursing by designated staff who care exclusively for these patients). Other isolation measures include the use of single bedded rooms, cohorts of patients on general wards (without designated nursing staff), and barrier precautions (use of aprons or gowns, gloves, and, in some cases, masks by healthcare workers as the only physical barrier to transmission).

Such control measures may place substantial burdens on hospital resources, and the value of their continued use has been questioned. Earlier narrative reviews have been undertaken, but the effectiveness of isolation measures in reducing transmission and controlling MRSA has not been assessed systematically. Moreover, as much of the research in this area is known to be of a quasi-experimental nature. The associated threats to valid inferences need to be considered. We therefore undertook a systematic review of the evidence for the effectiveness of isolation measures in the management of MRSA in hospitals.

Method

**Search strategy**

We developed a search strategy that covers the main subject areas of the review (MRSA, screening, and isolation of patients and control of infection). We searched the following databases, with no language restrictions: Medline 1966-December 2000, Embase 1980-December 2000, CINAHL 1982-May 2000, System for Information on Grey Literature in Europe (SIGLE) 1980-May 2000, and the Cochrane Library to December 2000. We also searched reference lists of retrieved articles and hand searched abstracts from key journals to verify the sensitivity of the search strategy.

**Study selection**

Two or three reviewers working together appraised abstracts. Full articles were obtained if abstracts mentioned endemic or epidemic MRSA and an attempt at control in a hospital setting.

As the number of studies was far greater than anticipated, we revised the original protocol (which had imposed no quality
restrictions). We imposed the minimal requirement that accepted studies should include a component of prospective data collection. If they were entirely retrospective comparisons should have been planned and not prompted by part of the outcome data. No such restrictions were imposed for studies using the most intensive forms of isolation (isolation wards and nurse cohorting) as these have the greatest implications for the allocation of resources and organisation of services.

Two investigators reviewed the papers independently, to confirm that they met the above criteria. We rejected studies not mentioning an isolation policy or without relevant MRSA related outcomes.

**Data extraction**

We divided each study into phases, where appropriate, that were defined by major changes in isolation or other aspects of infection control policy and extracted data on study design, patient population, isolation details, screening, other infection control measures, and MRSA related outcomes for patients.

We documented potential threats to the internal validity of accepted studies. We considered the vulnerability of each study to selection, performance, detection, and attrition bias (see table 2). We documented measures taken to prevent bias and noted potential confounders and attempts to record and adjust for these. We documented threats to validity because of underlying trends, seasonal effects, and regression to the mean effects, which we defined as "a tendency for extreme measurements to be followed by less extreme measurements for imperfectly correlated variables that often results in wrong conclusions about the effects of interventions." We assessed the appropriateness of any statistical analysis undertaken.

We wrote to authors when isolation or screening policies or their timing were unclear. We excluded studies if either the main isolation policy or the timing of interventions were unclear, or if the only outcome reported was MRSA colonisation but the screening policy was unclear or had changed sufficiently to make interpreting outcomes impossible.

### Table 1 Characteristics of the 46 accepted studies

<table>
<thead>
<tr>
<th>Highest level of isolation</th>
<th>Isolation ward</th>
<th>Nurse cohorting</th>
<th>Other isolation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>18</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Range of study durations</td>
<td>3 months-15 years</td>
<td>3.5 months-4 years</td>
<td>1 month-9 years</td>
</tr>
<tr>
<td>Whole hospital setting</td>
<td>16</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Hospital unit setting (such as burns, intensive care)</td>
<td>2</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

### Table 2 Selection, performance, detection and attrition bias

<table>
<thead>
<tr>
<th>Type of bias</th>
<th>Cause</th>
<th>Studies vulnerable</th>
<th>Measures taken to identify or prevent bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection</td>
<td>Differences in intervention groups on study entry</td>
<td>Studies without randomisation (29 studies)</td>
<td>Four of 35 interrupted time series studies where isolation or screening changes presented data allowing comparisons of patient characteristics between phases ( ^{16} ) ( ^{17} ) ( ^{18} ) ( ^{19} ) Two studies presented partial adjustment for confounders ( ^{20} ) ( ^{21} )</td>
</tr>
</tbody>
</table>

### Performance bias

- **Differences in antibiotic prescribing**: 31 interrupted time series studies
  - Four presented details of antibiotic use \( ^{16} \) \( ^{17} \) \( ^{18} \) \( ^{19} \) Two studies alluded to unquantified changes \( ^{20} \) \( ^{21} \)

- **Differences in lengths of stay**: 29 interrupted time series studies
  - Changes in length of stay could be assessed in four \( ^{16} \) \( ^{17} \) \( ^{18} \) \( ^{19} \)

- **Differences in bed occupancy and staff workload**: 31 interrupted time series studies
  - Comparisons of bed occupancy between phases possible in four \( ^{16} \) \( ^{17} \) \( ^{18} \) \( ^{19} \) Changes in staffing levels or workloads could be assessed in five \( ^{16} \) \( ^{17} \) \( ^{18} \) \( ^{19} \) \( ^{20} \)

### Detection bias

- **Differential outcome assessment between intervention groups**: All studies
  - Three reported some blinding of outcome assessors \( ^{16} \) \( ^{17} \) \( ^{18} \) \( ^{19} \)

- **Differences in diagnosis of infections**: 26 studies
  - 16 specified diagnostic criteria. 14 reported MRSA bacteraemia

- **Differences in screening practices**: 10 studies with colonisation data only
  - In all cases screening effort either reported not to have changed or to have changed in opposite direction from outcomes, suggesting screening effort could not explain the changes

### Attrition bias

- **Differential loss to follow up between treatment groups**: Studies where outcomes are infections (26 studies) and with substantial changes in length of stay could lead to attrition bias
  - None: no studies followed up patients after discharge to detect hospital acquired infections
Disagreements between reviewers were resolved by discussion and recourse to third parties. Reviewers were not permitted to play any part in appraising a study in which they had participated.

Data synthesis
Two reviewers independently evaluated the strength of evidence in each study by examining the study design, quality of data, and presence of plausible alternative explanations of outcomes. They characterized the evidence on a case by case basis as “none,” “weak,” “of intermediate strength,” or “stronger.” We considered formal meta-analysis inappropriate because of heterogeneity in outcome measures and patient populations. Full details of the search strategy, study selection, and data extraction are available in a technical report.15

Results
The electronic search selected 4382 abstracts. Hand searching produced no additional papers. Appraisal of abstracts selected 254 papers, including 20 in languages other than English. The final review included 46 studies (table 1).17–65

Study design
We found no randomised controlled trials and only four prospective planned comparison studies with predefined study phases.22 40 52 65 Most designs were interrupted time series—that is, time series of outcome measures recorded before and after one or more interventions. However, eight of 38 interrupted time series studies presented only collapsed data, summarising time series from each phase in a single data point. One retrospective cohort study used survey data from all Dutch hospitals.64

Ten studies did not compare isolation or screening measures with respect to isolation or screening.22 30 37 44 49 59 60 62 Review of the 36 studies allowing comparisons between isolation policies indicated that in 27 the comparisons being made were dependent on knowledge of the outcome data. Short retrospective studies with successful outcomes were particularly vulnerable to this problem; in at least seven the decision to intervene was influenced by part of the outcome data reported. This, and the predominance of unplanned retrospective reports, shows that reporting bias is likely to be important.

Threats to internal validity of evidence
In the absence of cluster randomised trials, all comparative studies were vulnerable to selection bias, yet recording and adjustment of potential confounders was minimal (table 2). In two cases we considered reported changes in case mix to represent a plausible explanation for changes in the incidence of MRSA.43 66

We identified changes in antibiotic prescribing, staff workload and ratios of staff to patients, and lengths of stay as the main potential sources of performance bias. Again, few studies reported data allowing an assessment of these, and none provided adjustment in the analysis (table 2). In a few cases some

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### Table 3 Studies providing stronger evidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting and study population</th>
<th>Design</th>
<th>Main interventions</th>
<th>Patient outcomes</th>
<th>Assessment of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coello et al, 199425</td>
<td>Teaching hospital 1500 beds</td>
<td>Prospective interrupted time series. Three phases: 8, 8, and 26 months</td>
<td>Phases 1 and 2: minimal isolation and screening Phase 3: single room isolation and nurse cohorting, contact screening, prompt discharge of MRSA cases Topical eradication of MRSA carriage with neomycin nasal cream in phase 1 and with mupirocin in phases 2 and 3</td>
<td>Figure: A 476 infected patients throughout</td>
<td>Evidence that a major outbreak was controlled by combined interventions. Lacks information on many potential confounders</td>
</tr>
<tr>
<td>Coisner-Zeilbik et al, 199830</td>
<td>Pediatric ICU 20 beds</td>
<td>Hybrid retrospective and prospective interrupted time series. Two phases: 21 and 24 months.</td>
<td>Phase 1: screening for last 11 months Phase 2: single room isolation, cohorting, screening, feedback, handwashing education, barrier nursing, chlorhexidine soap, and other measures</td>
<td>Figure: B MRSA infections: Phase 1: 50 Phase 2: 6</td>
<td>Evidence that interventions reduced MRSA infections. Regression to mean and Hawthorne effects supply less plausible alternative explanations</td>
</tr>
<tr>
<td>Duckworth et al 1998,30</td>
<td>Teaching hospital 645 beds</td>
<td>Retrospective interrupted time series. Six phases: 4, 3, 13.5, 4, 1.5, 26 months</td>
<td>Initial isolation: mainly single rooms and some cohorting (phases 1-3), changing to mainly isolation ward (phases 4-6). Simultaneous changes to screening, eradication and other measures</td>
<td>Figure: C 408 MRSA infections throughout</td>
<td>Evidence supporting efficacy of combined measures in reducing incidence. Many potential confounders not recorded</td>
</tr>
<tr>
<td>Fasagali et al, 199230</td>
<td>Teaching hospital 1200 beds</td>
<td>Retrospective interrupted time series. Two phases: 7 and 8 years</td>
<td>Isolation ward throughout Phase 1: minimal overflow from isolation ward Phase 2: overflow isolated in single rooms Additional measures in phase 2 include: pre-screening of admissions and transfers in; handwashing education; antibiotic restriction</td>
<td>Figure: D</td>
<td>Evidence that combined measures in both phases failed to prevent MRSA spreading and becoming endemic</td>
</tr>
<tr>
<td>Farrington et al, 199830</td>
<td>Teaching hospital 1000 beds</td>
<td>Retrospective interrupted time series. Two phases: 9.5 and 2.5 years</td>
<td>Continual operation of isolation ward Phase 1: minimal overflow from isolation ward Phase 2: overflow cohorted and isolated in single rooms Screening, ward closure and eradication policies relaxed slightly in phase 2</td>
<td>Figure: E 221 MRSA acquisitions, 206 colonised on admission, 61 uncertain</td>
<td>Evidence supporting control of MRSA for 9.5 years by combined measures followed by eventual control failure related to rise in numbers colonised on admission or to change in strain rather than changed control measures</td>
</tr>
<tr>
<td>Harbath et al, 2000; Pittet et al, 200030</td>
<td>Teaching hospital 1300-1600 beds</td>
<td>Hybrid retrospective and prospective interrupted time series. Three phases: 4, 2, and 3 years</td>
<td>Phase 1: No control measures Phase 2: Single room isolation, screening, mupirocin Phase 3: as phase 2 + hand hygiene, education, and feedback programme</td>
<td>Figure: F 1771 MRSA colonisations and infections, 158 bacteraemias</td>
<td>Evidence supporting control by combined interventions Some potential confounders, but these provide less plausible explanations for the changes</td>
</tr>
</tbody>
</table>
information was available that implied that performance bias could plausibly explain changes in MRSA outcomes.31 32 45 53 Similarly, studies took few measures (such as blinding of outcome assessors) to prevent detection bias, although we considered studies reporting infections with specified diagnostic criteria and bacteraemias as primary outcomes to be less vulnerable to this bias.

**Trends, regression to the mean, and seasonal effects**

Of 30 studies with two or more phases and pre-intervention time series, clear trends were apparent in 13. In all cases the trend was for increasing MRSA levels before major interventions. Trends in the number of patients colonised on admission may also complicate interpretation of outcomes. Of 35 studies presenting time series data, only five of the 18 studies that assessed whether patients were colonised on admission presented sufficient data to assess trends. In two cases there was an increasing trend,22 24 in one a decreasing trend,31 and in two no clear trend.32 49 In two cases these trends provided a plausible explanation for changes in outcome measures.31 34

Regression to the mean effects were considered likely when unusually high MRSA incidence data promoted the intervention and when these data were included in the study. We considered this threat to provide a plausible explanation of outcomes in seven studies.20 21 25 26 47 48 59 Inspection showed that seasonal effects may have been important in two of 14 studies with time series of 18 months or more. In the 21 studies with shorter time series it was not possible to disentangle seasonal from intervention effects.

Changes in MRSA strain types may explain changes in outcomes. Fourteen studies reported no typing details. In one study we considered the documented introduction of a new strain believed to have greater epidemic potential to plausibly explain increased MRSA incidence and control failure.52
Outcome of studies considered to present the strongest evidence interrupted time series for: A: Coello et al; B: Castronovo Zerbib et al; C: Duckworth et al; D: Faaggli et al; E: Farrington et al; F: Harbath et al. Table 3 gives explanatory text. Asterisks indicate phases with most intensive isolation policies. In D and E isolation policies in both phases were similar (isolation wards), but in the second phase the capacities of the isolation wards were exceeded in both cases, and the overflow was cohorted or isolated in single rooms.
Statistical validity
Of the 36 interrupted time series, 24 reported results of statistical analysis. In all but one study, where the analysis could be assessed patient outcomes were assessed by authors to be independent. Such assumptions are inappropriate when transmission from patient to patient occurs and would cause inflated rates of type I errors. In one study we considered the independence assumption to be justified as outcomes at hospital level from distinct hospitals were used.

Evidence for control of MRSA
In 45 of the 46 studies multiple simultaneous control measures were apparent. It was not possible to assess the relative contribution of individual measures.

In 14 studies it was impossible to draw any conclusions about the effect of interventions. Most of the remaining 32 reported evidence consistent with reduction in MRSA transmission. The evidence in 18 of these we considered weak, because of poor study design or clear alternative explanations. This often applied to small and successfully controlled outbreaks managed by isolation wards or nurse cohorting. None the less, it remains possible that immediate deployment of nurse cohorting or an isolation ward may be successful. Fourteen studies provided “stronger” evidence or evidence of intermediate strength (tables 3 and 4).

The strongest evidence came from six longer time series, with detailed information on interventions and fewer plausible alternative explanations (table 3, figure). In four cases major outbreaks were controlled or MRSA numbers substantially reduced over prolonged periods; the main isolation measures were single room in two studies, nurse cohorting in one, and isolation ward in one. Another isolation ward study reported failure to control the spread of MRSA, and another reported control by an isolation ward for many years followed by eventual failure.

We considered eight studies (table 4) to present evidence of reduction of MRSA by measures that included an isolation ward, nurse cohorting, or other interventions. One presented data indicating the failure of an isolation ward to control MRSA. However, these studies either had plausible alternative explanations or reported smaller changes in MRSA and did not record some important potential confounders. The evidence was therefore considered weaker than that from the first six. We found evidence from only one study that supported the hypothesis that MRSA replaces methicillin-sensitive Staphylococcus aureus (MSSA). MRSA and MSSA bacteraemia data from the longer time series contradicted this and showed that MRSA added to the total burden of infection.

Discussion
Our primary conclusion is that major methodological weaknesses and inadequate reporting in research into the effectiveness of isolation measures mean that many plausible alternative explanations for reductions in MRSA cannot be excluded. We have produced guidelines to facilitate the planning and publication of better quality studies.

The secondary conclusion is that, despite the limitations of existing research we found evidence that concerted interventions that include isolation measures can reduce MRSA transmission substantially, even in settings with endemic MRSA. We found no evidence to show that current isolation measures recommended in many countries are ineffective at reducing transmission from isolated patients: the only two studies that directly measured this reported large reduction in the transmission rate per source. None the less, we found reports of control failure despite the employment of intensive isolation measures including isolation wards. These studies indicate a need to investigate precisely how such isolation measures should be used. We address this question in detail elsewhere, using mathematical models to explore the effectiveness and cost effectiveness of isolation wards under different assumptions.

Strengths of the study
In contrast with narrative reviews, where study selection may be biased, our systematic comprehensive search strategy, data extraction and documentation of component threats to validity provided a rigorous evaluation of the shortcomings of existing research. In particular, no studies tell us anything about the relative effectiveness or cost effectiveness of individual measures in different clinical situations. These would be fertile areas for further research.

Nevertheless, a lack of evidence of an effect associated with specific measures should not be mistaken for evidence of lack of effect. Having considered the evidence we believe isolation measures recommended in national guidelines should therefore continue to be applied until further research establishes otherwise.

The six studies considered to present the strongest evidence for assessing the effect of isolation, although they often failed to consider potentially important confounders, provide testable hypotheses that could be assessed in future studies.

Priority for research
MRSA is associated with substantial morbidity and mortality. The emergence of glycopeptide resistant Staphylococcus aureus
strains, which further reduce therapeutic options, makes the implementation of well designed interventional studies to inform the choice of control measures a research priority.

Contributors: SPS coordinated writing grant proposal and conduct of review. BSC was employed as a full time postdoctoral research fellow to develop the search strategy together with CCK and SPS. BSC, SPS, and CCK jointly appraised abstracts. SPS and independently appraised articles initially. BSC appraised articles fully and extracted data for all papers, with review of SPS, CCK, BDC, JR, GFM, and GD chosen in accordance with area of expertise. BSC with SPS and the other reviewers analysed the data. Writing up of the Health Technology Assessment report was done principally by SPS and BSC, with review and input from the whole review team. SE advised on systematic review methods in grant application and throughout review and writing up phase. The study was funded for two years by the Health Technology Assessment Programme of the NHS R&D HTA Programme.

Competing interests: None declared.

1 Public Health Laboratory Service. The first year of the Department of Health's mandate for methicillin-resistant Staphylococcus aureus (MRSA) was critical to the successful control of MRSA. The first year of the Department of Health's mandate for MRSA was critical to the successful control of MRSA.

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79 Bacteriological Subcommittee. The first year of the Department of Health's mandate for MRSA was critical to the successful control of MRSA.
Few events in biology offer a more powerful demonstration of the wonders of natural selection than the spread of antibiotic resistance. Hospital staff struggling to contain the golden staph may, of course, take a more jaundiced view of its triumph.

Fortunately the microbe is not invincible. This week’s review by Cooper and colleagues is a reminder that strict isolation measures can limit the spread of methicillin-resistant Staphylococcus aureus infection. Benzene J Aust 1982;2:472-4.

In short, while antibiotics do give the golden genie a selective advantage over its susceptible brethren once it has escaped its bottle, squeezing it back from whence it came depends principally on sustained efforts at preventing transmission. When it comes to regular hand washing, at least one survey has suggested that doctors are more blameworthy than nurses.

So, once more unto the sink, dear friends, once more...


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