Control of Endemic MRSA Current Evidence and Controversies

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Outline

- SHEA Guidelines
- What is the Quality of the Data?
  - Limitations of epidemiologic study methods
    - Few randomized clinical trials
    - Multiple simultaneous interventions
    - Regression towards the mean
  - Recent critical review of data on hospital MRSA control
    - Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39
    - Boyce et al. *ICHE* 2004. Vol 25. No.5 pgs 395-401
- Unintended consequences of contact isolation for infection control
  - *JAMA.* 2003;290:1899-1905
- Conclusion

SHEA Guidelines May 2003

- Measures for the control of MRSA
  - Gloves IA
  - Gowns IA
  - Active surveillance cultures to identify the reservoir for spread IA
  - Periodic (eg. weekly) surveillance cultures are indicated for patients remaining in the hospital at high risk for MRSA (IA)

IA- Strongly recommended for implementation and strongly supported by *well-designed experimental, clinical, or epidemiologic studies.*

But the question is…

What is the quality of the data and how is the body of current studies best interpreted?

It is important to consider the limitations and challenges of epidemiologic study methodology.

Epidemiology

- The study of how disease is distributed in populations and of the factors that influence or determine this distribution.
  - Determine risk factors for a given disease
  - Determine the extent of disease in a population
  - Study natural history of a specific disease
  - Evaluate existing and new preventive and therapeutic measures
  - Provide the foundation for developing public policy and regulatory decisions related to healthcare

Epidemiologic Approach

- Define associations between exposure and an outcome
  - Associations are not always causal!!!!!!!!
- Most data:
  - Descriptive
    - Case control
    - Cohort
  - Observational
    - Retrospective
    - Prospective (less common)
  - Frequently non-randomized
  - Frequently not 'controlled'
  - The 'prospective, randomized clinical trial' is a rarity in epidemiology

Guidelines for Evaluating the Evidence of a Causal Relationship

- Temporal relationship
- Biological plausability
- Consistency
  - Single studies are rarely definitive!
- Alternative explanation
  - Confounding assessed
  - single vs multiple simultaneous interventions
- Dose-response
- Strength of association
- Cessation effects

Leon Gordis. ***Epidemiology.*** 2nd Ed.W.B Saunders. 2000

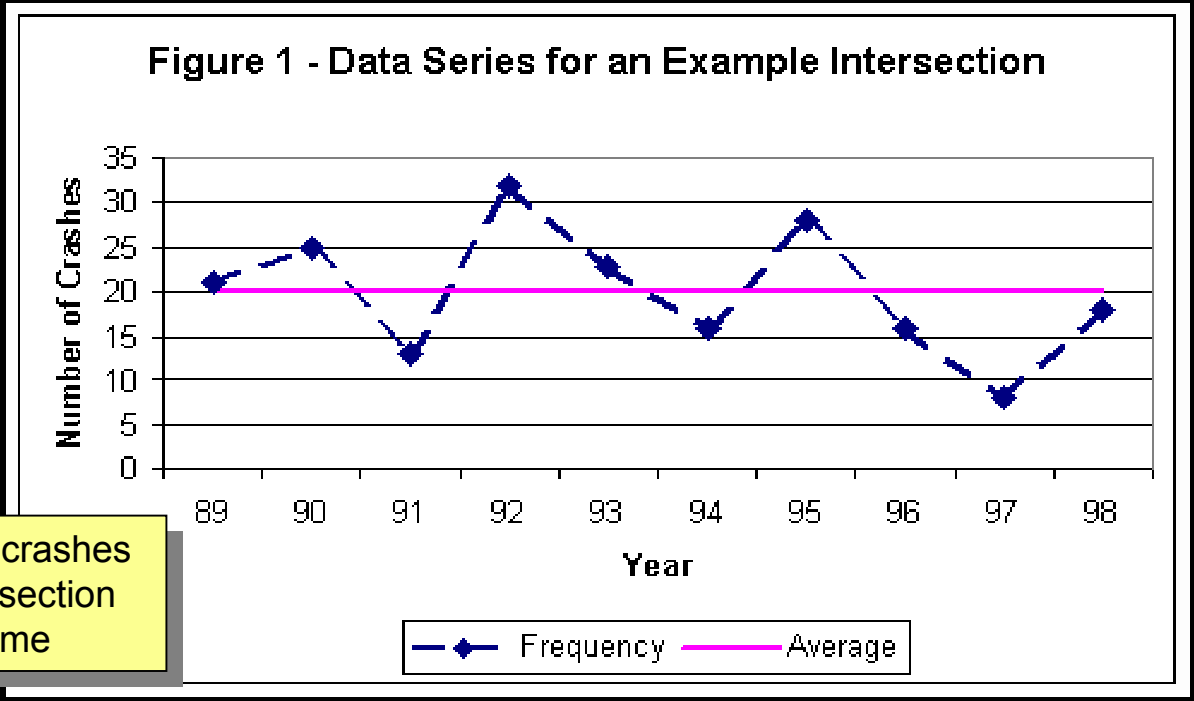
So prospective, randomized trials are a rarity in epidemiology.

Additionally, there are 2 other phenomenon which make many hospital epidemiology studies problematic:

1. Multiple simultaneous interventions:Relative effect of each is impossible to define
2. Regression toward the mean :Introduction of bias and threat to validity

Regression Toward the Mean

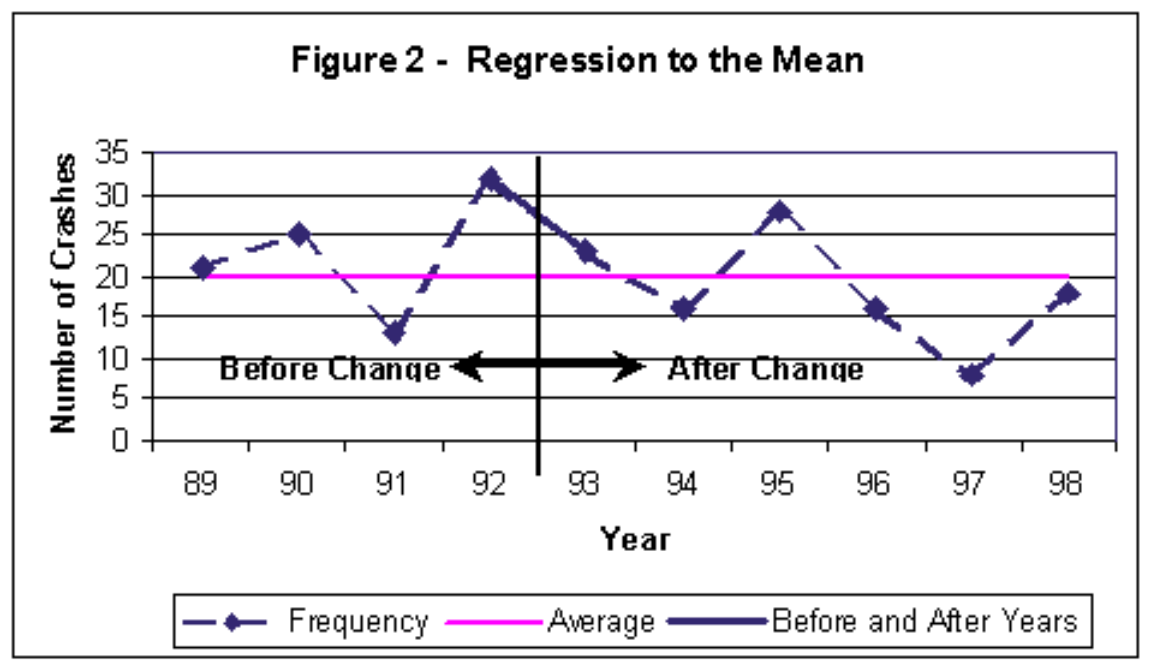
- **What is it?**
  - **Regression to the mean is a statistical phenomenon that is a fact of life in statistics.**
  - **Variation:**
    - **The variations are usually due to the normal randomness of occurrence that is present**



Number of crashes at an intersection over time

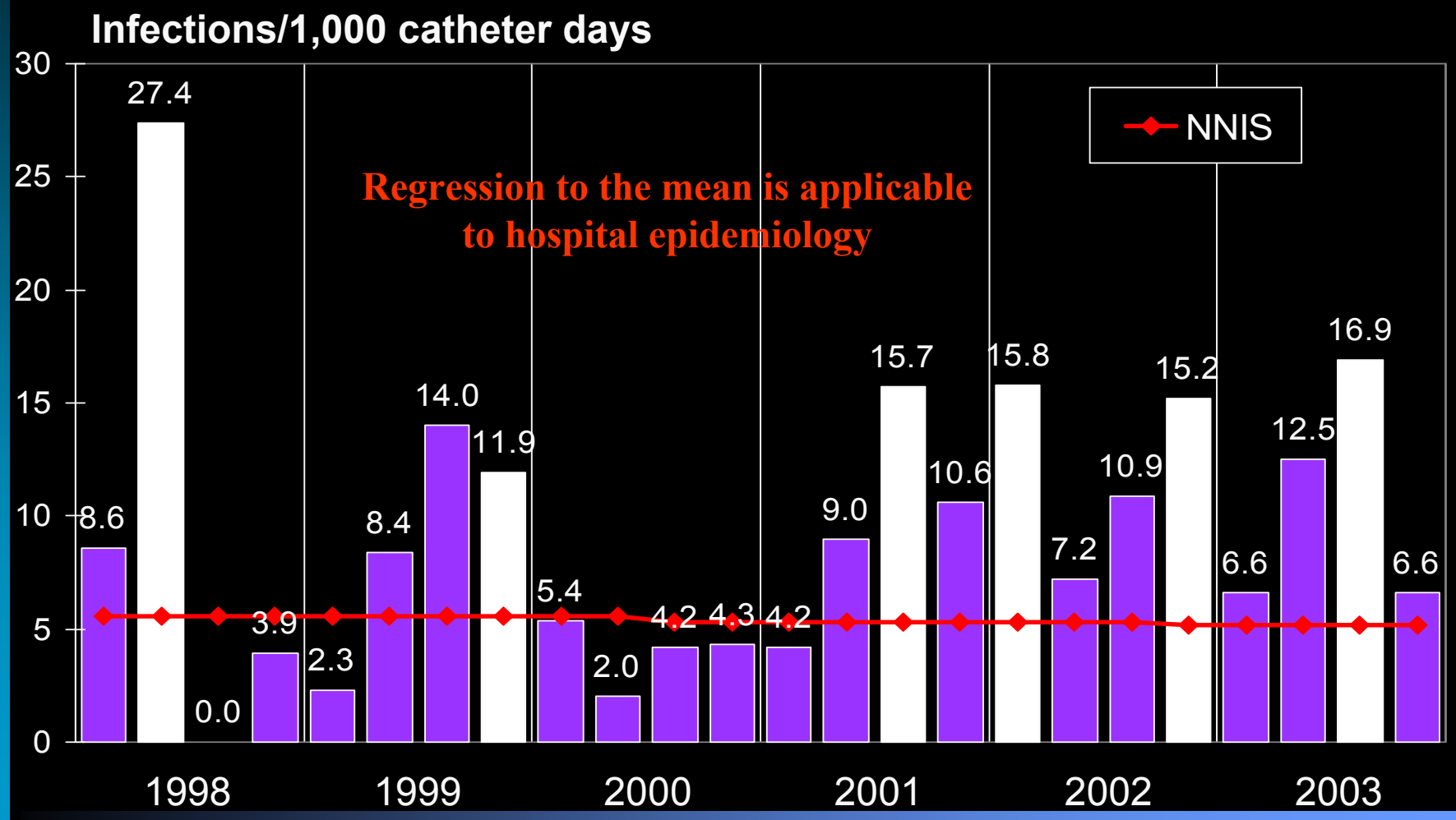
Regression Toward the Mean

- The average does not change



NSICU Bloodstream Infections

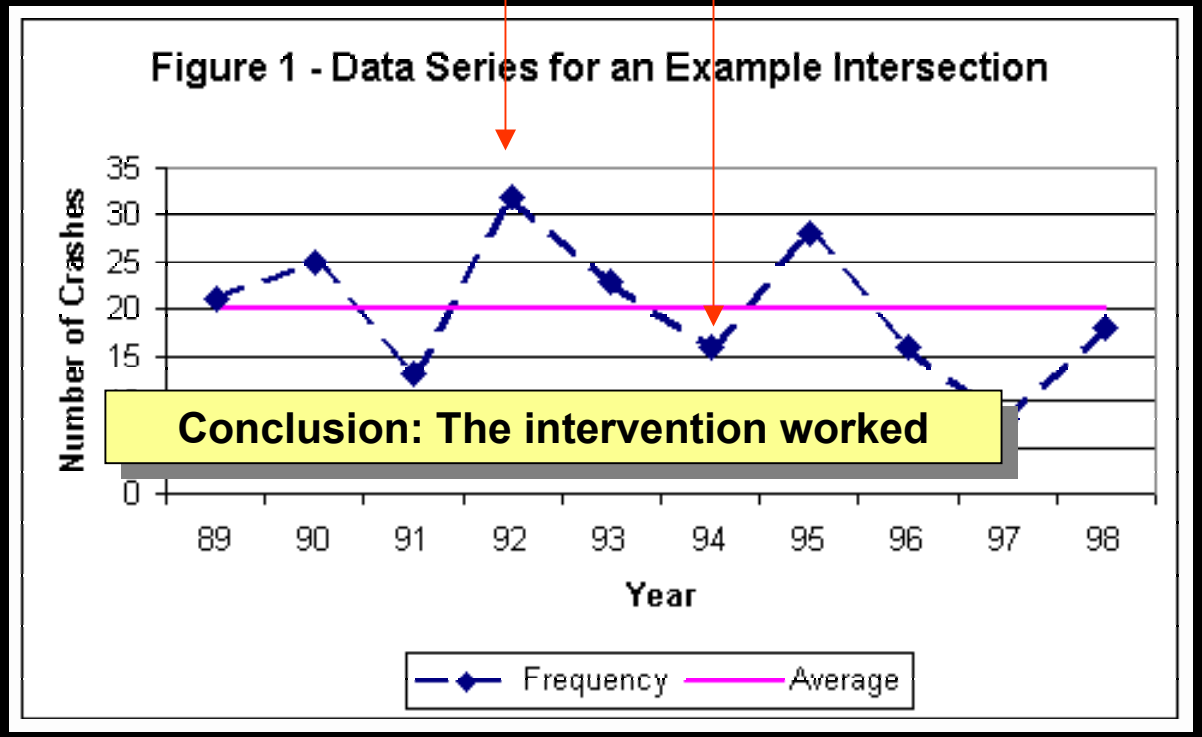
Quarterly Rates, 1998-2003



Regression Toward the Mean

Intervention introduced at first arrow

Effect of intervention measured at second arrow



Conclusion: The intervention worked

Kudos to you!!!!! This is a great study!!!…or is it really?

Regression Toward the Mean

- **Why is it important?**
  - **It is an important phenomenon to take note of in conducting experiments because it affects the internal validity of the experimental design.**
  - **One can end up concluding that the significant difference or effect is due to the treatment when in fact it is due to chance and by this phenomenon known as regression toward the mean.**
  - **Occurs in all experimental designs and especially in quasi-experiments where nonequivalent groups and non-random assignment are used.**

Regression Toward the Mean

- When interventions under investigation are made because of unusually high MRSA levels, there is a risk that subsequent reduction in MRSA will be attributed solely to that intervention
  - Reporting bias is usually assumed to result from authors' and journals' preferences for publishing positive results.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling

BS Cooper[1]
SP Stone[1]*
CC Kibbler[2]
BD Cookson[3,4]
JA Roberts[4]
GF Medley[5]
GJ Duckworth[6]
R Lai[7]
S Ebrahim[8]

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Background

The incidence of patient infection and colonisation with methicillin-resistant *Staphylococcus aureus* (MRSA) continues to rise in UK hospitals

Poses a considerable socio-economic burden.

Management of this problem includes screening to detect asymptomatic carriers and the use of various isolation measures to control its spread.

There has been much debate about the rationale and cost-effectiveness of these measures.

MRSA guidelines have been published but there was an urgent need for a systematic review to examine the evidence base for these recommendations.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Objectives

- To review the evidence for the effectiveness of different isolation policies and screening practices
- To develop transmission models to study the effectiveness and cost-effectiveness of isolation policies in controlling MRSA.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Data sources

- Searches of electronic databases MEDLINE (1966–2000), EMBASE (1980–2000), CINAHL (1982–2000), The Cochrane Library (2000) and SIGLE (1980–2000).
- Manual searches of the principal hospital infection journals to validate electronic database searches.
- No language restrictions were imposed.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Study selection

- Abstracts were appraised by two or three reviewers
- Two investigators reviewed the full papers independently
- Data Extracted where studies were
  - prospective
  - employed planned comparisons using retrospective data
  - isolation wards or nurse cohorting were used (designated nurses for the care of MRSA-affected patients).

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Data extraction:

- details of all populations under investigation
- details of patient isolation, screening and other infection control measures (e.g. eradication of carriage, antibiotic restriction, hand-hygiene, feedback, ward closures)
- information on outcomes (e.g. infection, colonisation, bacteraemia, death)
- details of potential confounders or effect modifiers including length of stay, antibiotic use, strain change, pre-existing trends, numbers colonised on admission, seasonal effects, staffing levels and aspects of study design that might introduce biases.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Data synthesis

- Data were summarised in table form.
- Formal meta-analysis was considered inappropriate owing to heterogeneity in study design and patient populations.
- The strength of evidence was assessed
  - study design
  - quality of data
  - size of effect and presence of plausible alternative explanations due to confounders and biases.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Study interventions

- Eighteen studies described the use of isolation wards.
  - Study durations ranged from 3 months to 15 years
    - involved between 11 and 5345 MRSA cases.
- Nine studies described the use of nurse cohorting (NC).
  - Study durations ranged from 3.5 months to 4 years
    - involved between 5 and 1074 MRSA cases.
- Nineteen studies described other isolation policies.
  - Study durations ranged from 1 month to 9 years,
    - involved between 9 and 1771 cases.
- In nearly all the studies isolation was combined with at least one other simultaneous intervention.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Results: systematic review

- There were 4382 abstracts
- 254 full-article appraisals
- Forty-six were included in the final review.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Study designs

- one prospective cohort cross-over study
- two prospective cohort studies with historical controls
- nine prospective interrupted time series (ITS) (three had prospective data collection but unplanned interventions)
- six prospective observational one-phase studies
- five hybrid retrospective/prospective ITS
- one retrospective cohort study with systematic data collection and the comparison decided on in advance of examining the data
- two retrospective studies with the comparison decided on before examination of the data
- eighteen retrospective ITS
- two retrospective observational studies.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Quality of studies

- There were few formally planned prospective studies with predefined pre- and postintervention periods.
- Systematic assessment and adjustment for potential confounders was lacking.
- Regression to the mean effects and confounders were plausible threats to the validity of many studies.
- The predominance of unplanned retrospective reports suggests that reporting bias may be important.
- Statistical analysis was absent or inappropriate in all but two studies.
- There was no robust economic evaluation.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Results

- No conclusions could be drawn about the effect of isolation in one-third of studies.
- In studies with multiple simultaneous interventions it was not possible to assess the relative contribution of individual measures.
- Most others provided evidence consistent with reduction of MRSA.
  - In half of these, the evidence was considered weak because of poor design, major confounders and/or risk of systematic biases.
- Two studies presented evidence consistent with immediate isolation reducing transmission.

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

6 Studies of note

- **Three presented conflicting evidence of the effectiveness of isolation :**
  - **one study reduced infection**
  - **one study did not reduce infection**
  - **one study resulted in control for many years until a change in strain and/or an increase in the number of patients colonised on admission overwhelmed the institution.**
- **One study presented evidence that single-room isolation with screening, eradication and an extensive hand-hygiene program reduced MRSA infection and colonisation hospital wide.**
- **One study provided evidence that NC in single rooms with screening and eradication reduced infection hospital wide.**
- **One pediatric intensive care unit study provided evidence that single-room isolation and patient cohorting in bays (with screening, feedback of infection rates and hand-hygiene education) reduced infection**

Cooper et al. ***Health Technology Assessment 2003***; Vol. 7:No. 39

Conclusions

Implications for healthcare

- **Intensive concerted interventions that include isolation can substantially reduce MRSA**
- **Little evidence was found to suggest that current isolation measures recommended in the UK are ineffective, and these should continue to be applied until further research establishes otherwise.**
- **It was not possible to draw any conclusions about the cost-effectiveness of the interventions because of the poor quality of the economic evaluative work presented.**

ICHE 2004. Vol 25. No.5 pgs 395-401

- ***Do Infection Control Measures Work for Methicillin-Resistant Staphylococcus aureus?***
- *John M. Boyce, MD; Nancy L. Havill, MT; Cynthia Kohan, MT, MS; Diane G. Dumigan, RN, BSN; Catherine E. Ligi, RN, BSN*

ICHE 2004. Vol 25. No.5 pgs 395-401

- Design
  - To review evidence regarding the effectiveness of control measures in reducing transmission of methicillin resistant *Staphylococcus aureus* (MRSA) in hospitals.
- Setting
  - A 500-bed, university-affiliated, community teaching hospital.

ICHE 2004. Vol 25. No.5 pgs 395-401

- Results:
  - The percentage of nosocomial *S. aureus* infections caused by MRSA increased significantly between 1982 and 2002
  - Ineffectiveness of control measures may be due to several factors including the failure to identify patients colonized with MRSA.
    - Stool specimens submitted for *Clostridium difficile* toxin assays
      - 12% of patients had MRSA in their stool
        - » 41% of patients with unrecognized colonization were cared for without using barrier precautions.
    - Poor adherence of healthcare workers (HCWs) to recommended precautions
    - Transmitting MRSA, and importation of MRSA by patients admitted from other facilities.

ICHE 2004. Vol 25. No.5 pgs 395-401

- Evidence that implementing SHEA guidelines for the control of MRSA is possible
  - Their intervention
    - Staged approach to implementing and expanding MRSA surveillance cultures
      - SICU
        - » Cultures of anterior nares obtained on all SICU admissions and then q 7 days
        - » Contact precautions and individual patient rooms? (not specified in text)

ICHE 2004. Vol 25. No.5 pgs 395-401

- 5 months of intervention data
  - 442 active surveillance cultures (84.5%) of patients admitted to SICU
    - 38 (8.6%) Pts had previous MRSA history
      - 23 (5.2%) of 442 had positive MRSA surveillance culture
    - 404 (94.4%) of those cultured had NO MRSA by history
      - 24 (5.4%) of these had a positive surveillance culture. Unrecognized ***COLONIZATION***
      - ***Only 4 (0.9%) of 404 with negative screening cultures ultimately had a positive MRSA culture on surveillance***

ICHE 2004. Vol 25. No.5 pgs 395-401

- Impact of their intervention:
  - 6 month study period prior to intervention
    - Proportion of patients in SICU with MRSA associated nosocomial infection- 2.2%
    - 0.48 MRSA infections per 100 patient days
  - After 5 months of intervention
    - Proportion of patients in SICU with MRSA associated nosocomial infection- 0.7% (P=0.033)
    - 0.22 MRSA infections per 100 patient days
      - NO P Value or TEST OF SIGNIFICANCE CITED

ICHE 2004. Vol 25. No.5 pgs 395-401

- The authors' conclude:
  - 'MRSA control programs are effective if they include ASCs of high-risk patients, use of barrier precautions when caring for colonized or infected patients, hand hygiene, and treating HCWs implicated in MRSA transmission'
- HOWEVER:
  - Study design
    - Intervention of limited time frame (5 months)
      - No data on patient acuity in pre/post intervention
      - No data on device specific/nosocomial infection type
      - No data on compliance with hand hygiene and contact precaution
    - Regression to the mean is a *significant* threat to validity
    - No economic or cost benefit analysis; instead authors cite prior studies to justify the expense

The bottom line:

- SHEA guidelines suggest that current MRSA isolation practices are supported by incontrovertible evidence.
  - However, a critical review of the literature suggests that much of the supporting data is limited by flaws of study design, confounding and analysis.
    - The quality of the data in many studies is weak
  - There is no significant evidence that current MRSA control practice is *ineffective*.
  - The cost effectiveness of MRSA control practices is still largely inconclusive

What may be some of the unintended consequences of contact precautions?

JAMA. 2003;290:1899-1905.

Safety of Patients Isolated for Infection Control

Henry Thomas Stelfox, MD; David W. Bates, MD, MSc; Donald A. Redelmeier, MD, MSc

JAMA. 2003;290:1899-1905.

- **Context**
  - Hospital infection control policies that use patient isolation prevent nosocomial transmission of infectious diseases, but may inadvertently lead to patient neglect and errors.
- **Objective**
  - To examine the quality of medical care received by patients isolated for infection control.
- **Design, Setting, and Patients**
- Adults isolated with MRSA at 2 academic centers
  - General cohort (patients admitted with all diagnoses between January 1, 1999, and January 1, 2000; n = 78)
  - Disease-specific cohort (patients admitted with a diagnosis of congestive heart failure between January 1, 1999, and July 1, 2002; n = 72).
  - Two matched controls were selected for each isolated patient (n = 156 general cohort controls and n = 144 disease-specific cohort controls).

JAMA. 2003;290:1899-1905.

- **Main Outcome Measures**
  - Quality-of-care measures
    - encompassing processes
    - outcomes
    - patient satisfaction
  - Adjustments for study cohort and patient demographic, hospital, and clinical characteristics were conducted using multivariable regression.

Safety of Patients Isolated for Infection Control: Process Measures

	General Cohort		CHF Cohort		Isolated vs controls	
	Isolated N-78	Controls N-156	Isolated N-72	Controls N-144	Test statistic	*P*
VS incomplete	10%	8%	19%	10%	1.92	<.001
Days w/ no VS recorded	6%	1%	5%	1%	2.55	.02
Days w/ no nursing notes	11%	11%	17%	9%	1.77	<.001
Days w/ no MD progress note	43%	24%	7%	2%	2.91	<.001

Stelfox HT et al. JAMA 2003;290:1899-1905.

Safety of Patients Isolated for Infection Control: Outcome Measures

	General Cohort		CHF Cohort		Isolated vs controls	
	Isolated	Controls	Isolated	Controls	RR	*P*
Adverse events/1000 days	17.0	7.0	47.3	24.5	2.20	<.001
Supportive care failure*	6.1%	0.8%	16.2%	1.8%	8.27	<.001
Patient complaint	38%	5%	17%	5%	23.5	<.001

*falls, pressure ulcers, fluid/electrolyte disorders

Stelfox HT et al. JAMA 2003;290:1899-1905.

JAMA. 2003;290:1899-1905.

- **Conclusion**
- Compared with controls, patients isolated for infection control precautions:
  - Experience more preventable adverse events
  - express greater dissatisfaction with their treatment
  - have less documented care.

Conclusion

- There is reason to debate aggressive MRSA control policies as advocated by SHEA
- A critical review of the literature suggests that the quality of the supporting data, as referenced by SHEA, does not allow for a conclusive and definitive position on MRSA control.
- There may be unintended consequences of infection control contact isolation and these may pose a threat to patient safety and healthcare quality.
- …..the debate continues