



Research Integrity

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Health Watch USA

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This presentation is the explicit
opinion of Kevin T. Kavanagh, MD, MS



Research Integrity

Dr. Richard Horton, the Editor of *The Lancet*, stated, “The case against science is straight forward: much of the scientific literature, perhaps half, may simply be untrue.”(1)

Charles Seife from the Arthur L. Carter Institute of Journalism at New York University has stated, “When the FDA finds significant departures from good clinical practice, those findings are seldom reflected in the peer-reviewed literature, even when there is evidence of data fabrication or other forms of research misconduct.”(2)

(1) Horton R. Offline: What is medicine’s 5 sigma? *The Lancet*. Vol 385 April 11, 2015 Accessed from <http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736%2815%2960696-1.pdf>

(2) Seife C. Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature. *JAMA Intern Med*. 2015 Apr;175(4):567-77. doi: 10.1001/jamainternmed.2014.7774. PMID: 25664866.

MRSA Evidence Based Policy

The United States Is Missing Its Targets For MRSA Reduction:

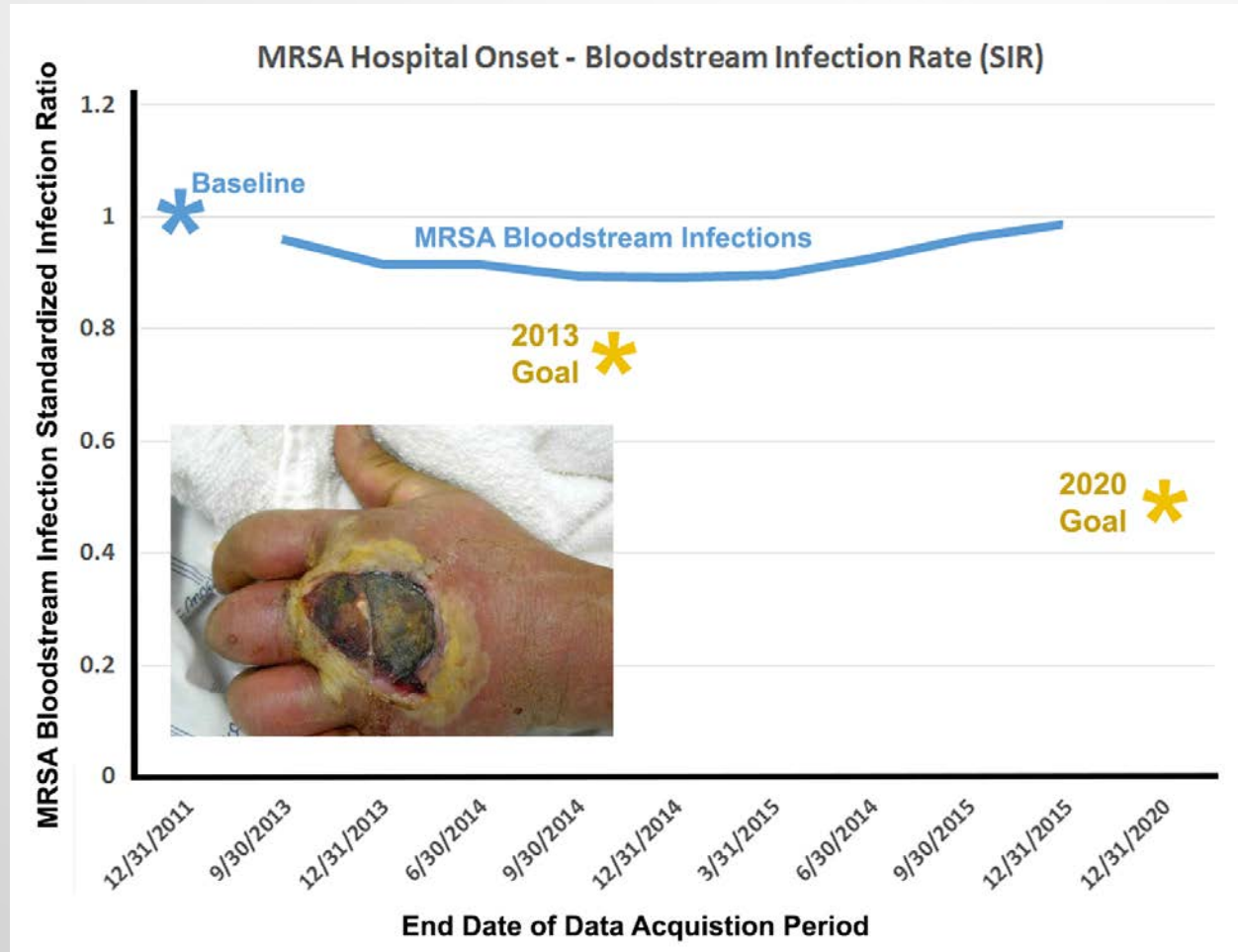
Table 1: 2013 Targets and Progress Made by 2014

Measure (and data source)	Original target for 2013 (from 2009 baseline)	Progress made by 2014
Invasive MRSA (NHSN)	50% reduction	36% reduction
Facility-onset MRSA (NHSN)	25% reduction	13% reduction

From: National Targets and Metrics. Office of Disease Prevention and Health Promotion.
Accessed on Oct. 22, 2016 from <https://health.gov/hcq/prevent-hai-measures.asp>

MRSA Evidence Based Policy

There May Be Little Or No Improvement In Control:

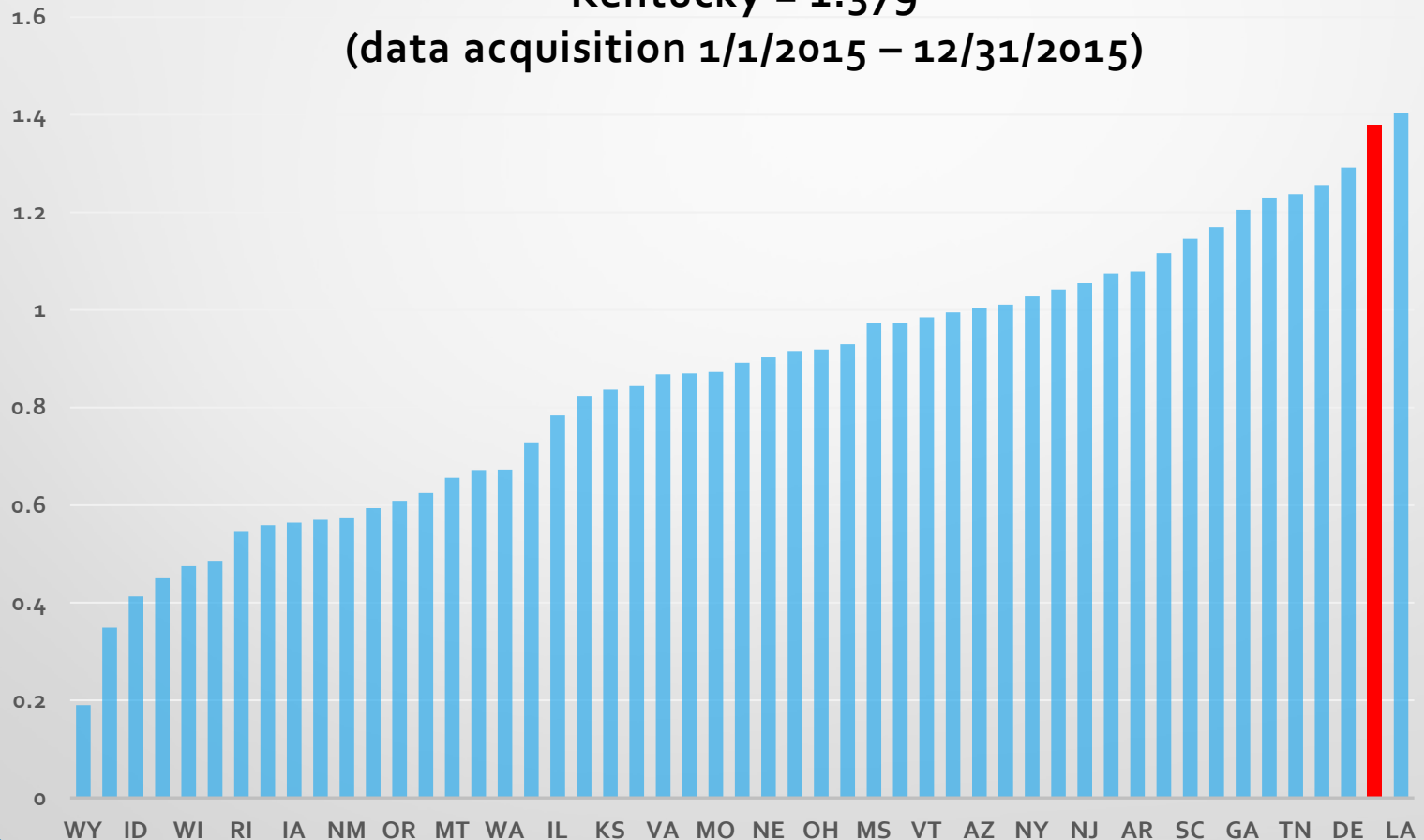


MRSA Evidence Based Policy

MRSA Standardized Infection Ratio in The 50 States

Kentucky = 1.379

(data acquisition 1/1/2015 – 12/31/2015)



Two Basic Strategies

The United States Is Missing Its Targets For MRSA Reduction:

- Surveillance and Isolation – Adopted Nationwide By The United Kingdom.
- Unit Wide Daily Chlorhexidine Bathing Protocols. This has been adopted by many facilities in the United States.

Daily Chlorhexidine Bathing

One Study Had a Large Impact on Policy Adoption:

- **Reduce MRSA Study – But Research Integrity Problems.**
 - Only the surrogate metric had scientific significance. MRSA Bacteremia did not reach significance.
 - Spinning of the data.
 - Multiple Metrics Changed.
 - Non-reporting of Data.

Huang SS, Septimus E, Kleinman K, et al.; the CDC Prevention Epicenters Program; the AHRQ DECIDE Network and Healthcare-Associated Infections Program. Targeted versus universal decolonization to prevent ICU infection. *N Engl JMed.* 2013;368:2255–2265.

Reduce MRSA Study

Use of Surrogate Metrics (Measures)

- The Primary Outcome was a Surrogate Metric of MRSA Clinical Cultures. This reached statistical significance. (AHRQ Task Order states the primary outcome Was “Hospital-Associated MRSA Burden”)
- The Secondary Outcome was MRSA Bloodstream Infections. This did not reach significance.

The argument can be made that if the ‘N’ was bigger then the secondary outcome of MRSA Bloodstream Infections would become significant. However, this was a large study, comprising 160 hospitals. It could also be that the observed change was due to chance.

Reduce MRSA Study

Spinning of Results

- “The abstract stated that MRSA screening and isolation were “implemented” in group 1 and that there was little reported difference between the intervention and baseline periods in MRSA clinical isolates (3.2 versus 3.4 per 1000 days).”
- “This wording may lead one to conclude that screening and isolation were ineffective.”
- However, there was no difference in the intervention between the baseline and intervention arms. This group was used to control for changes over time.

From: Kavanagh KT, Tower SS, Saman DM. A Perspective on the Principles of Integrity in Infectious Disease Research. *Journal of Patient Safety*. 2016 12(2):57-62

Reduce MRSA Study

Spinning of Results

- The Reduce MRSA Study's Abstract Concludes: "In routine ICU practice, universal decolonization was more effective than targeted decolonization or screening and isolation in reducing rates of MRSA clinical isolates and bloodstream infection from any pathogen."
- However, "The largest area of significant reduction was with a reduction in infections in the "Any Pathogen" metric, but the organisms that accounted for the vast majority of the reduced infections were skin commensal bacteria." (1)
- Thus, "Any Pathogen" does not mean "ALL" Pathogens but refers to a metric which groups many bacteria together.

Kavanagh KT, Calderon, LE, Saman DM. Viewpoint: a response to "Screening and isolation to control methicillin-resistant Staphylococcus aureus: sense, nonsense, and evidence" . Antimicrobial Resistance and Infection Control 2015, 4:4 (5 February 2015)

Reduce MRSA Study

Changing Metrics

- 2009, Sept. 19: ClinicalTrials.Gov. HCA listed as a partner with the CDC for the Study.
 - First Received Study –Sept. 19, 2009.
 - Study Start Date. Sept. 2009
- 2011, Sept.: Study Completion Date and Primary Completion Date (Last Collection of Data for Primary Outcome Measure)
- 2012, Mar. 6: AHRQ Task Order for Analysis and Dissemination of the Results.
 - Secondary Outcome Evaluation – Central Line-Associated Blood Stream Infections.
 - Secondary Outcome Evaluation – Nosocomial Bloodstream and Urine Infections.
- 2012, Jun., 19: Clinical Trials.Gov.
 - Elimination of the Urinary Cultures.
 - Elimination of CLABSI Metrics Recorded.
 - Addition of All-pathogen Bloodstream Infection metric (a composite category)
- 2013, May 29: REDUCE MRSA Study Published in the NEJM.
- 2013, Oct. 7: Commentary by Kavanagh, et al published online which discussed changes in metrics which occurred in the REDUCE MRSA Study.
- 2013, Oct. 16: ClinicalTrials.Gov.
 - Reason for CLABSI Elimination Given. (“Note: CLABSI outcome was dropped due to an inability to acquire standardized denominators for this measure. “)
 - Added Urinary Tract Infections metric.
 - Added Emergence of Resistance to Mupirocin and Chlorhexidine metric, and
 - Added Blood Culture Contamination.
- 2014, July 7: ClinicalTrials.Gov.
 - The CLABSI elimination explanation was deleted.

Reduce MRSA Study

Delayed or Not Reporting of Data on ClinicalTrials.gov

- Emergence of Resistance to Mupirocin and Chlorhexidine.
-- Anticipated Reporting Date. March, 2015, Changed To Oct. 2016. No results reported as of 10/31/2016.
- Use of Chlorhexidine found to promote resistance to last resort antibiotic -- Colistin.
<http://outbreaknewstoday.com/bacteria-exposed-to-chlorhexidine-resistant-to-colistin-study-35853/>
- “Reduced susceptibility to chlorhexidine appeared to be independent of the expression of cepA, acrA and kdeA efflux pumps.” “Reduced susceptibility to chlorhexidine may contribute to the success of XDR K. pneumoniae as a nosocomial pathogen, and may provide a selective advantage to the international epidemic strain K. pneumoniae ST258.”

Naparstek L, Carmeli Y, Chmelnitsky I, et. al. Reduced susceptibility to chlorhexidine among extremely-drug-resistant strains of Klebsiella pneumoniae. J Hosp Infect. 2012 May;81(1):15-9. doi: 10.1016/j.jhin.2012.02.007. Epub 2012 Mar 30.

Reduce MRSA Study

Delayed or Not Reporting of Data on ClinicalTrials.gov

- Urinary Tract Infections.
-- Anticipated Reporting Date: June, 2015.
- 2015, Dec. Data from REDUCE MRSA Reported in the Lancet late and after the protocols for use have been widely disseminated and adopted by many hospitals. Huang SS, Septimus E, Hayden MK, et al. Effect of body surface decolonization on bacteriuria and candiduria in intensive care units: An analysis of a cluster-randomized trial. Lancet Infect Dis. 2016;16:70–79.

Antibiotic Resistance Determination

Invalid Methodology – MIC Testing

Using Mean Inhibitor Concentrations to Determine Resistance to Antiseptics. Remember, there are no white blood cells or antibodies on the skin to kill dormant bacteria. When the antiseptic dissipates the bacteria may reemerge.

- 1998, May. Letter from Platt (Author of the REDUCE MRSA Study) which stated that “...with antiseptics, it is dangerous to extrapolate from MIC values to clinical efficacy”. Platt JH, Bucknall RA. MIC tests are not suitable for assessing antiseptic handwashes. *J Hosp Infect.* 1988 May;11(4):396-7. PMID:2899594
- 2015, Oct 10. ID Week (Included REDUCE MRSA Authors: Weinstein, Septimus and Haung) presentation that used MICs to monitor for chlorhexidine resistance. “Mupirocin Resistance and Chlorhexidene (CHG) Non-Susceptibility in a Large Multi-Center Sample of Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Gram-Negative Rod (GNR) Isolates.”
- 2015, Oct. ID Week Poster (Included REDUCE MRSA Author: Weinstein) presentation that used MICs to monitor for chlorhexidine resistance. “Chlorhexidine gluconate (CHG) susceptibility of *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* isolates from skin cultures of patients in long-term acute care hospitals (LTACHs)”

Antibiotic Resistance Determination

Invalid Methodology – MIC Testing

“...recently, an article by Naparstek et al,²⁸ studying the emergence of the carbapenem-resistant Enterobacteriaceae epidemic, noted that reduced susceptibility to chlorhexidine may be a contributing factor and that chlorhexidine-resistant bacteria were observed independent of the MIC.”

From: Kavanagh KT, Tower SS, Saman DM. A Perspective on the Principles of Integrity in Infectious Disease Research. *Journal of Patient Safety*. 2016 12(2):57-62

