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# A Perspective on the Principles of Integrity in Infectious Disease Research

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**Abstract:** The medical literature is prone to overstating results, a condition not thoroughly recognized among policymakers. This article sets forth examples of potential problems with research integrity in the infectious disease literature. We describe articles that may be spun, categories lumped together in hopes of creating a significant effect (and sometimes an insignificant one), changes in metrics, and how trials may fail because of suboptimal interventions. When examined together, the examples show that the problems are widespread and illustrate the difficulty associated with interpreting medical research. The state of the current medical literature makes it of utmost importance that all sections of the manuscript are read, including associated letters to the editors and information on ClinicalTrials.gov before authors' recommendations are accepted.

**Key Words:** research integrity, spinning, data dredging, REDUCE MRSA, STAR\*ICU, infectious disease, MRSA, surveillance, chlorhexidine, standard of care, HAI, bacterial resistance, MDRO

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## PERSPECTIVE

### Introduction

The United States is on the precipice of a devastating infectious disease epidemic, a position it has not been in for well more than 60 years. Multidrug-resistant bacterial infections are becoming all too common with some bacteria threatening to make existing antibiotics obsolete, setting medicine back almost 100 years. Already, concerns are being expressed regarding the impact of antibiotic resistance on surgery and cancer chemotherapy.<sup>1</sup> Governments, agencies, and associations are preparing initiatives to confront and reverse this emerging epidemic. Their main weapon is science and research as reported in the peer-reviewed literature. However, nature evolves and adapts, which confounds medicine's advances. The recent Ebola outbreak highlighted the necessity of developing timely, effective, and systematic standards to contain contagions.<sup>2,3</sup>

The current state of the peer-reviewed literature has questionable reliability, making it difficult for our health care system to formulate and recommend a reliable course of action. A recent commentary by Horton,<sup>4</sup> the editor of *The Lancet*, stated, “The

case against science is straight forward: much of the scientific literature, perhaps half, may simply be untrue.” Self-policing is often lacking, as stated by the Food and Drug Administration:

*“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.”*<sup>5</sup>

Reversal of standards of care is also not uncommon. Prasad et al<sup>6</sup> found that of 363 articles that tested standards of care, 40% supported reversing the standard. Most disturbingly, some of the articles in question were published in top medical journals, with the field of infectious diseases being no exception. In a number of articles that had major impacts on infectious disease policy, there have been significant concerns regarding methodology, data collection, and interpretations. A closer evaluation of the recommendations in these studies is needed. The objective of this perspective was to identify several contemporary peer-reviewed publications that have had a high impact on infectious disease policy yet also have concerns regarding the publication's research integrity.

Concerns regarding research integrity can be classified as follows:

### Spinning Results

Spin is an often misunderstood term. It does not mean “lying” or presenting false information, but instead conveying the information in such a way that one may come to an opposite, incorrect conclusion. This is one of the most common integrity issues found in high-profile articles.

Readers usually first examine the conclusion sections in the abstract and article. They may be the only sections read. Sometimes, however, salient details are contained in the methods section, which would allow readers to realize that the author's conclusions might be overstated. In articles reporting randomized trials, Boutron et al<sup>7</sup> detected spin in the abstract's results and conclusion sections in 37.5% (27/72) to 58.3% (42/72), respectively. In addition, spin was identified in the results, discussion, and conclusion sections of the main article in 29%, 43%, and 50% of reports, respectively.<sup>7</sup> Similar findings were observed in wound care research by Lockyer et al,<sup>8</sup> who documented spin in 20 of 28 articles with a statistically nonsignificant result for the primary outcome.

An example of spin can also be found in The Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate methicillin-resistant *Staphylococcus aureus* (REDUCE MRSA) study's abstract, a study that evaluated the efficacy of unitwide daily chlorhexidine bathing in preventing infections.<sup>9</sup> The abstract stated that MRSA screening and isolation were “implemented” in group 1 and that there was a little reported difference between the intervention and baseline periods in MRSA clinical isolates (3.2 versus 3.4 per 1000 days).<sup>9</sup> This wording may lead one to conclude that screening and isolation were ineffective. However, group 1 was apparently designed for control of secular trends, with screening and isolation being performed in both the intervention and baseline periods. The

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authors of the REDUCE MRSA study agreed in a response letter that their “study provides no information about the absolute effect of screening and isolation.”<sup>10</sup>

### Changing or Not Reporting of Metrics

When additions, deletions, or changes in metrics are made, they should clearly be stated in the manuscript along with justification of the changes. The emphasis of an article can be altered by redefining the primary outcomes. Ramagopalan et al<sup>11</sup> studied 2555 completed interventional trials, which had 1 or more statistically significant primary outcomes and were registered on ClinicalTrials.gov. They observed that statistically significant primary outcomes were associated with changes in primary outcomes recorded on ClinicalTrials.gov after trial completion.<sup>11</sup> In addition, they found that significant primary outcomes were more likely in industry-funded studies.<sup>11</sup>

An example of metric additions and deletions can be found in the REDUCE MRSA study, where the “all-pathogen bloodstream infection” secondary outcome metric was added and the secondary outcome metrics for central line-associated bloodstream infections and urinary cultures were deleted. These changes were recorded on ClinicalTrials.gov for 6 months after the study completion date.<sup>12</sup> (In a clarification, the REDUCE MRSA authors stated, “All secondary outcomes were declared prior to the completion of the trial and prior to performing any analyses.”)<sup>13</sup> More than a year later, the metrics for urinary tract infections and emergence of resistance to mupirocin and chlorhexidine were added along with an explanation for dropping central-line associated bloodstream infections (“...inability to acquire standardized denominators for this measure”). Nine months later, the reasoning for nonreporting of the central-line associated bloodstream infections metric was deleted on ClinicalTrials.gov. The REDUCE MRSA urinary tract infection and emergence of resistance to mupirocin and chlorhexidine results were not available on ClinicalTrials.gov as of February 6, 2016.<sup>12</sup> Any change in metrics after trial initiation can be viewed as possibly having an impact on the overall conclusions proposed by the author.

Urinary tract infection data from the REDUCE MRSA study was published online in *The Lancet Infectious Disease* on November 26, 2015.<sup>14</sup> The data were split with multiple metrics and showed statistical non-significance for the prevention of clinically significant urinary tract bacterial infections in both male and female patients (bacteriuria count having  $\geq 50,000$  CFU/mL).<sup>15</sup> Moreover, there was no significant effect observed in female patients for any measure. The data did reach statistical significance for the composite “any bacteriuria” metric in male patients and for high-level candiduria for both the composite and among males. However, in an accompanying commentary by Rupp,<sup>15</sup> these results have been viewed as having questionable clinical importance. Currently, urinary catheter candiduria or having a bacteriuria count of less than 100,000 CFU/mL is not reportable to the National Healthcare Safety Network.

Unfortunately, the nonreporting of results on ClinicalTrials.gov is not uncommon, despite being required by law for applicable drug and device clinical trials.<sup>16,17</sup> Piller<sup>16</sup> from STAT reported that academic institutions' research results, which are subject to the reporting law, are reported late or not at all to ClinicalTrials.gov 90% of the time. Private industry does not do much better, with their research results being absent on or reported late to ClinicalTrials.gov 74% of the time.

As of February 7, 2016, Compare Project at the University of Oxford has checked 67 clinical trials (published in *The Lancet*, *Journal of the American Medical Association*, *New England Journal of Medicine*, *British Medical Journal*, and *Annals of Internal*

*Medicine*); only 9 were completely compliant; 301 outcomes were not reported, and 357 new outcomes were “silently added.”<sup>18</sup>

### Downplaying of Negative Findings

When a researcher does multiple tests but reports only the statistically significant results in the article's abstract and conclusion, then one could assume that there is not only spin but also an increased likelihood that the “statistically significant” findings occurred by chance alone. Lockyer et al<sup>8</sup> observed that at least 1 nonsignificant finding was present in nearly three quarters of articles without primary outcomes ( $n = 32/43$ ), but a non-significant finding was only found in 28% of the abstracts ( $n = 12/43$ ).

Data dredging is the performance of a single test on different comparisons to find a significant result. An article can then be written that reports only the positive finding. Similarly, different types of tests can be performed on a single comparison in an attempt to reach significance.

By convention, a scientific study achieves statistical significance if the likelihood of the result being caused by chance alone is less than or equal to 1 in 20. This is reported as a test's  $P$  value. A  $P$  value of 0.05 or less is considered significant. However, if a researcher performs 20 tests in an experimental protocol, the chances are that 1 test result will be positive, just by chance alone. If multiple statistical comparisons are performed (multiple looks), the authors should correct the interpretation of the results using a statistical procedure such as the Bonferroni correction, Scheffe method, or Fisher least-significant difference.<sup>19</sup>

### Combining Metrics

Results can be masked or augmented by lumping data from various measurements into a single category. This is of utmost concern if the category is defined and has been registered on ClinicalTrials.gov after trial initiation.

An example can be found in the “any pathogen” category in the REDUCE MRSA study<sup>9</sup> where only a subset of measured bacteria (the more benign or commensal bacteria) seemed to be responsible for a large portion of the significance, and if eliminated, the “any pathogen” category might have become nonsignificant.<sup>20</sup> The authors' reply justified not testing the individual contagions by stating, “We did not test the effect on gram-positive, gram-negative, and fungal pathogens, since such testing was not prespecified in our analysis plan.”<sup>10</sup> The all-pathogen bloodstream infection secondary outcome metric was recorded on ClinicalTrials.gov more than 6 months after the study completion date. (In a clarification, the REDUCE MRSA authors stated, “All secondary outcomes were declared prior to the completion of the trial and prior to performing any analyses.”)<sup>13</sup>

It can also be argued that there is spinning in the abstract conclusion section's description of the “any pathogen” category with the statement that universal decolonization was more effective than MRSA screening and isolation, or targeted decolonization in reducing “bloodstream infections from any pathogen.”<sup>9</sup> The reader may assume that this refers to all pathogens, individually, when it actually seems to be referring to the grouping together of observed effects into the aggregate “any pathogen” category.

Another example is in the Benefits of Universal Glove and Gowning study, which evaluated the efficacy of gloving and gowning on the acquisition of MRSA and vancomycin-resistant enterococci (VRE) in intensive care unit (ICU) patients.<sup>21</sup> The Benefits of Universal Glove and Gowning study was registered on ClinicalTrials.gov approximately 3 months after the study's start date.<sup>22</sup> The study found a lower acquisition of MRSA but not VRE.

The abstract's conclusion stated, “[t]he use of gloves and gown for all patient contact compared with usual care among

patients in the medical and surgical ICUs did not result in a difference in primary outcomes of acquisition of MRSA or VRE.<sup>21</sup> However, as explained in the article's methods section, "The primary outcome was the acquisition of either MRSA or VRE as a composite." The abstract's conclusion did not clearly specify that this metric was a composite measure.

The abstract's conclusion then reported the secondary outcome that MRSA acquisition was lowered but more research was needed. However, according to ClinicalTrials.gov, both the composite and individual measures were defined as primary study outcomes.<sup>22</sup>

It is unclear why the authors defined the individual measures of MRSA and VRE as secondary outcomes in the abstract and then called for a replication of the secondary outcomes to verify the results but did not call for a verification of the composite primary outcome. Arguably, in this case, the use of the composite category overemphasized the negative finding created by the VRE metric.

Another example of combining metrics is the article by Salgado et al,<sup>23</sup> who concluded that copper-lined surfaces can reduce the rates of healthcare associated infection (HAI) in ICUs by more than 50%. However, this study has been criticized for selective reporting and not reporting data for all metrics.<sup>24</sup> Harbarth et al<sup>24</sup> extracted the data for the 2 noncomposite primary outcomes of "any episode of HAI" and "any episode of MRSA or VRE colonization" and concluded that these metrics did not reach statistical significance. In addition, Harbarth et al<sup>24</sup> found a lack of "biological plausibility" in that covering 10% of the surfaces of the ICU would result in a 50% reduction in HAIs. This is inconsistent with the known pathophysiology of HAI transmission where endogenous flora is the major source, and health care workers' hand hygiene alone accounts for 20% to 40% of infections.<sup>24</sup>

### Unknown Validity or Out of Date Methodology

The use of invalid methodology is rare, but the use of methodological applications that are outdated or of unknown validity is relatively common.

An example is the Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Intensive Care Units (STAR\*ICU) study, which was designed to evaluate the clinical efficacy of unitwide MRSA admission surveillance cultures in the adult ICU setting.<sup>25</sup> However, the study used cultures for admission MRSA surveillance instead of rapid or polymerase chain reaction (PCR) testing. It could be argued that the STAR\*ICU study used an outdated methodology, but more accurately, the study could be viewed as outdated. In the almost 5 years between the study's August 2006 estimated completion date and publication in the *NEJM*,<sup>25,26</sup> rapid or PCR testing had increased in both clinical acceptance and use.

An example of technology of unknown validity may be found in the monitoring for reduced susceptibility to the antiseptic chlorhexidine. Cultures and Minimum Inhibitory Concentrations (MICs) have been used to monitor for antiseptic-reduced susceptibility. However, Platt and Bucknall<sup>27</sup> as early as 1988 stated in a letter concerning chlorhexidine that "...with antiseptics, it is dangerous to extrapolate from MIC values to clinical efficacy." More recently, an article by Naparstek et al,<sup>28</sup> 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.

Cultures and MIC testing do not differentiate between inhibition of growth (bacteriostatic effects) and the killing of the bacteria (bactericidal effects). Minimum Inhibitory Concentrations testing

can confirm resistance, but there are concerns on the test's ability to detect susceptibility because bacteriostasis has questionable clinical importance with topical antiseptics. There are few, if any, white blood cells and antibodies on the skin's surface to kill the bacteria, which could possibly reemerge when the antiseptic dissipates. Examples of using MIC testing to monitor for chlorhexidine-reduced susceptibility can be found in peer-reviewed studies by Popovich et al<sup>29</sup> and Climo et al<sup>30</sup> and also in presentation by Haffenreffer et al<sup>31</sup> and Moore et al.<sup>32</sup> Testing for the *qac*-resistant genes, either alone or in combination with MIC or Minimum Bactericidal Concentration testing, may be a more valid technique to monitor for chlorhexidine-reduced susceptibility. The issue is not that a test has been shown to be invalid but that only validated tests should be used in research and to establish standards.

### Suboptimal Interventions

Examples of this can be found in the Swiss-MRSA<sup>33</sup> and the STAR\*ICU Study.<sup>25</sup>

The Swiss-MRSA study by Harbarth et al<sup>33</sup> evaluated the efficacy of MRSA surveillance in surgical patients. However, in this study, less than half (43%) of the 266 patients who were identified as MRSA carriers before surgery received proper prophylaxis for MRSA. Another 120 patients were only identified as carriers after surgery. In addition, it could be argued that the standard of practice may have been violated in 10 patients who developed postoperative MRSA infections who were known MRSA carriers before surgery and did not receive proper perioperative MRSA prophylaxis.

A second example is the STAR\*ICU study's overnighting (6 d/wk) of cultures to the Clinical Microbiology Laboratory of the National Institutes of Health Clinical Center (instead of on-site PCR testing), which caused a 5-day delay in implementing isolation procedures.<sup>25,34</sup> Once implemented, contact precautions were suboptimal with gowns, gloves, and hand hygiene done in 77%, 82%, and 69% of the contacts, respectively.<sup>25</sup>

In both of these studies, it could be argued that effective intervention was given to less than half of the patients in the intervention group.

Finally, the article by Cepeda et al<sup>35</sup> evaluated the isolation of patients in single rooms to prevent the spread of MRSA. The authors were not able to identify a beneficial effect on cross infections of patients. However, the study used what was described as "standard plus precautions," which included the use of aprons instead of gowns and "gloves were not worn for simple comfort contact." Gloves were worn for "invasive procedures, washing and turning the patient, contact with mucous membranes or body fluids, and the disposal of body fluids, whether patients were known to have MRSA or not." Despite the abstract stating that hand hygiene was "encouraged," there was only 21% compliance.<sup>35</sup>

### Conclusion Is Not Supported by the Article's Data or Results

An illustration of the data not supporting the abstract's conclusion may be found in the article published by Horstman et al.<sup>36</sup> The article compared the rates of catheter-associated urinary tract infections determined by using 2 different metrics whose denominators were either device days or bed days. The main article concluded, "Our findings call into question the need to report infection rates with both device days and bed days as the denominator to limit any potential disincentive toward reduced device utilization." Of concern is that this statement seems to be based on comparisons of rates between the same group of hospitals over time where the rate of use did not change substantially. Thus, one would not expect a difference in metrics whose major difference was in how the metrics measured catheter use.

A second example is the contention by Stone et al<sup>37</sup> that the United Kingdom's national Cleanourhands Campaign was the primary driver of the reduction of MRSA bacteremia and *Clostridium difficile* infections. As discussed by Dancer,<sup>38</sup> factors other than hand hygiene alone may also have been involved because there was little change in methicillin-sensitive *S. aureus* bacteremia rates. In addition, there was a concomitant increase in multiresistant *Escherichia coli* for the same period.<sup>38</sup> Thus, it can be argued that this is an example of assuming that correlation is equivalent to causation. A more accurate interpretation of the results may be that targeted bundled approaches including screening and isolation for control of MRSA, deep hospital room cleaning, and antibiotic stewardship for the control of *C. difficile* were responsible for the observed reduction in MRSA but clearly had little effect on methicillin-sensitive *S. aureus* and multiresistant *E. coli*.<sup>38</sup>

A third example published by Jinadatha et al<sup>39</sup> evaluated the use of a pulsed Zenon UV light's effectiveness on the elimination of MRSA in the absence of manual cleaning. They concluded that their study suggests that MRSA colony counts are effectively reduced in the absence of manual disinfection. However, in the methodology, it is stated that "if visible soiling was observed, the samples for that surface were taken adjacent to the soiling." They also removed a significant outlier from their analysis because of "cross-contamination."

The effectiveness of any disinfectant is inversely proportional to the amount of debris on a surface.<sup>40,41</sup> The elimination of soiled surfaces from the study might be considered an acknowledgement by the authors that manual cleaning is necessary.

Other illustrations of unsupported conclusions may be found in three articles which appear to attribute the clinical efficacy of chlorhexidine and alcohol solutions to chlorhexidine alone.<sup>42-44</sup> Two of these articles compared chlorhexidine plus alcohol to iodine in the reduction of infectious disease, and then appear to attribute the findings to chlorhexidine alone in the studies' abstracts; a lopsided two against one comparison.<sup>42,44</sup> One of these articles also made this attribution in the body of the manuscript.<sup>44</sup> These articles along with others have led to a common misconception that chlorhexidine was the only active agent in alcohol combinations and an overestimation of the efficacy of chlorhexidine compared to other antiseptic products.<sup>45</sup>

### Controlling of Variables and Complex Statistical Tests

If not performed correctly, statistical testing and regression modeling can also create bias. Which variables are included in a regression model and analysis of variance testing, along with the inclusion criteria and weighting of studies for a meta-analysis, can skew the final results. Ideally, this information should be entered into ClinicalTrials.gov before study initiation.

An example of a meta-analysis with questionable inclusion criteria and conclusions is by Noorani et al,<sup>46</sup> who concluded that chlorhexidine was superior to povidone iodine in preoperative antisepsis but did not control for 2 (chlorhexidine plus alcohol)–versus–1 (povidone iodine) comparisons.<sup>47</sup> Another confounding issue with meta-analyses is that entire manuscripts may not be available for inclusion because of publication bias and the reluctance of both authors and journals to submit and publish negative results.

### Selective Reporting of the Literature

This is a factor in review articles, manuscript discussions, and meta-analyses. An example would be if one tried to support or refute standards of care on the basis solely of the information contained in our article. Our article is not designed to establish standards of care dealing with topics of surveillance, chlorhexidine bathing, or methods of testing for resistance. For example,

there is good evidence and logic behind using chlorhexidine (because of its longer action) plus alcohol to prevent infections associated with long-term device placement such as central lines.<sup>48</sup> The main objective of our article was to discuss how to detect problems of research integrity. A more comprehensive review would be required to set or refute a standard of care.

### CONCLUSION

There is mounting evidence that the medical literature has played up false uncertainty regarding the use of MRSA surveillance and overstated the effectiveness of chlorhexidine. Multiple and even large studies regarding surveillance have been all but dismissed for not controlling for secular (temporal) trends.<sup>49</sup> The dismissed reports are largely preintervention and postintervention studies. The concern is that some other unknown factors, which were not controlled for, may have created the significant finding. When this argument is applied to a single study, it is a cautionary note, but when applied to 30 plus studies, all of which have similar conclusion, the concern becomes less valid because unknown variables may bias a study in either direction. When multiple studies observe the same effect, the conclusion is more likely to be valid.

A preponderance of evidence is needed to form or deviate from a standard of care. For example, surveillance for MRSA carriers was an accepted standard of care in the United States before 2003.<sup>50</sup> This standard was deviated from using evidence based on the presence of nonharmonious results generated by different authors.<sup>49</sup> However, this is the nature of today's peer-reviewed literature. Policy makers will need to be able to differentiate between the reliability of the conclusions found in various studies and to formulate recommendations in the face of seemingly contradictory results.

It is difficult to determine with certainty what the driving force is behind the aberrations in any single article. Conflicts of interest (COIs) are possible explanations underscoring the necessity of candid disclosure. A 2007 study published in *JAMA* found that 60% of department chairs and 67% of academic departments reported a relationship with industry.<sup>51</sup> Observations regarding research integrity and their relationship to COIs are sound counterargument to a recent *JAMA* commentary, which seems to normalize COIs by renaming it "confluence of interest."<sup>52</sup> When questions arise regarding a study's methodology or conclusions, COIs become of utmost importance. Patterns of bias can then be found between multiple studies and authors. Such a study was undertaken by the Cochrane Center and reported that industry-sponsored studies lead to more favorable results than those sponsored by other sources.<sup>53</sup>

Many of the previous articles have more than 1 type of integrity issue, which makes categorization difficult. This underscores the magnitude of the problem in the infectious disease literature. Scientists and researchers are encouraged to plan, execute, and report their research correctly.

Registration of trials on ClinicalTrials.gov along with the archiving of the research data for public access is of utmost importance. Wicherts et al<sup>54</sup> observed that the reluctance to share data was associated with weaker evidence and apparent errors in describing statistical findings.

Adequate analysis of studies may take many hours to correctly unravel. Even then, these studies may still be confusing. As a rule, if one cannot easily understand an article's logic, then the study may be spun. The state of the current scientific literature makes it imperative to read all sections of the article along with any letters to the editor and to check the information recorded on ClinicalTrials.gov before formulating a final judgment regarding a researcher's recommendations and conclusions.

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