Prevention and Control of Methicillin-Resistant *Staphylococcus aureus* (MRSA): Biology, Research, and Intervention

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We live at a time of infectious disease threats from increasingly resistant bacteria that encompass what are referred to as multidrug-resistant (MDR) pathogens. These organisms have arisen in many parts of the world and then spread globally. When they cause clinical infection, the result is difficult-to-treat disease, leading to increased mortality and healthcare cost. The World Health Organization states that people infected with methicillin-resistant *Staphylococcus aureus* (MRSA) are 64% more likely to die than those whose disease is due to a sensitive variety of *S. aureus*.[1] If no action is taken, a conservative estimate is that by 2050 there will be 10 million annual deaths from antimicrobial resistant infections worldwide; this will be the leading cause of mortality with an economic cost exceeding $100 trillion each year.[2] Thus, it is imperative that we understand the biology relating to emerging resistance and spread of these organisms so that effective control strategies can be developed and deployed. Peterson and Schora recently reviewed the large studies performed whose main goal was to reduce MRSA infection.[3] From their analysis it appears that active surveillance testing (e.g., screening) is invariably linked to a successful program if the goal is very low rates of MRSA clinical disease and they proposed threshold targets for determining a successful program (Table 1).[3] In this review all the successful programs used real-time PCR (qPCR) as the laboratory screening test. However, much debate remains over the 'best' approach for control of MDR pathogens, with hand hygiene consistently stressed as the best core measure to effectively control all healthcare associated infections (HAIs).[4] However, when the impact of enhanced hand hygiene was prospectively studied in a multicenter trial, there was no impact on MRSA clinical disease.[5] For the understanding of MDR pathogen control, it is prudent to understand the biology of antimicrobial resistance development and spread in key pathogenic bacteria so as to devise solutions likely to be effective in preventing such events. The purpose of this commentary is to *i*) briefly describe biologic traits of MDR pathogens that influence what control measures are likely to be effective, *ii*) discuss key literature issues that contribute to controversy regarding best infection control practices for MRSA, and *iii*) present the argument that setting clinical disease threshold goals may be preferable to mandating process measures for solutions for MDR infection prevention.

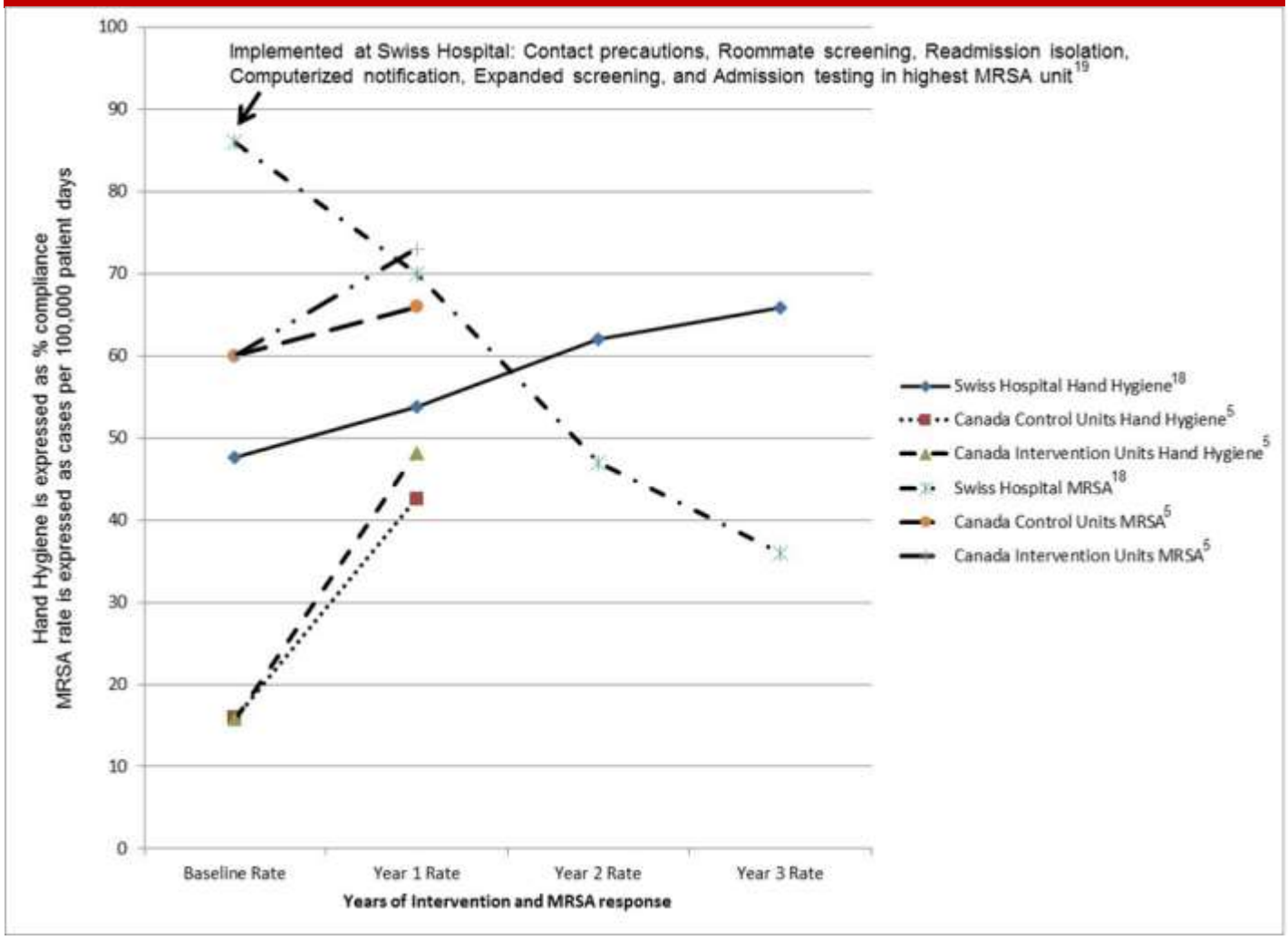
Antimicrobial resistance generally depends on two key elements, the first being loss of susceptibility to a therapeutic agent, occasionally during treatment, by either selection of resistant strains or the mutation/acquisition of genes coding for new resistance trait(s). This is followed by the second element of subsequent dissemination of the adapted organisms to additional persons locally, regionally, and globally.[6] While

Table 1. Recommended thresholds that if not met should trigger more intensive efforts for MRSA control.[3]

	Clinical Cultures	Blood Cultures
Target Rate	<0.3/1,000 patient days	<0.03/1,000 patient days

intervening in this MDR problem seems straightforward, it is critical to understand how these elements (MDR development and dissemination) interact in order to optimize the design of control strategies. In general, Gram-negative bacteria tend to have high genome plasticity and are capable of frequent new resistance acquisition (e.g., panmictic evolution) - they are currently considered a great MDR threat.[7-8] For this setting, antimicrobial stewardship can be critical in preventing the development of new resistance while infection control barrier precautions may be less important (e.g., to prevent spread) unless a particularly virulent clone(s) arises.[9] Conversely, Gram-positive MDR bacteria tend to be highly clonal,[10-13] with less ongoing emergence of new resistant strains, and are typically effectively managed using infection control surveillance with contact precautions (e.g., isolation) for those found harboring these strains.[14] MRSA is a good example of this MDR problem where spread of resistant strains is common (clonal evolution), with only 10 clonal complexes, or lineages, of *S. aureus* dominating in human disease and eight of these acquiring the mobile genetic element (e.g., staphylococcal cassette chromosome (SCC) that carries either *mec*A or *mec*C (SCC*mec*)) coding for methicillin resistance.[12-13, 15] Preventing infections from MDR bacteria with a clonal biology background seems best approached by preventing horizontal dissemination through use of infection control isolation often called 'barrier precautions'.[3, 14] A third avenue for outbreaks of nosocomial MDR bacterial infection is by dissemination from an environmental reservoir, or point source within the hospital setting. These events are less common, but when they occur require a diligent search for the source of the MDR pathogen followed by its elimination.[16] The point of this

Figure 1. Comparison of two hand hygiene investigations on MRSA control



discussion being that it should be expected that varying infection control practices will be needed in order to contain and prevent the differing types of healthcare-associated infections encountered within the acute care setting. Thus, it is unlikely that a single 'one size fits all' approach will be successful for comprehensively preventing HAIs when planning the best practice(s) to improve patient safety.

A reasonable question is, "Why is there no consensus on how to reduce MRSA infection and what is the reason(s) for the divergent literature?" An interesting commentary was recently published by Kavanagh and colleagues.[17] They make the case that when one reads the Infectious Diseases literature it is important to carefully examine the entire report as the data is not always fully represented by the abstract and discussion sections. While one could argue with the authors' assessment, it is helpful to consider their argument when the issue of MRSA control is discussed. For example, perhaps the critical report most cited to make the case for hand hygiene as the mainstay in MRSA control is that from Pittet et al.[18] This investigation concluded that "the (hand hygiene) campaign produced a sustained improvement in compliance with hand hygiene, coinciding with a reduction of nosocomial infections and MRSA transmission", but, as is the case with many Infection Control studies, more than one intervention was occurring at the same time. In this case, at the introduction of the hand hygiene intervention campaign, the hospital center also implemented contact precautions for MRSA positive patients, roommate screening for patients found to be positive, readmission isolation for known MRSA positive patients, computerized notification of nursing units as to patient MRSA status, expanded screening for MRSA carriers, and admission active surveillance testing in the highest MRSA unit.[19] The report describing this separate but simultaneous intervention concluded that 'infection control measures had a substantial impact on both the reservoir of MRSA patients and the attack rate of MRSA bacteraemia.[19] Separating the impact of enhanced hand hygiene from these other infection control measures is challenging at best.

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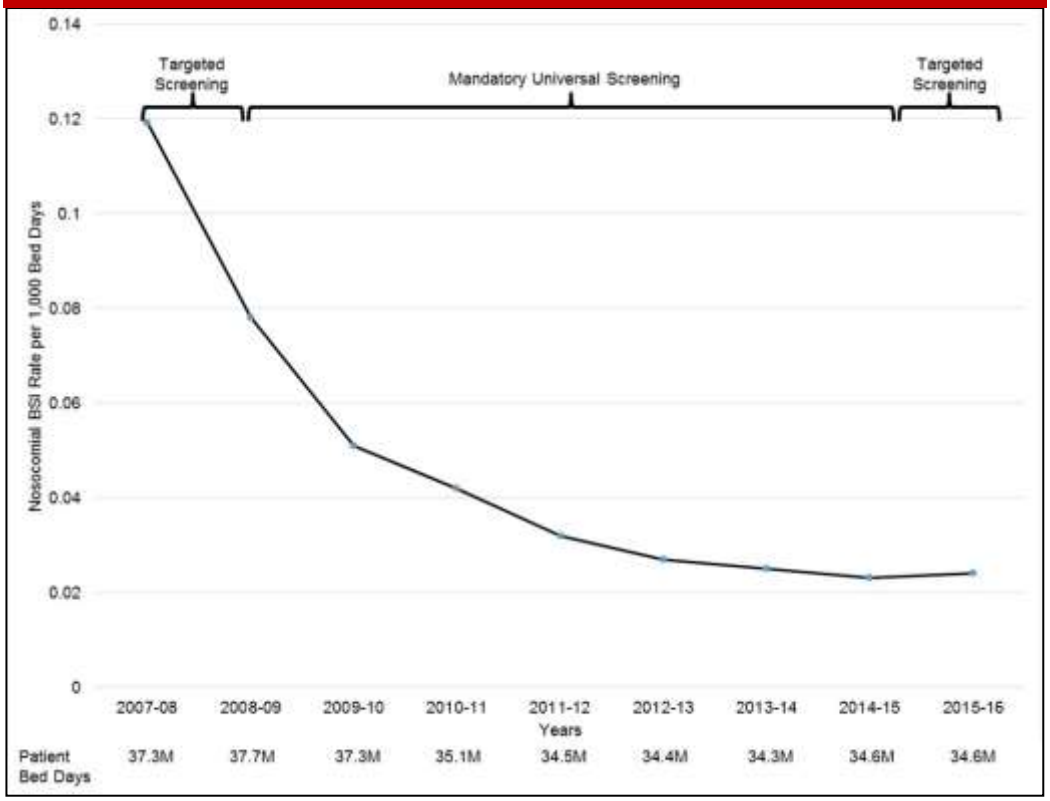
Another investigation was a prospective, cluster-randomized trial on the impact of improved hand hygiene on MRSA infection.[5] They found that even with a statistically significant improvement in hand hygiene, MRSA colonization was not reduced. A comparison of the results of these trials is in Figure 1, which demonstrates the complexity of interpreting published literature as well as the conflicting results.

A final report in this context is that from Grayson and colleagues who found that improving hand hygiene from 21% compliance to 48%/47% after 12 and 24 months, respectively, reduced MRSA clinical isolates from 139 positives per 10,000 patient discharges to 73, and reduced MRSA bacteremia from 5 cases per 10,000 discharges to 2 ($P \leq .035$ for MRSA trends).[20] This report suggests that hand hygiene improvement can modestly impact MRSA disease, particularly if clinical infection rates are high – but the final disease rate remained above the thresholds recommended in Table 1. A recent critical review of the topic concluded that "interventions to improve hand hygiene may reduce the incidence of HAIs and improve hand hygiene rates, but the quality of evidence is low".[21] All this suggests that hand hygiene alone cannot control MRSA.

As noted earlier, our recent review of large studies that focused on MRSA control concluded that active surveillance testing was part of all successful programs achieving a very low MRSA infection rate. We suggested that a key change in concept for policy makers, healthcare societies, and public health organizations would be to set threshold targets for levels of MRSA disease that were achievable, rather than mandating specific infection control processes – thus encouraging both historic and novel practices that can include expanded isolation, qPCR, and new technology.[3] The MRSA

Figure 2. MRSA hospital-acquired blood stream infection rates in British healthcare



clinical disease threshold targets we suggested were very low, but are based on disease rates from large published studies (Table 1).[3] One data set not included was from the English National Healthcare System that undertook a country-wide program to reduce MRSA bloodstream infection (MRSA BSI).[22] Over 9 years, which included nearly 320 million patient days, they achieved a large (>4-fold) reduction in MRSA BSI (Figure 2). In this program, while active surveillance testing was primarily performed using chromogenic agar culture;[23] their outcome suggests that a comprehensive, all inclusive, national program using active surveillance testing can detect the majority of MRSA colonized patients needing contact precaution isolation whenever in the hospital. This program was associated with a significant and meaningful reduction in MRSA blood stream infections that met the threshold suggested in Table 1. These results indicate a large national program achieving a very low rate of MRSA clinical disease remains achievable.

The United States has experienced a tortuous evolution in dealing with the significant threat of MRSA.[24] It is time for policy makers to take a new approach to elimination of this disease threat. MRSA infection remains one of the most cost-effective diseases to prevent, where the cost of treating MRSA clinical infection far exceeds the expense of prevention.[3,25-27] Solving this challenge will provide benefits of enhanced patient safety, healthcare quality, and reduced cost. Setting of acceptable MRSA clinical disease thresholds can be the 'winning' approach to this challenge in a society that embraces options and choices. Either penalizing hospitals for not achieving MRSA clinical disease goals, or rewarding those that do – or a combination of both – is a strategy that can facilitate reduction in MRSA disease and inspire innovation. Now is the time for U.S. policy makers to take patient safety seriously and embrace MRSA infection as a problem that can be solved.

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