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REVIEW

The relationship between hand hygiene and health care-associated infection: it's complicated

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Abstract: The reasoning that improved hand hygiene compliance contributes to the prevention of health care-associated infections is widely accepted. It is also accepted that high hand hygiene alone cannot impact formidable risk factors, such as older age, immunosuppression, admission to the intensive care unit, longer length of stay, and indwelling devices. When hand hygiene interventions are concurrently undertaken with other routine or special preventive strategies, there is a potential for these concurrent strategies to confound the effect of the hand hygiene program. The result may be an overestimation of the hand hygiene intervention unless the design of the intervention or analysis controls the effect of the potential confounders. Other epidemiologic principles that may also impact the result of a hand hygiene program include failure to consider measurement error of the content of the hand hygiene program and the measurement error of compliance. Some epidemiological errors in hand hygiene programs aimed at reducing health care-associated infections are inherent and not easily controlled. Nevertheless, the inadvertent omission by authors to report these common epidemiological errors, including concurrent infection prevention strategies, suggests to readers that the effect of hand hygiene is greater than the sum of all infection prevention strategies. Worse still, this omission does not assist evidence-based practice.

Keywords: compliance, epidemiological principles, study design, bacteria, control, multiple drug resistance

Background

History of the leading guidelines

The mid-19th century work of Labaraque,[1] a pharmacist, and Semmelweis,[2] an obstetrician, provided powerful historical support for the hypothesis that clinicians' hands carried pathogenic organisms that could be transmitted to susceptible patients who subsequently developed infection. By the late 20th century, evidence was mounting about the risk to patients from transient pathogens on health care workers' (HCWs') hands.[3–6] A handwashing guideline was developed by the Centers for Diseases Control (CDC) in 1975[7] and updated in 1985.[8] The CDC recommended nonmedicated soap and water for routine hand-washing and medicated soap and water hand-washing prior to invasive procedures.[8] Alcohol-based hand rub (ABHR) was indicated when soap and water washing was unavailable.[8] The Association for Practitioners in Infection Control produced a hand hygiene guideline in 1988, updated in 1995, which, for the first time, explicitly recommended HCWs use ABHR on leaving a patient's room.[9] In 2002, CDC hand hygiene guidelines provided evidence for the transmission of pathogens on hands, models of transmission, the association between hand hygiene and reduced risk

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of transmission of health care-associated infections (HAIs), and the actions and efficiency of hand hygiene agents.[10] This guideline was developed in collaboration with the Healthcare Infection Practices Advisory Committee (IPAC), the Society for Hospital Epidemiologists, and the Infectious Diseases Society of America. In 2009, the World Health Organization (WHO) launched the "Clean Hands Save Lives" campaign with the release of a guideline.[11] The guideline was developed with the aim that the content was to be appropriate for a wide range of resourced health care settings. Hand hygiene with ABHR was now specifically recommended for routine use within a new paradigm of indications, "My five moments for hand hygiene".[12] These five indications were chosen to maximize the interruption of the transmission route of pathogens: two before patient contact, two after patient contact, and one after contact with the patient's zone. An additional goal of the guidelines was to standardize hand hygiene training and provide the first standardized tool for the collection of hand hygiene compliance data to reduce inter-rater bias during the human auditing process.

As countries made pledges to the Clean Hands Save Lives campaign post its 2009 launch, a flourish of national or statewide hand hygiene awareness and improvement interventions ensued, including those in Australia,[13] the United Kingdom,[14] Italy,[15] Mali,[15] Pakistan,[15] Saudi Arabia,[15] and the United States.[16] During this period, other infection prevention strategies were implemented in highly resourced health care settings nationally or statewide.[17–24] These strategies include the reformist approach of packaging many infection prevention strategies of varying levels of evidence for prevention, which is referred to as a "bundle", and all elements of the bundle that must be complied with. Bundles have been developed for ventilator-associated pneumonia,[25] catheter-associated urinary tract infection,[26] and central-line-associated bloodstream infection (CLABSI),[27] which are widely adopted outside the US.[21–24,28–34] These bundles include hand hygiene. Effective singular infection prevention approaches that have been adopted include aseptic insertion of peripheral venous catheters,[27] chlorhexidine baths to reduce the incidence of CLABSI in intensive care units (ICUs),[35,36] hospital-wide antibiotic stewardship,[37] hospital-wide environmental cleaning,[38,39] isolation,[40] screening, and decolonization regimes,[14,41,42] and surveillance.[43,44] Therefore, it would be unusual for a hand hygiene intervention in high-resourced health care settings[45] to have been initiated in the absence of multiple concurrent infection strategies that would include bundles or several singular infection prevention strategies.[13,14,46,47]

Prior to the WHO guideline[11] release, two tertiary hospitals in the US evaluated the impact of an active methicillin-resistant *Staphylococcus aureus* (MRSA) screening of all ICU admissions. The hospitals also experienced multiple concurrent infection prevention strategies including the 5 Million Lives Campaign, surgical infection reduction initiatives, Keystone ventilator and central line bundles, and a CDC-led hand hygiene campaign.[44] The screening program commenced when hand hygiene compliance rate reached >70%, and after 6 months the ventilator-associated pneumonia rate reduced from 0.954 days to 0.171 per 1,000 patient-days and the bloodstream infection (BSI) rate from 0.219 to 0.128 per 1,000 patient-days.[44] The reduction in infection may have been the effect of screening or due to other singular or multiple strategies including high hand hygiene. Alternatively, the effect may have been an additive effect between hand hygiene and the other concurrent infection control strategies.

In response to the WHO guideline that was released in 2007 and since the final version was released in 2009, a plethora of hygiene campaigns have been published.[47,48] Yet, rarely have individual publications that report on national or local success in reducing HAIs considered the confounding impact of concurrent infection prevention activities in their health care settings on HAI rates. Powerful drivers for the implementation of multiple infection prevention strategies that could distort the effect of hand hygiene include expectations,[43] the need to reduce the cost associated with HAIs,[49] and pressure of public reporting of key performance indicators that may not have been fully validated or adjusted to allow sound comparisons to be made with prior rates.[50,51]

An overview of important epidemiology principles that can adversely impact the results is given below and will use hand hygiene compliance and HAI as examples. A selection of papers published after the WHO guideline was released in 2009, mostly national interventions or multicenter, will be used to illustrate how errors in the application of these principles may impact hand hygiene campaigns that attempt to directly link hand hygiene improvements with reduction in HAIs. These papers are used to discuss the inability to disentangle a posteriori the effect of one or more bundled or singular infection prevention strategies from the effect of a hand hygiene program on HAI rates.

Epidemiological principles and pitfalls of hand hygiene research

Errors inherent in study designs

Cost-effective study designs to test the impact of the provision of ABHR at point of care, hand hygiene education, antibiotic stewardship, and environmental cleaning on HAIs include the experimental design of randomized control trial (RCT) and quasi-experimental designs such as Before-Intervention-After (B-A), time series, and cohort.[52] It is ethically difficult to justify the RCT design unless the passive arm of the trial includes an alternative intervention. Similarly, cohort design requires two intervention groups with a follow-up period for infection and extrinsic risk data collection. A period for follow-up is typically restricted to less than 24 months because of resource costs. The pitfall in a cohort or RCT design with a short follow-up period in a high resourced ward or hospital is that the number of HAIs will be small after stratifying by each level of intervention. This makes it difficult to identify a statistical difference for HAI rates associated with the hand hygiene intervention groups. The use of B-A design has the advantage of having a high probability of sufficient numbers of HAIs in the entire before- and the entire after-period to establish a statistical difference. There may be the potential for intrinsic risk factors for infection to be different in the patient populations during the two periods. However, the likelihood that the level of intrinsic risk factors for HAIs being significantly worse during the before period is extremely low. With the small number of HAIs that remain after stratifying by two different arms of a prospective concurrent intervention, the B-A and time series designs are the logical choices. However, there are other important epidemiologic pitfalls that are inherent in all study designs, including measurement error, short follow-up periods, and the confounding of the effect of a study factor due to concurrent infection strategies.

The epidemiologic principle of measurement error

Measurement error is an important epidemiologic principle[52]concerned with the unintended variation in the measurement of the exposure factor, sometimes referred to as the "study factor" or "predictive variable". Measurement error can also occur in the measurement of the outcome factor. If a hand hygiene intervention uses online education components and in-service training sessions to improve hand hygiene compliance, then the education material and method is the exposure/study factor and compliance is the outcome factor. Alternatively, if improved hand hygiene is examined as a causal factor for the reduction in HAIs, then hand hygiene is tested as the predictor (study factor) of HAIs (outcome factor). Unacknowledged measurement error in either the study factor or outcome factor may cause the hypothesis that the study factor (intervention) caused the outcome factor (increase in hand hygiene or decrease in HAI) to be incorrectly accepted.

To answer whether there was measurement error in the study factor, ask of the paper "Was exposure to the study factor (eg, intervention) defined?" Exposure to the study factor should be defined and used to determine whether the participants received the study factor in full or in part, such as attendance to all online learning components and in-service training sessions. "Have participants been correctly categorized as being exposed or not exposed to the study factor?" and "Did every participant receive the intervention in a consistent manner during the intervention period?" will provide information about whether the researchers measured exposure or simply assumed exposure. In the absence of evidence that participants were exposed in accordance with the definition, one must assume that measurement error of participants' exposure to the study factor has possibly occurred. We must then decide how seriously this measurement error will impact the validity of the outcome.

To answer whether there was measurement error of the outcome factor, ask the paper "Was outcome defined?" This question will answer whether the definition of compliance was simply the observation of a sample of HCWs using ABHR in accordance with the Five Moments or whether they were also required to use the correct technique while performing hand hygiene. "Was the definition applied consistently to all HCWs observed by the rater (eg, auditor)?" will answer the level of intra-rater reliability of the measurement by the one auditor. "Was the outcome factor measured consistently over time by all the different raters (eg, auditors)?" will answer the level of inter-rater reliability of the measurement between multiple auditors to consistently apply the definition of hand hygiene and therefore correctly categorize HCWs into compliers and noncompliers.

Implications of measurement error

A hand hygiene intervention may not always result in a reduction in HAIs due to failure of full saturation of the exposure factor, eg, the intervention message. The Australian National Hand Hygiene Initiative commenced in 2009 and required HCWs at 521 hospitals to have undertaken and understood the online education about My Five Moments and attended in-service training (study factors).[13] However, the extent of exposure of HCWs to information on My Five Moments[12] or their level of understanding of these indications has not been publically reported. After 2 years, hand hygiene compliance increased from 43.6% (6,431/14,740 moments) to 67.8% (106, 851/157,708)

($P<0.001$).[13] However, this improvement did not affect the outcome factors (hospital-onset [HO] bacteremia) over this period for hospital-onset *S. aureus* bacteremia (HO-SAB) ($P=0.59$), HO-methicillin resistant *S. aureus* (HO-MRSA) bacteremia ($P=0.58$), and HO methicillin-sensitive *S. aureus* (HO-MSSA) bacteremia ($P=0.30$). Only after combining the rates of HO-MRSA with non-hospital-onset MRSA bacteremia was a statistical difference identified ($P=0.008$). These results suggest that measurement error has occurred in the study factor (hand hygiene) or in the outcome factors (HO-SAB, HO-MRSA, HO-MSSA), or the validity of the outcome factor (combining HO- with non-HO MRSA), or that the study factor was not associated with the outcomes. Error associated with measuring HO-MRSA is small, as the microbiological test before and during the study period is likely to be applied in a standardized method. Therefore, the most likely explanation is that error in measuring the study factor (hand hygiene) produced an overinflated rate of improvement or that the study factor was not associated with this particular outcome factor.

Direct observation and electronic monitoring of dispensers of hand hygiene solution produce different number of opportunities for hand hygiene and compliance rates.[53,54] The direct observation method may produce an unquantifiable proportion of compliance, which is due to the Hawthorne effect.[53] Hand hygiene may not always produce the positive impact we expect if the Hawthorne effect causes high compliance rates that are not sustained after the audit period. Hand hygiene compliance (study factor) was not predictive of a resolution of an outbreak (outcome factor) even when the median hand hygiene compliance rate prior to the outbreak was 100% and compliance in response to the outbreak was equally high, 98% ($P=0.93$).[55] The outbreak in the presence of very high hand hygiene compliance is counterintuitive unless the compliance rate (study factor) prior to the outbreak was falsely high due to measurement error, specifically the Hawthorne effect. Alternatively, improved surveillance of multiple drug resistant organisms (MDROs) during and after an outbreak may identify more MDROs during the outbreak, making hand hygiene compliance appear ineffective. Publication bias toward positive results prevents readers from knowing that surveillance bias occurs frequently.

Other measurement errors

Short duration of follow-up of a newly acquired behavior may falsely classify the actor as highly compliant when there has been insufficient time for the new behavior to be validated. In the case of hand hygiene, if the follow-up period is too short and the new level of compliance may be difficult to sustain without a maintenance stage,[56] then measurement error will occur. According to the "transtheorectical model",[56] there are five processes of change or stages before a new behavior can become embedded. Helder et al[57] understood that human behavior often returns to a comfortable pre-intervention level when they introduced a sequential hand hygiene campaign over a decade. A reduction in BSI (outcome) was achieved between 2000 and 2011,[57] and the follow-up period of a decade was extensive to allow for improved hand hygiene behavior to become embedded. However, when direct observation is used, there will always remain the possibility of overestimation of hand hygiene compliance due to the Hawthorne effect (measurement error).

The WHO guidelines[11] provide a hand hygiene compliance audit tool for ABHR or soap and water use and instructions for the technique of hand hygiene.[11] The audit tool does not include a measurement of the hand hygiene technique.[11] The correct hand hygiene technique requires the actor to perform seven poses while using ABHR: rubbing palms together in a circulation motion, fingertips moving in circular motion on the palm of the opposite hand, palm to palm with fingers from opposing hands interlocking, four fingers grip interlocking four fingers on the opposing hand, palm of hand onto the back of the opposing hand with fingers between fingers, rubbing thumbs, rubbing wrists. Ineffective hand hygiene technique may result in a hand hygiene intervention failing to affect the rate of MDROs.[58] The effectiveness of hand hygiene with ABHR to remove MRSA from fingertips relies on the technique of several of the above poses during approximately 20 seconds of rubbing. After contact with patient's environment, 10% of HCWs tested positive for MRSA on their fingertips of whom 41% had used ABHR or chlorhexidine soap wash.[59] When the aim of an intervention is to reduce HAIs (outcome factor) through hand hygiene (study factor), then the definition of hand hygiene may need to consider the inclusion of the technique.

Insufficient volume of ABHR can also impact the effectiveness of hand hygiene (study factor) on the recovery of pathogenic microorganisms on HCWs' hands (outcome factor). The European Norm (EN) 1500 is a standard used to approve ABHR for use in the health care setting. The volume of ABHR affects the EN 1500 pass criterion requiring a log10 reduction of microorganisms from hands. At least 2.5–3 mL of ABHR is required to achieve microorganism reduction in accordance with EN 1500.[60] Log reduction increases with the volume of product, but it plateaus when too much product is used. When ABHR (study factor) is linked to log reduction of microorganisms (outcome factor) from HCWs' hands, then the method of recovery of the microorganism and the choice of MDRO must not adversely impact the measurement of the outcome factor. The glove juice method of immersing the whole hand to recover MDROs[61] is superior to swabbing hands or fingertip plate method, but it is not always used. When MDRO isolation is restricted to just MRSA (outcome factor), low yields similar to the normal fingertip plate method are produced.[59,60] Poor association between infection rates (outcomes) and hand hygiene (study factor) may be the result of these errors.

Infection control strategies can impact the outcome or act as a proxy for the outcome (ie, directly or indirectly increase or decrease the outcome), and when these strategies are not the study factor of interest these strategies become potential confounders. Potential confounders have the ability to under- or overestimate the effect of the current study factor of interest.[62] Environmental cleaning, cohorting patients, and hand hygiene are classic responses to an MDRO outbreak. In fact, it would be unethical not to implement a bundle of interventions where patients' welfare and, indeed, lives are at stake. Unfortunately, this confounds the ability to elucidate which element of the bundle worked and which did not. Collection and discussion of confounders in multicenter sites is rare in hand hygiene interventions.[63–66] Confounding may have occurred during routine ICU surveillance between 1997 and 2010 in European hospitals.[67] Infections remained stable or trended down, but device utilization also declined.[67] The effect of surveillance on the downward trend in infection can be determined if the effect of the potential confounder (reduction in devices utilization) is controlled for in the study design or adjusted during analysis.

During a hand hygiene campaign, change to common risk factors for HAIs extrinsic to the campaign that may contribute to the improvement in MDRO rates are referred to as "potential confounders" until the effect of these factors are controlled by design or adjusted by analysis. New or reinvigorated infection prevention activities in the intervention ward or elsewhere in the hospital are potential confounders and include the following:

- improved surveillance definition,
- improved recovery methods for MDROs,
- improved appropriate local antibiotic prescribing practices,
- improved management of prophylaxis administration that includes correct time for initiation and correct duration,
- improved bed management,
- improved nurse-to-patient ratio,
- change in bed occupancy,
- change in diagnostic related groups (DRGs),
- screening for MDRO on admission with preemptive isolation,
- isolating or cohorting MDRO,
- adherence to new infection prevention bundle,
- timely removal of peripheral intravascular devices and removal of central venous catheters (CVCs) on discharge from ICUs, and
- new environmental cleaning regime or adherence to the cleaning schedule.

Evidence for the success of a hand hygiene program requires consideration of measurement error of hand hygiene and infection rates and measurement errors of other factors and potential confounders that are extrinsic to the hand hygiene program, as listed above. Post hoc failure to consider concurrent infection prevention strategies other than the hand hygiene intervention is discussed in the next section.

The inability to disentangle a posteriori effects of multiple infection prevention strategies

The launch in 2004 in the United Kingdom of a national MRSA screening program (study factor) was refreshed in 2006 and reviewed for success in 2008 and was identified as a national success.[68–70] Patients who were initially screened on admission were considered to have a higher risk of MRSA, and included certain emergency admissions and elective surgical procedures, renal patients, previously MRSA-positive patients, cancer patients, and patients admitted from residential aged care. The program resulted in significant declines in rates for MRSA (1.88–0.91/10,000 bed-days) and *Clostridium difficile* infection (CDI) (16.75–9.49/10,000 bed-days), but not MSSA bacteremia (outcome factors).[14] A reduction in infections for at least two quarters was attributed to visits by the Department of Health improvement teams to Trust hospitals.[14] The visits were either a potential confounder of the study factor if the authors were only interested in the effect of screening, or visits acted as a potential interaction term, increasing the effect of screening. There were other patient-safety activities (potential confounders) during the screening campaign, including the Cleanyourhands campaign in 2004 and the Saving Lives campaign in 2005[14] and an announcement by the Department of Health in late 2005 that all Acute Trust hospitals were to halve the rate of MRSA bacteremia.[71] During the Cleanyourhands campaign, the purchase of soap and ABHR trended up in the first 4 years, and by 2008 the product usage had tripled compared with procurement at baseline.[14] The amount of ABHR procured was associated with a significant decline in MRSA bacteremia and CDI, but only after 4 years when other multiple campaigns were also implemented. Therefore, ABHR procurement is a study factor when examined alone or as a potential confounder of screening if the aim was to establish the effect of screening on infection reduction alone. However, the contribution of each on reducing infection can be established during analysis if data for each potential confounder are measured.

After the early years of the Cleanyourhands campaign, the rate of MRSA bacteremia rate for 2005–2006 was 1.88 per 10,000 bed-days and fell to 0.91 per 10,000 bed-days by 2008.[14] The rate of CDI infection fell from 16.75 in 2004 to 9.49 per 10,000 bed-days by 2008. By 2011–2012, MRSA rates were further reduced by 18% to 0.32 per 10,000 bed-days.[69] A national 1-week prevalence survey in May 2011 found that 86% (144/167) of Trust hospitals were complying with screening (study factor): 61% of all emergency surgical admissions, and 81% of elective surgery admissions.[72] The directive of preemptively isolating patients before the results (study factor) were known was complied by just 16% of patients screened on admission, but just over half, 55%, of MRSA-positive patients were isolated after results were known. By 2011, colonization on admission was lower, 1.5%, than previously identified at 2.4% in emergency admissions,[73] and MRSA bacteremia declined between April 2009 and June 2011 by 38%.[74] Between 2010 and 2014, the pattern in declining numbers of positive screened admissions continued and was attributed to a general decline of MRSA in England.[74] The impact of universal screening on MRSA bacteremia rate was impressive, with rates declining even further from 1.24 per 100,000 bed-days in 2013 to 1.14 per 100,000 bed-days in 2014. The halving of the CDI rate could have been assisted by the isolation of patients when they screened positive for MRSA. Screening and isolation did not affect MSSA bacteremia, which remained stable, between 7.73 and 7.9 per 100,000 bed-days.[74] Universal screening and Cleanyourhands were concurrent study factors, and the authors acknowledged that to disentangle the multiple components of the screening program from hand hygiene was difficult.[14,69] Results from the multiple strategies was considered to result in a "heroic national effort" but the authors overtly acknowledged that a 50% plus reduction in MRSA over a 2-year period was likely to be the "contribution of other intervention(s)".[70] That is, they acknowledged that the effect of the screening program was confounded by other study factors, one of which was *Cleanyourhands*. The authors reported that the procurement of ABHR and a reduction in MRSA in the UK became significant only in the fourth quarter of each year of the study.[14] For every 10 mL of ABHR procured per bed-day, a reduction of MRSA of 4.9%–14.3% was achieved, while MSSA bacteremia was not influenced by ABHR procurement.[14]

The National Veterans' Affair hospitals implemented an MRSA bundle in 2007 that consisted of universal screening, contact precautions, hand hygiene, and an institutional culture for infection control.[75] By 2010, screening had reached 96%, and MRSA infection in ICU declined significantly by 62% and in non-ICU wards by 42%.[75] Other hospitals introduced MRSA screening and contact precaution in the USA in 2009 using the B-A design,[76,77] which were successful in reducing MRSA infection in medical and surgical ICUs.[76] A hospital-wide MRSA screening for all patients was compared with screening only high-risk patients along with single room and gloves and gown for HCWs.[78] Screening all patients was no more successful in reducing MRSA than screening only high-risk patients.[78] The rates for hand hygiene may have been different in the two periods of this B-A study and confounded the results; however, compliance rates were not provided. The Netherlands has aggressively implemented an MRSA control program for over a decade, which has been accredited with preventing 520,000 fewer infections per year.[79] However, disentangling the screening effect from other elements of an MRSA bundle or concurrent bundles aimed at reducing other HAIs was not undertaken, and the level of hand hygiene compliance was not provided. In France, no association could be found between hand hygiene, ABHR consumption, and MRSA infection.[80] In Scotland, the effect of MRSA screening,[81] hand hygiene alone, or hand hygiene in combination with screening was examined.[66] The rate of MRSA per 1,000 acute occupied bed-days (AOBDs) was declining during 2006 prior to a peak in the incidence of MRSA,[66] which coincided with the introduction of a national hand hygiene[82] program (study factor) in January 2007. Thereafter, the pattern of MRSA bacteremia remained chaotic until the introduction of a second study factor, the universal screening in July 2008. In response to an increase in the use of fluoroquinolones and cephalosporins, another study factor, namely the antibiotic stewardship program, was introduced in April 2009. In the period after the introduction of antibiotic stewardship, the rate of bacteremia remained low with an occasional spike in the incidence, but the stewardship program, the last study factor to be introduced, was credited with the reduction in MRSA by 0.027/1,000 AOBDs. The percentage of SAB infections involving MRSA fell by 52%. The Scottish national hand hygiene program, "Germs – wash your hands of them", was launched in 2007.[82] However, hand hygiene compliance did not have a significant effect on MRSA or MSSA bacteremia. The rate of *S. aureus* bacteremia infection between 2006 and 2010 declined by 41% and was attributed to a reduction in MRSA bacteremia after the introduction of universal screening.[66] A staggered introduction of study factors does not always provide clear results if study factors take time to impact or interact with other study factors.

The frequency of MRSA is approximately one-third of all *S. aureus* infections in inpatients,[83] and the ability to detect a statistically significant change in MRSA rates in a single facility can be difficult. In Australia, *S. aureus* infections, in particular MRSA, have been declining in the years preceding hand hygiene interventions.[84] For several years, MRSA was used as an indicator of patient safety and categorized as "MRSA sterile site" and "MRSA non-sterile site" infection stratified by ICU and non-ICU wards. The authors noted that the rate of "MRSA non-sterile sites" infection was trending down in Australia[84] before the New South Wales (NSW) statewide hand hygiene campaign commenced in 2006 before all Australian public hospitals joined the national hand hygiene program by 2010.[13] A decline in "MRSA non-sterile sites in ICU" and "MRSA non-ICU wards" occurred between 2005 and 2006 in Queensland, a state in Australia, which collected MRSA indicator data but had not yet introduced a statewide hand hygiene program.[84] The authors noted that, in this 2-year period, the Queensland rate of "MRSA non-sterile sites in ICU" declined by 11 infections, 22.66/1,000 patient bed-days to 11.21/1,000 patient bed-days (P=0.003), and in "MRSA non-ICU wards" by 156 infections, 2.72–1.09/1,000 patient bed-days ($P<0.001$).[84] During the same period, in Queensland no significant change was detected for "MRSA sterile sites in ICU", 10.96 to 6.73/1,000 patient bed-days (P=0.245).[84] Prior to a statewide hand hygiene program across Victoria, MRSA declined in one hospital with a hand hygiene program.[85] Prior to this program in Victoria, however, there was a downward trend in "MRSA from non-sterile sites in ICU" to achieve 2.66/1,000 patient bed-days, after 21 infections were saved ($P<0.001$) across the state.[84] In NSW, the statewide hand hygiene program was initiated in 2006 after collecting pre-implementation data in 2005.[86] By 2008, compliance had improved 14 percentage points, from 47% to 61%.[87] The rate of "MRSA non-sterile site in ICU" declined significantly by 14 infections, 41.7–24.22/1,000 patient bed-days ($P<0.001$), and "MRSA non-sterile sites in non-ICU wards" by 121 infections, 5.71–3.06/1,000 patient bed-days, P=0.001).[84] From the SAB and MRSA infection rates in Australia reviewed elsewhere,[88] a decline in rates commenced in 2002 prior to the 2006 NSW program and the Australian national hand hygiene program in 2010. These data[88] illustrate that, between 2002 and 2005, the MRSA rates in Australia were trending down by 39%, from 0.77/10,000 patient-days to 0.47/10,000 patient-days.[88] The SAB rates were also declining in Australia over this period by 20%, from 1.72 to 1.38/10,000 patient-days.[88] Between 2008 and 2009, the MRSA and SAB rates had declined by 12% and 18%, respectively;[88] this period represents the end of the NSW campaign and the commencement of the national campaign in all Australian hospitals. Factors associated with the downward trend in infection in Australia prior to the state-wide and national programs were not identified.[84] State rates were becoming statistically rare,[84,88] and any further significant downward trending will be difficult to detect and attribute to specific infection prevention strategies in an individual institute.

Prior to the Australian national campaign, NSW implemented a successful CLABSI aseptic insertion bundle in all ICUs between 2007 and 2008.[22] After 12 months of implementation, the CLABSI in NSW had reached close to zero.[89] The bundle required hand hygiene prior to gloving, Moment 2, and on removal of gloves, Moment 3/4. Integral to the bundle were selection of the preferred insertion site, skin preparation and fully draping the patient, CVC insertion training, and a check for the location of the CVC using a transducer or X-ray. Confounders included dwell time, which was associated with an increased probability of CLABSI,[89] daily chlorhexidine and chlorhexidine-impregnated dressings,[36,37,90,91] impregnated lines,[92] and locks.[93,94] The effect of the Australian National Hand Hygiene Initiative (study factor) on HAI rates (outcome factor) cannot easily be established, as another study factor that is a potential confounder of hand hygiene was the national roll out of the CLABSI bundle in late 2011.[95]

A multicentered study of ten hospitals employed an infection control strategy specifically for MRSA that used screening, contact precautions, and decolonization, and was compared with just an enhanced hand hygiene program.[65] The ten hospitals represented Europe and Israel and surgical ward subspecialties: abdominal, cardiovascular, general, orthopedic, neurosurgical, urology, and vascular. Four hospitals were allocated into each intervention, and two hospitals received the combined strategies. A difference in total admissions from the highest to the lowest admission rate, between the ten hospitals, was of a magnitude of 6 and the number of beds in the wards differed by as much as 8 times. The nurse-to-patient ratio ranged from 3.7 to 16.8. The effects of these potential confounders were adjusted for in the analysis. In clean surgery wards, MRSA reduction strategies were associated with decreasing the rates of MRSA clinical cultures per monthly (adjusted incidence rate ratio [aIRR] 0.85) and MRSA infections per 100 admissions (aIRR 0.83).[65] The baseline hand hygiene rates in the wards that experienced the combined strategies was 39.3% in the 230-bed surgical ward (abdominal, general, and orthopedic) that had a nurse-to-patient ratio of 3.7.[65] The baseline hand hygiene compliance was 76.5% for the 84-bed surgical ward (abdominal, orthopedic, and vascular) with a nurse-to-patient ratio of 6.1.[65] Post-intervention compliance increased by approximately 20 percentage points for both wards. After controlling for the effect of confounding, these wards had a significant downward trend (aIRR 0.88) in MRSA per 100 clinical cultures each month.[65] But neither intervention significantly reduced MRSA infection per 100 admissions or MRSA surgical infections per 100 procedures. Total MRSA in both wards was low at baseline, and no intervention resulted in a significant decline. Both wards had different levels of compliance improvement. Neither the percentage point improvement in hand hygiene nor the final compliance rate may have been sufficiently high to impact on the transmission rates. In the larger hospitals, the improvement was large, 20 percentage points, but the final compliance rate was just 60%. The baseline compliance in the smaller hospital was higher, 76%, but improvement was negligible, 4 percentage points. These compliance rates may have been too low to induce improvement in an already statistically low MRSA infection rate. The Lee et al[65] study has wide generalizability, as hospitals were enrolled from low to high resourced settings, and the exposure to enhanced hand hygiene and screening produced a steady rate of screening per month, 12%, and a steady rate of MRSA isolates over the entire study period. Even after adjusting the analysis for patient to staff ratio, the difference in patient risk factors and baseline hand hygiene rates may have prevented the study factors from succeeding.[65] The failure to produce a reduction in MRSA may not have been a failure of the interventions but due to statistically low rates of MRSA preventing an observed effect. Hand hygiene campaigns are unlikely to produce immediate impact because behavioral change requires a longer period to become embedded as normative behavior – years not months may be required to sustain any change.[57] When the Lee et al[65] study ceased, there was an increase in MRSA rates, suggesting that some impact had occurred but just not statistically measurable immediately after intervention. A selection of patients can help the success of infection prevention strategies (study factors) when particular risk factors benefit from the intervention better than other risk factors. This reduces generalizability of the study factor to a specific population. This was demonstrated in the effect of a solo intervention of decolonizing patients with MRSA using mupirocin.[96] Decolonization of patients having clean surgery, such as orthopedic and cardiovascular procedures, was more likely to have an immediate impact on the MRSA infection rate compared with decolonization of patients having general surgery.[96]

Follow-up of positive screening results to decolonize or isolate the patient will bias the report of a hand hygiene program toward the successful reduction of MRSA infection.[97] But hand hygiene campaigns may appear to have failed due to false-negative MRSA results from routine clinical cultures in patients who continue to be a silent reservoir of infection.[97] If a positive screening result from previously false-negative patients occurs during a poorly performing hand hygiene audit, a link between poor compliance and MRSA may be incorrectly made. Hand hygiene campaigns may also appear to underperform because the human audit method does not reflect accurate ABHR usage. A review of studies from 12 countries, where confounding for country and other factors were not controlled, identified that ABHR usage correlated with MRSA infection, but hand hygiene compliance did not.[98]

In conclusion: it's complicated

In highly resourced health care settings, patients are at increased risk of HAIs when they are exposed to peripheral catheters, CVCs for medication, and parenteral nutrition, surgery, and indwelling urinary catheters. It is common to link hand hygiene interventions to infection reduction without reporting other prevention strategies associated with these high-risk exposures. The logic that good hand hygiene compliance contributes to the prevention of HAIs is accepted. Yet, hand hygiene alone cannot singularly inhibit the influence of formidable risk factors such as HAI acquisition at an older age,[99] admission to the ICU,[74] length of stay longer than average,[100] or the fourfold increased risk of infection in patients colonized with *S. aureus*.[81,101–103] Attempts to prevent HAIs, specifically bacteremia, require multiple concurrent interventions,[34,104–106] and authors too eager to attribute a reduction in HAIs solely to a hand hygiene intervention do not advance evidence-based practice. Readers may be misled unless they are trained to recognize an inadvertent "spin" about the strength of the relationship between hand hygiene intervention and HAI reduction. The ORION 22-item checklist is an excellent attempt at assisting authors to systematically provide a critical appraisal of their RCT and non-RCT interventions to reduce HAIs.[107] The checklist requires authors to describe plausible threats to the validity of the results, and this can be achieved by following the list even when the epidemiologic principles are not fully appreciated. If the checklist is read prior to designing an intervention, forewarning the authors about important errors, then attempts can be made to minimize each through study designs such as increasing the follow-up period for measuring compliance, estimating or acknowledging the Hawthorne effect, measuring exposure to the intervention components, and adjusting for confounders during the analysis. In addition, readers can be assisted with a short, mandatory open disclosure statement made by the authors in the discussion section that overtly outlines all infection improvement activities concurrent with the hand hygiene intervention.

When authors attempt to link the contribution of hand hygiene to a statistically rare event such as HAI, epidemiologists think about the complications produced by the various measurement errors, biases, and confounders and will tell you that, like all statistical relationships, this one is complicated.

Disclosure

Between 2005–2013 ML McLaws was advisor to the World Health Organization (WHO) Clean Care is Safer Care Guidelines and WHO First Global Patient Safety Challenge Clean Care Saves Lives. Between 2005–2009 she was advisor to the Clinical Excellence Commission Clean Hands Save Lives Campaign, NSW, Australia. The author reports no other conflicts of interest in this work.

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