TAB 10 **FDA Reviewer's Literature Survey to Determine Correlation of Infection Rates to Microbiological Endpoints:**

- **Healthcare Personnel Handwashes – Colleen Rogers, Ph.D.**
- **Surgical Hand Scrubs – Michelle M. Jackson, Ph.D.**
- **Patient Preoperative Skin Preparations – Peter Kim, M.D.**

HEALTHCARE ANTISEPTIC DRUG PRODUCTS REVIEW

Division of Over-The-Counter Drug Products (HFD-560)
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I. Background

The purpose of this review was to find data to support an association between specific bacterial log reductions on the hands as a result of healthcare personnel handwash use and a specific reduction in the incidence of nosocomial infection. To do this, a literature search was performed with the goal of providing data for a meta-analysis. We sought a direct link between specific bacterial log reductions and decreased incidence of disease, but no evidence was found. Since insufficient data exist to perform a meta-analysis, this report will be confined to a review of the relevant literature. Several articles were found which examined infection rates after use of antiseptic handwash products, and are discussed below. Articles addressing the efficacy of antiseptic handwash products also were evaluated.

It is widely accepted that good hand hygiene practices are one of the most effective means of preventing hospital-acquired infections. Hand hygiene encompasses both traditional handwashing with nonmedicated or antiseptic soap and handrubbing with alcohol-based solutions or other "leave-on" products. The primary purpose of hand hygiene is to remove microorganisms transiently acquired in a healthcare setting and to prevent cross-transmission of these organisms. A distinction has been made between bacteria that persistently reside on the skin (i.e., resident or normal flora) and bacteria that are transiently acquired during patient care activities. Transient organisms are more easily removed from the skin through handwashing or handrubbing, however they are also more likely to cause disease than resident bacteria.[3] Despite this knowledge, compliance with appropriate hand hygiene is surprisingly low among healthcare workers. Thus, finding effective healthcare antiseptics that are also acceptable to the staff is of utmost importance.

In the June 17, 1994 Federal Register, the Food and Drug Administration (FDA) published an amendment to the tentative final monograph (TFM) for over-the-counter (OTC) healthcare antiseptic drug products for professional use. The proposed rule defines a healthcare personnel handwash drug product as: an antiseptic containing preparation designed for frequent use; it reduces the number of transient micro-organisms on intact skin to an initial baseline level after adequate washing, rinsing, and drying; it is broad spectrum, fast acting and, if possible, persistent [§333.403(c)(1)]. The TFM also provides for certain leave-on products (i.e., those not rinsed off the skin) in §333.455(c)(2). The FDA currently approves products for the healthcare personnel handwash indication based on a surrogate microbiologic endpoint of log reductions in bacteria cultured from artificially contaminated hands. The 1994 TFM proposes the following criteria for healthcare personnel handwashes: a 2-$\log_{10}$ reduction of the indicator organism on each hand within 5 minutes after the first wash and a 3-$\log_{10}$ reduction within 5 minutes after the tenth wash, when compared to a baseline value.

The following review is limited to articles written in English and published between 1994 and June 2004. Seven databases were searched: PubMed, EMBASE, CINAHL, IPA, Cochrane Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effectiveness. The following search terms were used: "hand," "antiseptic," "antisepsis," "hygiene," "washing," "disinfectant," "disinfection," "effect," "efficacy," "effectiveness," "nosocomial," "sanitizer," "alcohol," "benzethonium," "chlorhexidine," "chlorine," "chloroxylenol," "povidone," "triclosan," "health care personnel," and "disease transmission." In addition, pertinent references from the bibliographies of key articles and from the Centers for Disease Control and Prevention (CDC) guideline on hand hygiene[3] were reviewed. Over 200 articles were screened (see Appendix for complete listing). Articles were eliminated from the review if they were not relevant or did not include any microbiological or infection rate data. Please note that articles submitted by the SDA/CTFA Industry Coalition are not included here, but have been reviewed elsewhere.

II. Literature Review

A. Healthcare Personnel Handwash and Infection Rates – Hospital Studies

Upon review of the published literature, not a single article was found which could demonstrate an association between specific log reductions of bacteria as a result of antiseptic handwash use and a reduction of infection. This was not because the investigators failed to find as association, but rather because there were no studies designed to address this question. Consequently, we reviewed studies examining nosocomial infection rates after using antiseptic drug products. In addition, although not specific to the healthcare setting, several recent reports associate the use of "instant hand sanitizers" with reduced illness absenteeism in elementary school children and are reviewed here.

Pittet and colleagues implemented a hospital-wide campaign to promote the use of alcohol-based handrub for hand hygiene and measured nosocomial infection rates in parallel.[15] The primary endpoint of this study was overall hand hygiene compliance, with secondary endpoints of nosocomial infection rates, methicillin-resistant *Staphylococcus aureus* (MRSA) attack rates, and handrub consumption. Compliance with hand hygiene practices was monitored in hospital-wide observational surveys conducted twice yearly (June and December) for 3 ½ years. Infection control nurses recorded potential opportunities for hand hygiene according to recommended guidelines, as well as the actual number of hand hygiene episodes. Following the surveys, employees were given performance feedback. In addition, new employees were trained in proper hand hygiene technique. Other interventions included displaying posters in 250 areas within the hospital, providing healthcare workers (HCWs) with individual bottles of alcoholic chlorhexidine (CHG) handrub, and mounting handrub dispensers on each bedside. Furthermore, the hospital continued their detailed MRSA surveillance and control measures.

Overall, hand hygiene compliance improved from 47.6% to 66.2% ($P<.001$) during the study period. Although soap-and-water handwashing remained stable, compliance with alcohol handrubbing increased from 13.6% to 37%. Compliance with hand hygiene increased significantly among nurses, while doctors' compliance did not improve. However, doctors switched from soap-and-water handwashing to handrubbing with alcohol. During the study period, the prevalence of nosocomial infections decreased from 16.9% to 9.9% ($P=.04$). Furthermore, the incidence of MRSA infections decreased from 2.16 to 0.93 episodes per 10,000 patient days ($P<.001$). The authors conclude that the campaign produced a sustained improvement in compliance, mainly as a result of handrub use. As a result, MRSA transmission and nosocomial infections were reduced.

The strength of this study lies in its long duration and large number of observations. But, the study employed multiple interventions, making it impossible to attribute the reduced infection rates to hand hygiene alone. In fact, the purpose of this study was to increase hand hygiene compliance, and the investigators encouraged the use of only one antiseptic. Consequently, we do not know whether the reduced infection rates are a result of improved compliance, the specific antiseptic, or other factors. This study did not evaluate other factors that may have influenced the observed infection rates, such as shifts in patient populations, antibiotic use, or changes in the types of procedures performed. Perhaps improved compliance using a different antiseptic would have the same effect on infection rates. Indeed, the authors state that the results and impact of the intervention must be tested to see whether it can be generalized to other healthcare institutions.

Brown and others describe prospective surveillance of hand hygiene compliance, nosocomial colonization, and antibiotic administration in four 6-bed units of a neonatal intensive care unit (NICU) in Russia.[1] The primary endpoints of this study were compliance with hand hygiene and the incidence density of nosocomial colonization. Secondary endpoints included antiseptic consumption and antibiotic use. Compliance with hand hygiene was covertly assessed during three 2-month periods: at baseline, after an educational intervention and introduction of an alcohol-based handrub (79% ethanol/ 0.1% quaternary ammonium compound), and after a quality improvement intervention. Handrub dispensers were placed at each sink and bedside to supplement the bar soap and multiuse towels that were normally supplied. Bacterial colonization was monitored and considered nosocomial if a species first appeared ≥72 hours after admission to the NICU.

Initial hand hygiene compliance was 44%, decreasing to 42% in the second period and 48% in the final period, which was not significant. But, if relaxed criteria were used (i.e., donning gloves before patient contact in lieu of hand hygiene), there was a significant increase in compliance from period 1 to period 3 ($P=.004$). The amount of soap-and-water handwashing decreased during the study while handrub use increased significantly (period 1 to period 2,

P=.001; period 2 to period 3, P<.00001). Over the course of the study, the incidence of *Klebsiella pneumoniae* colonization decreased significantly (from 21.5 to 3.2 cases per 1000 patient days). Decreased colonization with *Enterococcus faecium* and *Candida albicans* were also noted.

The authors conclude that the study interventions resulted in increased use of antiseptic and decreased cross-transmission of several pathogens. However, there were several limitations to this study. The study periods were short and the sample size was fairly small (283 admissions). As a result, the investigators state that data on infection rates were not standardized or validated. Actually, only colonization rates are given; the authors do not provide information on how many infants acquired nosocomial infections as a result of their colonization. Microbial sampling was performed from a variety of sites, however it is not clear that each site was sampled consistently throughout the study. There were fewer small infants (<1 kg of body mass) during the two intervention phases. Also, catheter and ventilator incidence densities decreased across the study periods, all of which may confound the association between nosocomial colonization and handrub use.

Gopal Rao et al. present a case study of hand hygiene promotion in a 600-bed teaching hospital.[7] An educational and promotional campaign was developed and implemented using societal marketing techniques and followed by 12 months of surveillance. Containers of Spirigel (70% industrial methylated spirits) were placed on each bed frame and in other strategic places throughout the ward. The incidence of hospital-acquired MRSA infection or colonization and *Clostridium difficile*-associated diarrhea (CDAD) was recorded. In the year prior to the alcohol gel promotion, on average nearly 50% of the MRSA culture positive patients acquired the organism in the hospital. During the surveillance year, the average was 39%. In addition, the incidence of CDAD decreased by 17.4%, from 11.5 cases/1000 admissions before the intervention to 9.5 cases/1000 in the year following (P=0.2).

The authors conclude that the principles of societal marketing can be used to effectively increase hand hygiene compliance by HCWs which, in turn, will lead to considerable reduction in nosocomial infections. But, the authors provide only limited detail on how the data was collected. Also, this study did not assess other factors that may have affected the infection rates. As seen with similar studies, the intervention is multifactorial, therefore reduced nosocomial infection rates cannot be attributed solely to the hand hygiene product.

Swoboda and coworkers describe a 15-month quasi-experimental study to determine whether an electronic monitoring device improved hand hygiene compliance and reduced nosocomial infection rates.[16] The primary endpoint was to document an increase in hand hygiene compliance with the use of a voice-prompt system. Secondary outcomes included nosocomial infection rates and detailed patient demographics for patients with a length of stay >48 hours. A review committee determined which infections were nosocomial based on clinical signs, symptoms, and radiologic and microbiologic data. Monitored infections included bacteremia, respiratory tract infection, urinary tract infection (UTI), and surgical site infection (SSI). This study was conducted in three phases in a nine-room, 14-bed intermediate care unit. HCWs had access to non-antimicrobial soap and an alcohol-based product, which were not modified for the study. Phase I consisted of electronic monitoring for 6 months, including an 8-week period of direct observation. Monitoring consisted of motion detectors which sensed entry and exit from patient rooms, along with computer systems that detected the use of toilets, sinks, and soap/antiseptic dispensers in the entire unit. Compliance was defined as a hand hygiene event after patient contact. Investigators defined a window of time (i.e., from just before to just after exiting the patient room) that was used to classify compliance. The compliance rates from electronic monitoring were compared to that of direct observation. In phase II, which lasted 7 months, a voice prompt was added to the electronic monitoring system. A recorded message instructed the individual to wash their hands if hand hygiene was not detected. Only the electronic monitoring system was used in phase III.

Compliance with hand hygiene after exiting a patient room improved by 38% in phase II and 41% in phase III. When adjusted for patient admissions, nosocomial infections were decreased by 22% in phase II and 48% in phase III. The infection rate decreased by 10% during phase II and 40% during phase III when adjusted for patient days. Despite an overall decrease in nosocomial infections when phases II and III were combined, the association between nosocomial infection and study phase was not significant. During phase I, 19% of the patients were either colonized or infected with MRSA or vancomycin-resistant *Enterococcus*. This rate dropped to 9% in phase II and 11% in phase III. The authors conclude that ongoing monitoring and feedback improved hand hygiene compliance and reduced nosocomial infection rates.

One of the strengths of this study was continuous monitoring of hand hygiene compliance. On the other hand, the electronic monitoring was also a limitation because the system counted anyone who entered a room, regardless of patient activity. The computer recorded the absolute number of events but could not determine when hand hygiene was indicated. In fact, the authors state that the monitored compliance rate was lower than the observed rate by 20%. Moreover, the sample size was not sufficiently powered to detect changes in specific infections, although the trends were toward a decrease in infections. Additionally, some patient factors, such as isolation status and use of antimicrobials, were different between phases and may be confounding variables. Finally, the proportion of hand hygiene events using soap compared to alcohol were not reported. Consequently, this study suggests that an increase in hand hygiene compliance alone, regardless of the product used, may decrease nosocomial transmission.

Zafar et al. did not examine compliance with hand hygiene but, rather, described the measures used to eradicate a nosocomial outbreak of MRSA from a 57-bed neonatal nursery.[19] After an index case of MRSA in the nursery, multiple infection control procedures were instituted. These included: cohorting of infants; donning gloves whenever handling babies; handwashing with Hibiclens; change of umbilical cord care from Hibiclens to triple dye; change of circumcision care from Hibiclens to Betadine; surveillance cultures of newborns and staff; treatment of colonized patients and HCWs; daily environmental cleaning with quarternary ammonium detergent; and MRSA education. Despite strict enforcement of these control measures, the outbreak spread and included 18 new cases of MRSA skin infections in the following seven weeks. Two months after initiating the stringent control measures, Hibiclens was removed and replaced with Bacti-Stat (0.3% triclosan) for handwashing and bathing of infants. Subsequently, only one infant per month became infected with MRSA for three months, followed by no new cases for 3 ½ years.

The investigators credit the success of terminating the outbreak to using Bacti-Stat for handwashing and bathing of infants. Although the authors performed a long-term follow-up, they do not mention whether all of the stringent control measures were in effect the whole time. Also, three new cases of MRSA began even after changing to Bacti-Stat. Since so many new infection control procedures were instituted, it would be impossible to attribute an effect to only one of the measures. Finally, this study is fairly small, performed in a single-center, and not blinded, randomized, or placebo-controlled.

Numerous recent studies describe campaigns to promote hand hygiene compliance among healthcare workers. Four of the articles reviewed above exemplify studies of this type.[1,7,15,16] These authors conclude that increased compliance with handrubbing results in a decrease of hospital-acquired infections. It seems logical that increasing the number of hand hygiene events for each HCW should reduce the number of transient bacteria on the hands, thereby reducing cross-transmission of these organisms and the number of nosocomial infections. However, these studies do not address the role of the antiseptic directly. All the trials employed multiple interventions and usually, a single product, making it difficult to ascribe the results to a specific antiseptic. None of the studies reviewed here included a placebo or even a "standard practice" arm. Furthermore, HCWs were not randomized to different treatment arms nor were they blinded to the antiseptic or interventions. Finally, all of these studies were performed at a single site.

B. Healthcare Personnel Handwash and Infection Rates – Non-hospital Studies

The following studies are similar to those discussed above in that they examine the effect of hand hygiene promotion on communicable illness. However, these studies were performed in either school or home settings. Dyer and colleagues conducted an industry-sponsored 10-week, open-label crossover study of alcohol-free hand sanitizer use in conjunction with at-will soap-and-water handwashing in one elementary school.[4] All of the students received education on the importance of handwashing before the study began. Seven classrooms then received instant hand sanitizer (SAB; active ingredient: benzalkonium chloride), and seven were assigned to the control group. Sanitizer was used for 4 weeks, followed by a 2-week wash-out period, then test and control groups were switched. In addition to at-will handwashing with soap and water, children in the study group used the hand sanitizer under teacher supervision immediately after entering the classroom, before eating, after sneezing or coughing, and after using the restroom. Children in the control group were told only to wash before eating and after going to the restroom but were not monitored for handwashing.

Absences were categorized as gastrointestinal (GI)-related (symptoms included vomiting, abdominal pain, and diarrhea), respiratory-related (symptoms included coughing, sneezing, fever, bronchitis, headache, mononucleosis, and acute exacerbation of asthma), or other (e.g., non-transmissible UTIs, broken limbs). In the first phase of the study, the total number of absences due to communicable illness was 33.6% lower in the sanitizer group than in the control group. Total GI- and respiratory-related absences were decreased by 37.5% and 30.9%, respectively, compared to controls. In the 2-week wash-out period, no significant difference was noted between the two groups. In the second phase of the study, there was a significant decrease in total illness-related absences in the sanitizer group, and the number of respiratory-related absences was 76% lower. The authors conclude that daily use of hand sanitizer was associated with significantly lower rates of illness-related absenteeism.

One limitation of this study is that the students were not formally randomized; they were grouped by classroom (i.e., clustered). The authors do not provide details of their statistical methods and do not account for the clustering. But, the use of a crossover design helps confirm that the reduced illness rates are not due to differences in the two groups. In addition, this study was performed at only one site, a private school, therefore the socioeconomic diversity of the subjects may be limited. Furthermore, neither the subjects nor the study coordinators were blinded, and there was no placebo control. There was no monitoring of the students while washing with soap and water, compared to strict monitoring with the sanitizer. Consequently, there is no way to know if students complied with handwashing when they were in the control group. More importantly, there is no way to know if the decreased illness rates were due to monitoring of hand hygiene alone, rather than use of a specific antiseptic.

White and coworkers performed a 5-week, double-blind, placebo-controlled study which was modeled after the Dyer study.[18] Seven hundred sixty-nine children in three schools were included in the study: 381 received SAB sanitizer and 388 received placebo. All students attended a 22-minute presentation on hand hygiene technique, including a video. The children rubbed their hands six times a day under teacher supervision, and washed with soap and water at-will. Absenteeism data was collected for a five-week period (March-April), and absences were categorized as GI-related, respiratory-related, or other (using the same criteria as Dyer et al.[3]). The total number of illness-absence days was 31% lower in the study group than in the placebo group (*P*<.001). Total GI- and respiratory-related absences were decreased by 32.8% and 30.3%, respectively. The authors conclude that use of an instant hand sanitizer with at-will soap-and-water handwashing significantly decreases absences due to common communicable illness in elementary school children.

Overall, this study was well designed. It is one of very few studies to include a placebo formulation, so it is regrettable that these investigators did not use a crossover design, including a washout period, to confirm their findings. Furthermore, the duration of the study was fairly short and does not take into account seasonal variation in illness. Similar to the Dyer study, there was no monitoring of the students while washing with soap and water, compared to strict monitoring with the sanitizer. Finally, more than half of the initial participants were dropped from the analysis due to noncompliance with the study protocol, although how these dropouts were handled in the analysis was not described.

Guinan and others performed an industry-sponsored three-month, open-label study of absenteeism in elementary school children using an alcohol-based gel.[8] Children from five elementary schools were enrolled in the study for a total of 145 control and 145 test students. Students in the test classrooms received the interventions of education (video, pamphlet, and demonstration) and hand sanitizer (Purell gel), while control groups received no intervention. Absenteeism data was collected by the teachers for three months (March – May). Illness was defined as an infectious process, such as cold, flu, or gastroenteritis.

Overall, the test group had 50.6% fewer absences than the control group (*P*<.001). The authors suggest that a hand hygiene program which incorporates both education and hand sanitizer use can lower student absenteeism and be cost-effective. In contrast to the studies noted above, Guinan et al. do not describe when hand sanitizer is used by the children or whether they are supervised or encouraged to use the sanitizer. Several other limitations were noted. Namely, the study was not blinded and did not have a placebo control. The subjects were not randomized; they were divided by classroom and clustering was not accounted for in the analysis. Although several schools were used for this study, they were all in the same geographic location and had limited socioeconomic diversity. In addition, the authors do not mention which types of illnesses resulted in absenteeism (e.g. GI, respiratory).

Morton and Schultz performed a 100-day crossover study of alcohol gel use in elementary school children.[14] Two hundred fifty-three students participated; classrooms were assigned as experimental or control groups. The first phase lasted 46 days, followed by a 1-week washout period and a second phase of 47 days. The school nurse gave a 45-minute presentation to each class about germs and hand hygiene, and the study protocol was posted in each classroom. Gel dispensers (AlcoScrub) were mounted near the door of each classroom so gel use could be monitored by the teachers. Absences were reported to the school nurse. Respiratory illnesses were defined as symptoms of nasal congestion, cough, or sore throat. Asthma symptoms in the absence of an upper respiratory infection were not included. GI illnesses were defined as symptoms of flu, diarrhea, nausea, or vomiting. Significantly fewer children were absent when using alcohol gel as an adjunct to handwashing (P=.0053). Except for kindergarteners, GI illnesses were reported less frequently in the alcohol gel group. Overall, using alcohol gel as an adjunct to soap-and-water handwashing reduced illness absenteeism by 43%. The authors do not describe when hand sanitizer is used by the children. Furthermore, the authors report the number of days of respiratory or GI illness, but do not provide the number of illnesses. Finally, the study is not blinded, randomized, or placebo-controlled.

In addition to studying elementary school children, one recent report describes illness rates of university students after using alcohol gel.[17] Three hundred ninety-one students living in four residence halls were included in this study; 188 used Purell alcohol gel and 203 were controls. Participation was voluntary, but students were given cash incentives. In the product groups, alcohol gel dispensers were installed in the dorm rooms, bathrooms, and dining hall. Also, a handwashing message campaign was implemented in the product group residence halls one week before commencement of the study. All participants filled out weekly surveys about health and exercise habits for 8 weeks. As part of the surveys, students were asked to report any of the following symptoms: cough, sore throat, stuffy nose, ear pain, painful/swollen neck, chest congestion, sinus pain, or fever. Significant differences in illness rates were seen for only three of the eight weeks, but overall, the alcohol gel group had a 20% improvement in illness rate. Forty percent less absenteeism (missed school or work) was noted in the product group versus controls. The authors conclude that hand hygiene education and access to hand sanitizers leads to improved hand hygiene behavior, resulting in lower illness rates.

This study has several deficiencies. The results are based on self-reported illness derived from a list of symptoms. In addition, only data on upper respiratory tract symptoms was collected. The rate of GI-related infections was not examined. The authors made no observations of handwashing and did not monitor compliance. The study was not blinded or placebo-controlled, nor was there a crossover design. In fact, the authors acknowledge that some of the control subjects reported using hand sanitizers. Finally, it is worth noting that subjects in the product group washed their hands with soap more frequently than controls (P<.02), so the illness rates reported here can not be attributed solely to use of alcohol gel.

Despite the limitations of the studies described above, overall they suggest that use of hand antiseptics, specifically leave-on products, can reduce infectious illness rates. However, a study published by Master et al. demonstrates reduced illness rates in elementary school children after scheduled handwashing with non-antimicrobial soap.[13] Fourteen classrooms from one school were divided into control or test groups. Children in the handwashing classrooms (n = 143) were required to wash their hands after arrival at school, before eating lunch, after lunch recess, and before going home. The teacher instructed the children to go to the restrooms to wash their hands at these times, although handwashing was not observed. Children in control classrooms (n = 162) washed as normal with no prompting from the teachers.

Data were collected for 37 days (Jan.-Feb.) and absentee information was recorded by the school secretary. Illnesses were categorized as GI (abdominal pain, diarrhea or vomiting), respiratory (coughing, sneezing, sinus trouble, bronchitis, fever, headache, mononucleosis, or acute exacerbation of asthma), or other (UTI). The investigators observed a 25% decrease in illness absenteeism in the test group. Although there was not a significant difference in the days of absence due to respiratory illness, there was a statistically significant decrease in GI symptoms in the handwashing group (P=.0024). The limitations of this study are similar to the hand sanitizer studies described above. Namely, the subjects were from a single school and the study was not blinded or randomized. Furthermore, the study was short, did not have a crossover design, and did not take clustering into account. However, the results of this study call into question the efficacy of any hand sanitizer for the reduction of illness absenteeism. The decreased illness absenteeism may be due to mandatory or supervised hand washing alone, rather than use of a specific antiseptic.

Although the elementary school studies suggest a trend toward reduced germ transmission, none of them, with the possible exception of White et al.,[18] are designed to address the efficacy of the antiseptic product versus supervised hand hygiene alone. Moreover, since these studies were only conducted during school hours, the influence of out-of-school hygiene practices on the outcomes cannot be determined. Most of the studies were open-label and all of the studies employed multiple interventions, such as educational programs. Several of the studies were not formally randomized,[4,8,13] and none of the studies mentioned addressing the cluster design when analyzing their results. The definition of illness varied with each study, and several studies included exacerbation of asthma, which may not be a communicable factor. Finally, none of the studies except White et al.[18] included a placebo arm. Providing a placebo for alcohol gels may not be possible, but placebo formulations are available for other products. Overall, the results of these studies must be interpreted with caution.

The following two studies are noteworthy even though they address the effect of antibacterial soap on illness rates during household use. Larson and others performed a randomized, double-blind trial to evaluate the effect of antibacterial cleaning and handwashing products on the occurrence of infectious disease symptoms.[10] Two hundred twenty-four households that had at least one preschool-age child in an inner-city neighborhood completed the study. Households were randomly assigned to use either antibacterial or non-antimicrobial products for general cleaning, laundry, and handwashing. The antibacterial group was given liquid handwashing soap containing triclosan, a hard-surface cleaner containing a quaternary ammonium compound, and laundry detergent containing oxygenated bleach. The non-antimicrobial group received parallel products with similar compositions. Hygiene practices and infectious disease symptoms were monitored for 48 weeks by weekly telephone calls, monthly home visits, and extensive quarterly interviews. If one or more symptoms were reported, the subject was asked whether any treatment or antibiotics were administered, and whether the illness resulted in missed work or school.

The most commonly reported symptoms were runny nose and cough (23.2-26.8%), with less than 3% of either group reporting vomiting or diarrhea. Differences between treatment groups in rates of any symptom by household-month were not statistically significant. Among all participants, the cumulative incidence of infectious disease symptoms for the antibacterial and non-antimicrobial groups was 38% and 32.1%, respectively. The authors conclude that the antibacterial products did not reduce the risk of viral diseases, although they did not discount a potential contribution to reducing symptoms of bacterial diseases in the home.

This is a good study, but has a few limitations. First, the urban setting may not be generalizable to other settings. Also, telephone calls and visits from interviewers may have led to increased product use, potentially biasing the study toward fewer infectious disease symptoms. On the other hand, there was no observation of product use and therefore, no guarantee that products were used as directed. The authors tried to match antimicrobial-containing products with non-antimicrobial products, thus serving as placebos. It is possible that participants were not accurate in reporting their symptoms; however the first 100 reports of illness were confirmed by a household visit. Finally, the study employed multiple interventions, thereby limiting the demonstration of the contribution of the antiseptics.

Luby and colleagues conducted a cluster randomized, controlled trial to assess the effect of household handwashing on the incidence of diarrhea in children in Karachi, Pakistan.[11] Twenty-five neighborhoods were randomly assigned to handwashing intervention: 300 households (1523 children) received non-antimicrobial soap and 300 households (1640 children) received antibacterial soap containing 1.2% triclocarban. Eleven neighborhoods (1528 children) served as the control. Field workers visited intervention households at least weekly for a year and encouraged all family members to use soap daily for handwashing and bathing. During visits, field workers recorded episodes of diarrhea and supplied soap as needed. Both the families and field workers were blinded to the type of soap.

Children living in intervention households had a 50% (antibacterial soap) to 53% (non-antimicrobial soap) lower incidence of diarrhea than children in control neighborhoods. Diarrhea was reduced by 39% in infants, compared to 57% in children aged 5 to 15 years who were able to wash their own hands. The authors conclude that improving handwashing in the household reduced the incidence of diarrhea among children at high risk of death from diarrhea.

This is a well-designed study because they randomized the households, blinded the subjects and the field workers, and included both a placebo formulation and negative control group. Furthermore, data analysis accounted for the cluster design of the study. The investigators found essentially no difference between using antibacterial soap and nonmedicated soap. However, the antibacterial soap contained triclocarban, which is not generally recognized as safe and effective for this use by the FDA. Finally, although households were blinded to the type of soap, they were not blinded to the intervention and may have changed other behaviors besides handwashing.

C. Healthcare Personnel Handwash Efficacy Studies

Due in part to the CDC guideline on hand hygiene[3] and recent reports of improved hand hygiene compliance after the introduction of alcohol-based products (see section A), an emphasis has been placed on use of these products in healthcare settings. Consequently, many recent studies have addressed the efficacy of alcoholic solutions versus antiseptic or soap-and-water handwashing for reducing bacterial counts on the hands of healthcare workers. Most of these studies compare the number of bacterial colony forming units (CFUs) obtained from healthcare workers' hands before and after hand hygiene using a contact plate (imprint) technique. This method is used so that samples can be taken repeatedly during patient care activities with minimal disruption to the healthcare workers' routine. We found only one study where healthcare workers' hands were sampled during actual use using the glove juice method.[5]

The first three efficacy studies (reviewed below) compared alcoholic handrub with other handwash agents in a hospital setting.[6,12,20] Faoagali et al.[5] compared two different antiseptics, but did not evaluate an alcohol solution. Nevertheless, all four studies have some of the same deficiencies. Only a small number of subjects were enrolled and the trials were conducted at only one location. None of the investigators included a placebo, and only half the studies[12,20] incorporated a nonmedicated soap arm. Although the consistency of alcohol-based antiseptics precludes blinding, placebo soap formulations or groups randomized to "standard practice" could have been used. Alcohol is well known to have rapid, but not persistent, activity. These studies were not designed to demonstrate persistence of the antiseptic. If a different study design was used, antiseptics with known persistent activity, such as chlorhexidine, may have performed better. It should be noted that none of these studies were performed in the United States and other countries do not necessarily require antiseptics to be persistent. Furthermore, none of these studies were designed to determine if pathogens were actually transmitted to susceptible patients. Finally, unlike most laboratory studies, the efficacy against normal flora was investigated; no artificial contamination was used.

Girou and colleagues conducted a prospective, randomized clinical trial to compare the efficacy of handrubbing with an alcohol-based solution to conventional handwashing with antiseptic soap on hand contamination during routine patient care.[6] The study site consisted of three intensive care units in a single hospital. Twenty-three volunteers were randomly assigned to use either standard handwashing with Hibiscrub (4% CHG; n=11) or handrubbing with an alcohol-based solution (Sterillium[†]; n=12). Subjects in the alcohol group whose hands had become visibly soiled were instructed to wash with antiseptic soap and their session was ended. Each subject participated in one session of five patient care activities (10 hand samplings). When an opportunity for hand hygiene occurred, an imprint was made of the palm and fingertips of the dominant hand both before and one minute after cleansing. Each fingertip and palm was pressed onto contact agar plates containing neutralizers. If gloves were worn, these were removed prior to sampling.

Bacterial counts were always lower after hand hygiene, regardless of the test agent. But, handrubbing with alcohol gave a significantly higher reduction of CFUs than Hibiscrub (83% vs. 58%, P=.012). For the handrubbing group, there was an 88% reduction in CFUs after the first rub and a 95% reduction after the fifth rub. The amount of time performing hand hygiene also was monitored. The median time spent washing with soap was 30 seconds, although 65% of the handwashing procedures were less than 30 seconds. The median duration of handrubbing also was 30 seconds, which is the recommended amount of time for this product. The investigators conclude that handrubbing with alcohol is more effective in reducing hand contamination than antiseptic soap. Furthermore, the authors speculate that antiseptic soap was less effective than the alcohol solution because healthcare workers did not spend enough time washing with soap,

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[†] Sterillium contains 45% 2-propanol, 30% 1-propanol, and 0.2% mecetronium ethyl sulfate.

which is a reasonable supposition. It is not known whether monitoring of hand hygiene practices influenced the study participants. Although the trial was randomized, the number of subjects was small, and it was performed at a single site. Due to the nature of the products tested, blinding was not possible. However, plain soap or standard practice could have been included.

Lucet et al. performed a prospective, randomized clinical study to assess both the factors associated with bacterial hand contamination after patient care and the efficacy of several hand hygiene agents.[12] Five to seven volunteers in each of seven hospital wards participated in the study for a total of 43 subjects. Each volunteer performed one of six hand hygiene techniques in random order immediately following a healthcare procedure. The techniques were: washing with non-antimicrobial soap for 10 or 30 seconds, washing with antiseptic soap (4% CHG or 10% povidone-iodine) for 10, 30, or 60 seconds, or handrubbing with an alcohol-based solution (Sterillium). After the healthcare procedure, all five fingertips were pressed onto an agar plate for 15 seconds. The handwashing procedure was performed and fingers were sampled again after 1 minute. Neutralizers were not used.

Before hand hygiene, hand contamination was highest in HCWs working in a medical ward (vs. ICU) and in physicians (vs. nurses). Hand contamination was not significantly different after either patient contact, contact with body fluids, or contact with the patients' environments, although it was higher in those HCWs without direct patient contact (e.g., housekeeping). Wearing gloves during the procedure significantly reduced hand contamination. When multivariate analysis was performed, the factors associated with increased hand contamination were: working in a medical ward, job as physician, and not wearing gloves. The bacterial reduction factor was significantly greater after using antiseptic or alcohol rub compared to using non-antimicrobial soap. However, there was no significant difference between using antiseptic or alcohol rub. Reduction factors were similar when either CHG (n=27) or povidone-iodine (n=16) was used. Transient flora was recovered from 11 baseline samples (4.6%). Two of these 11 cases were still positive after handwashing using nonmedicated soap.

The authors conclude that hand hygiene with antiseptics is more effective than handwashing with non-antimicrobial soap in reducing the number of bacteria on the hands of HCWs. They further conclude that alcohol-based antiseptics should be preferred over nonmedicated soap and possibly antiseptic soap. However, their data does not support the preferential use of alcohol over other antiseptics. No significant difference in bacterial recovery was seen when using alcohol, CHG, or povidone-iodine. There may be several reasons for this observation. The log reductions are fairly small, but they are starting with low numbers of resident flora, not the artificial contamination used in laboratory studies. Alternately, since neutralizers are not added to the sampling plates, this may result in artificially high log reductions for some active ingredients.

Zaragoza et al. determined the number of CFUs on healthcare workers' hands both before and after washing with either non-antimicrobial soap or an alcohol hand rinse (Sterillium).[20] This study was conducted in four of 20 randomly selected wards and three of 6 ICUs of a single hospital. Forty-three volunteers used either soap or alcohol for 15 days in a crossover design with no washout period. Baseline samples were obtained by contact plate before any handwashing procedure on the first day. A second sample was obtained immediately after handwashing, but before any patient care activity was performed, and a third sample was collected after 10-30 minutes of regular activity.

The mean number of CFUs found before and after handwashing with either agent did not show a statistically significant difference. In addition, there was no statistically significant difference between wards. When both methods were compared, alcohol handrubbing showed a significant decrease in the number of recoverable organisms ($P<.001$). In 30% of the soap and water group, the mean number of CFUs was higher after handwashing than before. No organisms could be recovered after use of the alcohol rinse in 33% of the subjects. The number of bacteria recovered from the subjects' hands at the beginning of the study (i.e., normal flora) was not very high (mean of 75-82 CFUs). Even after healthcare activities, the mean number of CFUs recovered was not high (61-76 CFUs). The authors conclude that alcohol is safe and effective and deserves more study. It is hard to know whether the hand hygiene agents would be equally effective against heavily contaminated hands.

Faoagali and coworkers performed a comparative study to determine the effect of chlorhexidine and triclosan on resident bacterial flora of the hands of clinical staff of a vascular surgery unit.[5] The study was divided into three periods: Hibiclens (4% CHG) was used for 12 weeks, followed by Novaderm R (1% triclosan) for 34 weeks, and reintroduction of Hibiclens for 12 weeks. Forty-one subjects were recruited and each subject performed a total of 18 handwashes. One staff member was randomly selected each day to undertake three supervised handwashes and glove juice collection. Samples were taken immediately before commencement of duty, before lunch, and at the end of the shift. Baseline samples were collected from each hand using 50 milliliters of sampling solution, which contained appropriate neutralizers. Then subjects washed with the product for 30 seconds and rinsed for 1 minute. The post-wash sample was taken as above. Samples were plated on trypticase soy agar and selective media.

The baseline amount of bacteria recovered from the hands of HCWs before handwashing was approximately 4-$\log_{10}$. This number decreased slightly for each subsequent wash during the day. Overall, the amount of bacteria recovered after handwashing was lower than baseline, but the difference never exceeded 0.32-$\log_{10}$. The prewash-postwash difference was always statistically significant for CHG (P=.001), but was only significant for Novaderm for the first wash of the day. Subjects who used Hibiclens were 1.75 times more likely to have a positive MRSA culture compared to using Novaderm (P=.0001). Interestingly, MRSA carriage was nearly eliminated during the Novaderm period, but returned during the third period when Hibiclens was reintroduced. Conversely, subjects who used Novaderm were 1.39 times more likely to have gram-negative bacteria on their hands compared to those who used Hibiclens (P=.0001). The authors conclude that triclosan is effective at removing MRSA from the hands of HCWs, while CHG does not have the same effect. In contrast, CHG showed an effective immediate and residual antibacterial effect, especially against gram negative bacteria.

Lastly, one laboratory study has been included in our analysis. Kampf and Ostermeyer performed a meta-analysis of 35 laboratory experiments to assess the accuracy and reproducibility of the European handwash reference procedures.[9] For both EN 1499 (hygienic handwash)[‡] and EN 1500 (hygienic handrub), 12-15 subjects were used in a crossover design. Subjects first washed their hands with nonmedicated soap and dried them. Then, their fingers were immersed in contamination fluid (*E. coli*) to the mid-metacarpals for 5 seconds and air-dried for 3 minutes. To determine pre-values (i.e., baseline), contaminated fingertips were rubbed in a dish of broth for one minute and the broth was plated. For product application, 2 x 3

[‡] EN = European Norm; EN 1499/1500 = Chemical disinfectants and antiseptics test method and requirements.

mL soap (EN 1499) or alcohol (EN 1500) was applied to the hands and rubbed in for one minute. Post-values were taken by rubbing fingertips in a dish of broth containing neutralizers.

Twelve experiments according to EN 1499 and 23 according to EN 1500 were evaluated. This represents 178 handwashes using the reference soap and 342 using the reference alcohol. The overall mean log values (± sd) for the reference soap were 6.32 ± 0.41 (pre-value) and 3.50 ± 0.51 (post-value). This resulted in a mean reduction factor of 2.82 ± 0.49. ANOVA analysis of the means of the 12 experiments revealed a significant difference between means, possibly due to the small standard deviations of these results. Linear regression revealed a correlation between a higher pre-value and a higher reduction factor.

For the reference alcohol, the mean pre-value was 6.42 ± 0.46 and post-value was 1.78 ± 0.91. This resulted in a mean reduction factor of 4.64 ± 0.93. Although the means of two of the 23 experiments were significantly different from the mean of the remaining data (one higher and one lower), analysis of all of the means by ANOVA showed no significant difference. Therefore, the reference alcohol provided very reproducible test results. Similar to what was seen with soap, a significant correlation was seen between the pre-values and reduction factors. Finally, the range for accuracy of both reference procedures was very small, indicating good reproducibility. For both soap and alcohol, a significant correlation was seen between the baseline value and the reduction factor. In other words, a higher pre-value led to a higher reduction factor. One explanation for this is that when more bacteria were removed from the hands in the pre-value sampling, a lower bacterial load remained on the hands, which was more easily removed by the washing agent.

From the methods, it was not clear exactly how the EN 1499 and EN 1500 tests were carried out. It appears that the pre-value sample is taken and then the hands are washed with the test agent without recontamination of the hands. Consequently, the amount of bacteria that is actually subjected to the wash agent is less than the initial inoculum. Some studies have shown that wash agents are more efficient at removing a small inoculum compared to a large one.[2] Therefore, this aspect of the testing may lead to inflated reduction factors. In addition, the ability of the contamination procedure to lead to a consistent inoculum was questioned. The results of this analysis show that the experiment-to-experiment variation of the pre-values is very small and therefore, this contamination procedure appears appropriate.

III. Summary

In summary, we have found no evidence to suggest that specific bacterial log reductions on the hands as a result of healthcare personnel handwash use are associated with a specific reduction in the incidence of nosocomial infection. Ideally, multi-center, randomized, double-blind, appropriately powered, placebo-controlled studies should be conducted to demonstrate the efficacy of an antiseptic in reducing the incidence of disease. We have not found any studies that employ all of these measures. However, it may be overly burdensome or unfeasible to conduct such a trial. In lieu of these, we have reviewed several well-designed, relevant studies that were found during an extensive literature search. The underlying message gleaned from these studies is that increasing the number of hand hygiene events (handwashing or handrubbing), whether by monitoring (e.g., with children) or by providing convenient products (e.g., alcohol), leads to decreased infection rates. Furthermore, one of the studies suggests that antiseptic efficacy may vary against different microorganisms, but this has not been conclusively demonstrated. Additional research is needed in this area.

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