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Brief Report

# Randomized controlled trial evaluating the antimicrobial efficacy of chlorhexidine gluconate and para-chloro-meta-xylenol handwash formulations in real-world doses

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Chlorhexidine gluconate-based soaps have become the gold standard for handwashing in critical care settings and para-chloro-meta-xylenol is an effective alternative antibacterial active ingredient. This study benchmarked 2 novel foaming handwashes, compared to a bland soap for antimicrobial effectiveness using the health care personnel handwash method at realistic soap doses (0.9 mL and 2.0 mL). To our knowledge, this is the first published efficacy study on realistic soap doses. Both soaps met Food and Drug Administration success criteria.



Studies by Semmelweis[1] clearly demonstrated clinical benefit from hand disinfection using chlorinated lime, however long-term acceptance was hindered by both skin tolerability and aesthetic issues. Handwashing with soap and water has been a longstanding means of personal hygiene and was the first line of hand hygiene (HH) in US health care settings until the 2002 Centers for Disease Control and Prevention HH guidelines shifted to alcohol-based handrubs (ABHRs).[2] ABHRs offer greater convenience, time savings, and overall better antimicrobial efficacy. Furthermore, ABHR formulation innovation enabled improved skin health over handwashing, which is often associated with skin irritation and dermatitis.[3] Today, handwashing accounts for approximately 15% of HH events in US hospitals,[4] and occurs as frequently as 15-20 times per shift.[5]

ABHRs have been studied many ways, including the importance of formulation,[6] dose,[7] and contact time[8] on pathogen reduction on hands. Despite being used less frequently than ABHRs, handwashing remains an important infection prevention practice in health care. Chlorhexidine gluconate (CHG)-based handwashes have gained importance recently, as they are now often used in critical care areas (eg, intensive care units). Chloroxylenol, also known as para-chloro-meta-xylenol (PCMX), is an alternative antibacterial active ingredient that has been used in hand soaps for decades. When formulated properly, both CHG and PCMX are more effective alternatives to other soaps—such as hand cleansers without an antimicrobial active ingredient.

CHG-containing antimicrobial skin antiseptics are only approved through the Food and Drug Administration (FDA) new drug application process in the United States. Efficacy criteria have required antimicrobial handwashes to achieve >2.0 $\log_{10}$ reductions (LR) in bacteria after 1 wash and >3.0 LR after 10 washes using the health care personnel handwash method.[9] To fulfill new drug application efficacy requirements, products are required to be evaluated at a 5.0 mL dose, which is substantially greater than volumes typically used by health care personnel (HCP) for routine hand disinfection, as typical wall mounted soap dispensers provide 0.9 mL in 1 pump and approximately 2.0 mL in 2 pumps (GOJO unpublished data, 2018).[4,6] The purpose of this study is to benchmark 2 novel foaming handwashes, 1 containing 2% CHG and the other containing 0.5% PCMX, for antimicrobial effectiveness relative to FDA health care personnel handwash success criteria at realistic soap doses.

## METHODS

### *Test products*

Three commercially available handwash products were evaluated in a blinded study: a nonantimicrobial "bland" foam handwash (Provon Clear and Mild Foam Handwash [GOJO Industries, Inc, Akron, OH]) as a control and 2 antimicrobial foam handwashes (Purell

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Healthcare Healthy Soap 2.0% CHG Antimicrobial Foam [GOJO Industries, Inc] and Purell Healthcare Healthy Soap 0.5% PCMX Antimicrobial Foam [GOJO Industries, Inc]).

*In vivo antimicrobial efficacy determination*

Test products were evaluated per ASTM E1174-13[9] (Standard Test Method for Evaluation of the Effectiveness of Health Care Personnel Handwash Formulations) using *Serratia marcescens* (ATCC #14756) as the challenge microorganism after 1 and 10 handwashes in July-August 2017. A neutralizer effectiveness study was conducted per ASTM E1054-08[10] and demonstrated that antimicrobial activity was quenched by the neutralizer in the sampling fluid. Jehangir Clinical Development Centre ethics committee institutional review board pre-approval and subjects informed consent was obtained. Inclusion criteria included: subject of either sex, age (18-70 years), no skin disorders, both hands, and avoid any antimicrobial agents for 1 week prior to and during the study. Exclusion criteria included: use of antimicrobial agents in the past week, pregnant, or unhealthy subjects (other conflicting medical conditions). A study coordinator at the study facility enrolled subjects in the study and on enrollment randomly assigned the subject to a soap and dose group. A total of 84 subjects (N = 84) were randomly assigned to handwash groups (12 subjects per group) evaluating each test article (bland, CHG, PCMX). Subjects were then assigned to dose groups of 0.9 mL (CHG, PCMX), 2.0 mL (CHG, PCMX), and 5.0 mL (bland, CHG, PCMX), with all doses controlled to deliver the target volume ± 0.1 mL. All testing occurred over 25 days, and tested on multiple days. Test products were applied to wetted hands, lathered (30 seconds), and rinsed (30 seconds), per the standard method.[9] LR were calculated by subtracting postwash $\log_{10}$ recovery from baseline $\log_{10}$ recovery. The primary endpoint of the study was if the handwashes achieved antibacterial activity with real-world doses as compared to FDA approved doses after 1 and 10 washes.

*Statistical analysis*

To compare products at different doses, linear mixed effects models were fit to the LRs after 1 wash and separately to the LRs after 10 washes with a random effect for day and a fixed effect for product, dose, and the interaction. Tukeys follow-up tests maintained a family-wise significance level of 5%. To estimate the mean LR for each product and dose combination separately, a linear mixed effects models was fit to LRs with a random effect for day. Follow-up upper 1-sided Student *t* confidence intervals (CI) for the mean LR were constructed with a Bonferroni correction to maintain a family-wise confidence level of 95% (ie, each CI had an individual 98.3% confidence level). For graphical purposes, a family of 3 Bonferroni 2-sided 90% CIs are presented that give the same lower confidence bound as the family of Bonferroni upper 1-sided 95% CIs.

**Table 1**
Handwash efficacy. Average LR, SE, and the 95% LCB on the mean LR at 5.0 mL dose

| Foam soap | Wash 1 | | | Wash 10 | | |
|---|---|---|---|---|---|---|
| | Mean LR | SE | 95% LCB | Mean LR | SE | 95% LCB |
| **Bland** | 2.04 | 0.29 | 1.61 | 2.05 | 0.27 | 1.36 |
| **CHG** | 3.09 | 0.35 | 2.73* | 4.65 | 0.44 | 3.67* |
| **PCMX** | 3.70 | 0.43 | 3.43* | 4.50 | 0.33 | 4.18* |

*CHG*, chlorhexidine gluconate; *LCB*, lower confidence bound; *LR*, log reductions; *PCMX*, para-chloro-meta-xylenol; *SE*, standard error.
*The asterisks indicate the product and dose combinations that satisfied the Food and Drug Administration criterion at a 95% family-wise confidence level.

## RESULTS

A total of 86 subjects were randomly assigned, but there were 2 subjects that dropped out of the PCMX treatment groups: 1 subject in the 0.9 mL group owing to *S marcescens* plate contamination, and 1 subject in the 2.0 mL group owing to redness and itching of their skin, which resulted in a total of 84 subjects that completed the study. Table 1 presents in vivo efficacy results for the handwashes evaluated at the typical testing dose of 5.0 mL. Both antimicrobial soaps produced significantly higher LRs than the bland soap control after both 1 and 10 washes ($P < .001$). Figure 1 presents efficacy results for both antimicrobial handwashes evaluated at more typical use volumes (2.0 mL and 0.9 mL). Because the lower bound of the 90% CI did not

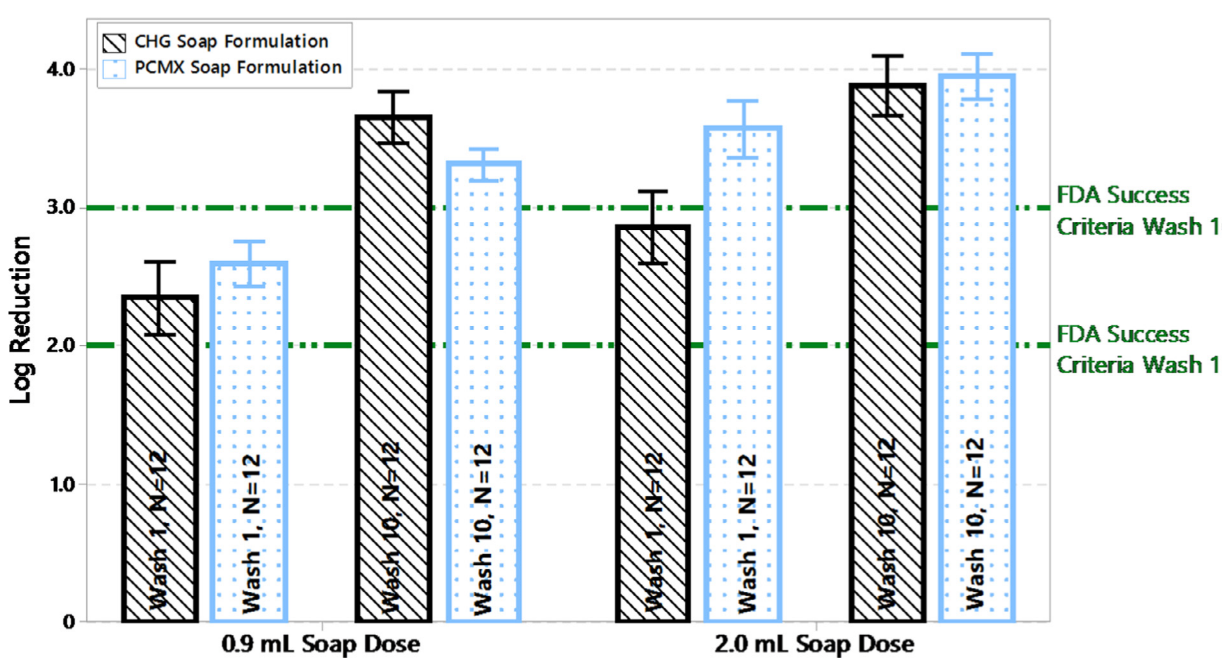


**Fig 1.** Handwash efficacy. Average log reductions at more typical use volumes (0.9 mL and 2.0 mL doses) with error bars representing 90% confidence intervals.

cross 2 after 1 wash and did not cross 3 after 10 washes, then we conclude, at 95% confidence, that both the CHG and PCMX handwashes met FDA efficacy success criteria (>2LR after wash 1 and >3LR at wash 10). Consistent with CHG science, mean LRs after 10 washes were statistically greater than after 1 wash. As expected, the mean LRs followed the canonical dose response curve and increased with increasing application volumes.

## DISCUSSION

These results confirm previous reports that CHG handwash antimicrobial efficacy improves with repeated use (ie, cumulative activity) and provides support that PCMX can also display cumulative activity.[3] This study also demonstrated the CHG and PCMX meet the FDA criteria for antimicrobial efficacy at all 3 doses (0.9 mL, 2.0 mL, and 5.0 mL), the lower doses are more representative of 1 or 2 pumps of soap dispensers found in hospitals (GOJO, unpublished data, 2018).[4] For these antimicrobial foam handwash formulations efficacy is directly correlated to product volume, whereas the bland handwash did not result in a significant impact on test organism removal after repeated washes. This could be explained by bland soap achieving a maximal threshold for cleaning well below 5.0 mL, whereby increasing doses and number of washes does not improve bacteria removal. The formulation of any effective handwash, with or without an active ingredient, should also contribute to microbe removal—for example, the ability of the soap to spread and reach into skin cracks and crevices to lift away soil and pathogens. Wash efficiency (the ability to wash away germs) is an important component of overall effectiveness and worth further study.

Antimicrobial efficacy is critical for any handwash, and it is equally important that they support good skin health and have favorable aesthetics. Unfortunately, handwash products are difficult to formulate and often are irritating in high-use environments like health care, as there is a natural scientific trade-off between antimicrobial efficacy, skin health, and aesthetics. HCP with irritated skin are less likely to clean their hands, which increases risk for patient infections.[2,3] Another important driver of HH compliance is aesthetics (eg, lather, smell, skin feel). Therefore, a trial for skin tolerability and HCP acceptability is strongly recommended for all new HH interventions.[3] Additionally, CHG-based handwashes used in the hospital setting should provide a strong benefit to risk ratio through optimized antimicrobial efficacy and skin care performance, to minimize the potential for bacterial resistance and skin hypersensitivity.

## CONCLUSIONS

This study examined a limited number of products with a relatively small number of subjects. In the future, we encourage more in vivo performance testing of handwashes, and infection prevention personnel to review in vivo data when selecting soap for their health care facility. Another limitation is that only 1 microorganism was evaluated, with a high level of wet soil. It would be interesting to understand the performance of handwashes with other pathogens under more typical wash times and lower soil levels, and on dry and irritated skin, as is often the case for health care**.**

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