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Peters, Alexandra; Cave, Charlotte; Carry, Jennifer; Sauser, Julien; Pittet, Didier

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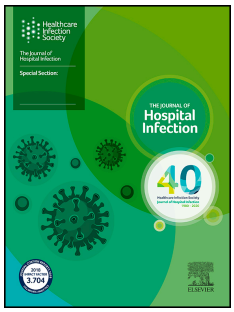

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Alexandra Peters, Charlotte Cave, Jennifer Carry, Julien Sauser, Didier Pittet

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Tolerability and acceptability of three alcohol-based handrub gel formulations: a randomized crossover study

Authors: Alexandra Peters[1], Charlotte Cave[2], Jennifer Carry[3], Julien Sauser[1], Didier Pittet[1]

Affiliations: [1]Infection Control Programme and WHO Collaborating Center on Patient Safety, University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland; [2]Nouvelle Aquitaine Healthcare-Associated Infection Control Centre, Bordeaux University Hospital, Bordeaux, France; [3]University of Geneva, Geneva, Switzerland

Correspondence: Professor Didier Pittet, Infection Control Programme, University of Geneva Hospitals and Faculty of Medicine, 4 Rue Gabrielle-Perret-Gentil, 1211 Geneva 14, Switzerland. Tel: +41 22 372 9828 /+41 22 372 9833 (direct); e-mail: didier.pittet@hcuge.ch

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Abstract

Introduction: Healthcare workers often experience skin dryness and irritation from performing hand hygiene frequently. Tolerability and acceptability are barriers to hand hygiene compliance, but there is little in the literature about exactly which types of alcohol-based handrubs (ABHR) have a higher dermal tolerance.

Objective: To compare the tolerability and acceptability of three different ABHR gel formulations in a population of adult volunteers.

Methods: Thrity-eight participants were randomized to three different sequences, testing three handrub gel formulations: (1) isopropanol-based (Hopigel®), (2) ethanol-based (WHO gel formulation) and (3) ethanol-based containing superfatting agents (Saniswiss Sanitizer Hands H1). Participants tested each of the formulations over a series of three 5-day interventions, followed by a 9-day washout period. At the end of each intervention, skin condition was assessed and feedback was collected.

Results: While no statistically significant difference was observed regarding tolerability between the three ABHR gel formulations tested, there were differences in acceptability. Participants preferred the smell of the H1 and WHO gel formulations (P=0.003 and P=0.040, respectively); H1 had a better texture than the WHO gel formulation ($P < 0.001$); and H1 was considered more

pleasant overall than Hopigel® (P=0.037). Overall preference varied, but H1 was rated the favorite most often among participants, and the least favorite least often.

Conclusion: We observed a great variability in the participants' reactions to the different formulations tested. These results highlight the importance of giving healthcare workers a choice between different high-quality handrubs to ensure maximum acceptability.

Background

Hand hygiene prevents healthcare-associated infections and antimicrobial resistance.[1,2] Performing hand hygiene (HH) with alcohol-based handrubs (ABHRs) is the gold standard for most care given in healthcare settings.[3] Good tolerability of hand hygiene formulations is key to successful HH implementation strategies, and balancing efficacy and skin tolerability has been one of the key challenges of ABHR manufacturers over the last 25 years. Though the precise effect of ABHR tolerability on healthcare worker (HCW) compliance has not been quantified, it is generally considered one of the critical elements.[1] Providing HCWs ABHR with a high dermal tolerability is both important for protecting their skin from breaking down, potentially providing an entry point for microbial pathogens, and for increasing HCW comfort and thus, compliance.[1]

Though the literature directly tying tolerability to compliance in clinical practice is relatively sparse, tolerability is nonetheless accepted as one of the prerequisites for any ABHR made for use in a healthcare environment. The current WHO Guidelines[1] contain two sections on tolerability concerning product selection and skin reactions, as well as two protocols; one for determining if an ABHR formulation has sufficient skin tolerability to be used in a healthcare setting, and the other for comparing tolerability and acceptability of different ABHRs.[4,5] Both isopropanol and ethanol are used in ABHR formulations and there is very little literature about which type of alcohol is best for maximizing skin tolerability. One in vitro study published as a conference poster in 2013 showed less dryness when using an ethanol-based vs. an isopropanol-based handrub,[6] and there is increasing evidence concerning the irritant characteristics of isopropanol on hands with repeated use.[7]

A number of different emollients and humectants are added to ABHR formulations to protect the skin, either through attracting water to it, or by creating a barrier to prevent water loss. Adding them to formulations is therefore crucial for user acceptance and skin tolerability. The WHO gel formulation uses glycerol as it is inexpensive and widely available; however, increasing glycerol content in a formulation is at the expense of its antimicrobial efficacy.[8,9] Other emollients exist that do not necessarily have this effect, but though manufacturers' ABHR formulations vary greatly, there is little published literature on the comparative tolerability of these specific formulations.[10] Superfatting or relipidizing agents are used in the personal care industry to add moisture back into the skin that the formulation would otherwise take away, and give skin a soft feel.[11] The most well-known example is in soapmaking, where adding extra oil to the oil/lye ratio can make soap that is moisturizing for skin.[12,13] The same is true for other detergents or formulations containing solvents, such as ABHR.[14,15] A number of additives can be used as superfatting agents in ABHRs.[11,16,17]

We compared the tolerability and acceptability of three different ABHR formulations in a population of adult volunteers and determined which types of ABHRs are most likely to be associated with high dermal tolerability in situations of heavy use, such as in healthcare. This was tested in a laboratory setting by simulating intense frequency of ABHR exposure similar to conditions in clinical care by HCWs.

Methods

Each of the 38 participants tested three different ABHR gel formulations in a random order: Hopigel®, which is isopropanol-based with chlorhexidine digluconate, and the WHO gel formulation and Saniswiss Sanitizer Hands H1, which are both ethanol-based. Concerning the formulations' humectants, the WHO gel formulation gel contains glycerol, Hopigel® contains isopropyl myristate and bisabolol, and H1 contains superfatting agents. All of these formulations passed the EN1500 standards[18] and are used in healthcare settings.

The tolerability assessment was based on the WHO "Protocol for Evaluation and Comparison of Tolerability and Acceptability of Different Alcohol-based Handrubs: Method 2".[5] Participants were only included if they did not use ABHR over 10 times per day, therefore excluding most categories of HCWs. Skin type was designated by color according the WHO tool.[5]

Data collection occurred from Monday May 17th to June 18th, 2021. The study design consisted of three 5-day intervention weeks, each followed by a 9-day washout period. During each intervention week, participants were randomized to one of three sequences of the three intervention handrubs.

All handrubs were prepared in identical bottles with only the coded labels differing; study investigators were blinded to the contents. Though the isopropyl alcohol formulation smelled differently, the investigators did not have any close contact with the ABHR, thus keeping the blinding intact. Recruited participants were randomized to their sequence in which they tested

each formulation, determined by a computer generated randomization. Because the study required six in-person meetings, participants were each given a total of CHF100 for their time.

To establish a baseline, pictures and a hand condition form was completed for each participant. As 90% of the population is right-handed, and because the dominant hand often has worse skin condition, participants donned gloves on their left hands when testing the formulations, so that left hands could serve as a control.[19] As drier hands tend to be more reactive to increased handrubbing with ABHRs, gloving the left hand ensured that investigators could observe the greatest possible difference in skin condition in the majority of the test population.[20]

The initial application of the test formulations was performed under supervision by investigators in order to ensure optimal compliance and understanding of the procedure. All participants performed hand hygiene 20 consecutive times with 3mL of ABHR formulation, allowing the skin to dry in between applications. Participants continued this protocol at home for the remainder of the intervention week, and signed and dated a sheet confirming the continuation of this protocol. Participants were also be given 100mL pocket-sized bottles of the ABHR that they were testing for personal use, so that they only used a single ABHR formulation during the intervention week. If participants experienced adverse reactions or discomfort, they could choose to stop for that day or for the remainder of the week, and were be asked to record any and all adverse reactions.

On day five, after their last test session, the participants completed another skin assessment. In addition to the self-assessment, participants and investigators recorded their observations. Investigators provided accurate assessments of participants' skin condition,[21] scoring for scaliness, redness, and fissures. Observation bias was reduced by training observers together to maximize interobserver agreement, and there were always two observers looking at skin condition at any given moment. Any disagreements were discussed and subsequently resolved by a minimum of two observers.

Participants self-reported their skin condition on appearance, integrity, hydration level and sensations. They gave feedback on the test formulation's acceptability including color, smell, texture, irritation, drying effect, ease of use, speed of drying, application, and overall evaluation. Additional feedback concerning the experience with the formulation was collected in a short semi-structured interview, and the volume of ABHR used by each participant was recorded.

Each intervention phase was followed by a 9-day washout period, and in the 2nd and 3rd intervention weeks, participants were given their answers from the previous weeks to reduce bias and encourage consistent scoring. After all three phases, the participants gave their overall impressions and designated their most and least favorite formulation.

Tolerability was evaluated by observers who scored redness (0-4), scaliness (0-5) and fissures (0-3). Primary analyses were based on tolerability outcomes and considered the change from baseline as the primary endpoint . Secondary analyses were based on acceptability outcomes,

i.e. scoring for color, smell, texture, irritation, drying effect, ease of use, speed of drying, and application and used the follow-up values as endpoints (Appendix). Overall evaluation was both calculated as an average of these elements and as a separate question. Primary analyses used mixed-effects models adjusting for baseline score, period and intervention with a subject-specific random effect, whereas secondary analyses did not include baseline score as a fixed effect as it was not measured. We conducted Friedman tests as supportive analyses (Appendix).

As this study concerned in-hospital care practices, it did not fall within the framework of the human research act of the 30 September 2011 (HRA, SR 810.30), and no approval by the ethics committee was needed. Participation was voluntary and all participants signed informed consent forms. All participant data were kept confidential and anonymized before use. The data are property of University of Geneva Hospitals and Faculty of Medicine.

Descriptive statistics show mean (SD), median and interquartile ranges [IQR] or frequency (%) as appropriate. Estimated intervention effects are displayed with 95% confidence intervals (95% CI) and were assessed between the three ABHR formulations. For each outcome, we corrected for multiplicity using the Bonferroni method. All statistical analyses were performed using R version 3.6.3.

Results

All participants completed a previously used and tested questionnaire on hand hygiene and personal habits.[22] Thirty-nine volunteers were recruited to complete the trial; 38 tested each of

the three formulations, and one dropped out of the study due to scheduling conflicts. The participant who only tested one formulation was included in the analysis. The study resulted in a total the 230 baseline and follow-up measurements, and a total of 574 handrubbing sessions. Four participants had one intervention week that consisted of four instead of five handrubbing sessions; one due to an adverse event, and the others due to personal reasons unrelated to the formulations. A total of 30 (76.9%) participants were female; the median age was 24 years (range 21-37). Data on skin color, activities that might impact skin condition, hand cream use and history of dermatitis are shown in Table 1.

Skin tolerability: objective assessment

Table 2 shows the differences in skin tolerability assessed by observers between baseline and follow-up after the use of the three formulations. Neither the primary analyses nor the supportive analysis showed any statistically significant differences between the three formulations (Table 3, Appendix 2).

The mean change from baseline for redness was 0.026 (0.434) for H1, -0.179 (0.683) for Hopigel® and -0.079 (0.428) for the WHO gel formulation. H1 was the only formulation that showed a redness reducing effect. For all formulations, most participants showed no difference, 34/38 (89.5%) for H1 and the WHO gel formulation, and 35/39 (89.7%) for Hopigel®.

Concerning scaliness, all formulations were drying to the skin (Table 2). The WHO gel formulation was the least drying, with a mean change of -0.421 (0.826), and H1 had a very similar result with a mean change of -0.474 (1.01). Hopigel® was the most drying with a mean change of -0.692

(1.15). For the WHO formulation, 27/38 (71.1%) of participants had either no change in scaliness or an improvement in skin condition. For H1, 22/38 (57.9%), and for Hopigel® 20/39 (51.3%) of all participants showed either maintenance or improvement from baseline.

Fissures were quite rare in the participants in all three of the interventions (Table 2). Hopigel® scored lower than the other two formulations with a mean of -0.077 (0.354). The WHO gel formulation had a slight protective effect mean = 0.026 (0.162), and the H1 formulation showed a mean of -0.053 (0.324).

Skin tolerability: self-evaluation

Participants were asked to evaluate their skin's appearance, integrity, level of hydration and physical sensations on a scale of 1-7. The total was calculated, and participants were asked whether their hands were better or worse than usual. The H1 formulation garnered the most positive self-evaluation for the smallest difference between baseline and follow-up with a mean of 0.447 (2.67). The WHO gel formulation had a mean of 2.33 (4.59), and Hopigel® had a mean of 2.13 (3.51). We did not observe any statistically significant difference for changes from baseline through self-evaluation between the three formulations (Table 3). The Friedman test showed a statistically significant association for self-assessed total tolerability score between the formulations (P=0.043, Appendix 2), but not for individually scored parameters. The discrepancies observed between the two analyses can be explained by the fact that the Friedman test does not account for the period effect and regression towards the mean through the adjustment of the baseline score, whereas the mixed-effect model does.

Acceptability

For some comparisons, smell and texture and addition of scores of the formulations showed statistically significant differences for user acceptability (Table 3). Participants preferred the smell of the H1 and WHO gel formulations compared to Hopigel® (P=0.003 and P=0.040, respectively). However there was no statistically significant difference between them. H1 had a better texture than the WHO gel formulation (P<0.001); and H1 was considered more pleasant overall than Hopigel®, scoring higher for the total addition of acceptability elements (P=0.037).

H1 scored the highest in all of the categories except for "color" where the WHO gel formulation scored the highest (though the difference was negligible), and in "speed of drying" where Hopigel® received the same score (Table 3). The average and overall evaluation categories were quite close, with the average of the individual elements scoring slightly higher for all three formulations than the number assigned to the overall evaluation. The Figure shows the overall acceptability of each ABHR gel formulation. Though overall preference varied, H1 was rated the favorite most often among participants, and the least favourite the least often (Table 4).

Discussion

Though there were no discernable differences in the tolerability of the three formulations, there were differences in acceptability and preference. The results concerning the formulations' tolerability are unsurprising, as all three formulations tested were of high quality, already known to have good tolerability and acceptability, and were manufactured specifically for use in

healthcare environments. It is to be expected that the differences between the products would be greater if inferior formulations were tested against any of them. A larger sample size may have been able to show some additional differences, but this was not feasible due to limits on time and resources. The 39 participants who enrolled were only one less than the 40 participants recommended in the WHO protocols.[5] Furthermore, the sample size and study design was similar, and in several aspects more robust than other in vitro studies of ABHR tolerability in the literature.[23–25]

Because participants were not already using high volumes of ABHR in their daily routines, the average skin condition was better than what is often observed among healthcare workers. Fissures, for example, were quite rare among the participants. The fact that the study was performed in summer as opposed to winter may have made the effect of the interventions less obvious as hands tend to be drier and more fragile in winter due to cold and lower humidity.[26] Concerning redness, Hopigel® was the only product where no participant saw an improvement in redness. H1 was the only formulation that showed a very slight (statistically insignificant) net improvement over baseline. It is possible that the superfatting agents were responsible for making H1 a formulation that seemed to protect hands from redness, even improving redness in a few cases. Still, like the other formulations, it had an overall drying effect on the skin. H1 improved skin condition in the highest percentage (11%) of participants, while the WHO gel formulation was the least drying overall, with only 29% of participants experiencing increased dryness. Concerning fissures, only the WHO gel formulation had no participant whose fissures worsened, and one who improved. Outcomes for tolerability and acceptability were not analyzed

by skin color or lifestyle factors, but future research may investigate such potential confounders. The role of the skin microbiome in hand condition, tolerability, and product preference is also a further avenue to explore in the future.

H1 was more pleasant for participants than Hopigel® and the WHO gel formulation in terms of acceptability, though only significant for the former. As highlighted in Table 3, formulations often scored closely in terms of acceptability, and minor differences can be due to natural variability in participants' answers; for example, the formulations all scored slightly differently for "color" although all formulations were clear. For "texture" element, H1 performed higher than both Hopigel® and the WHO gel formulation, with the P value close to statistical significance for H1 vs. Hopigel® (P=0.052). This could be due to the fact that the H1 gel is thixotropic and designed to turn into a liquid once rubbed onto the hands.

It is difficult to say with certainty exactly which elements cause the differences in the formulations. The low scoring for Hopirub® for smell is consistent with the fact that isopropyl alcohol is known to have a stronger odor than ethanol. Still, a minority of participants thought that the other two formulations had a less tolerable smell.

The superfatting agents in H1 may have also been responsible for the "coated" feeling of hands once washed after the intervention, though it may be due to other ingredients in the formulation. Acceptability was sometimes more important than tolerability when it came to preference. The WHO formulation, for example, scored less highly in preference than expected considering the

fact that less participants had skin dryness when using it. Often, participants mentioned smell, drying time, and a moisturizing sensation as elements that were important to them.

Adverse events were quite rare. One severe skin reaction was reported, where a participant developed contact dermatitis from Hopigel® and had to discontinue use due to oedema, redness, swelling, and pain (Appendix 3a). There was also an instance where a participant experienced wrinkling of the skin after applying H1 following a long shower (Appendix 3b). The adverse event lasted for a short time only and did not occur when the participant repeated the 20 frictions the next day.

The most commonly reported feedback concerning each of the three formulations was that Hopigel® smelled strongly and caused little ball-like deposits on hands after the 20 frictions (Appendix 3c), the WHO gel formulation was very sticky and formed “strings” after numerous applications (Appendix 3d), and that H1 gave the sensation of leaving a film on the hands when washing after the handrubbing session. Participants had a wide and polarized range of preferences; some liked very much that the H1 left a film on their hands, and said it made their hands feel protected, while others disliked the sensation and said it felt “slimy”.

Out of the total of 115 follow-up visits, there were three incidents where participants missed a meeting and sent a close-up video of their hand condition on the day the visit was scheduled. Combined with their daily log and feedback, we are confident that this was sufficient for using the data. Due to the repeated and monotonous nature of the intervention, it is possible that the

quality of the applications decreased over time within a given session, though this was not studied. We did analyze total volume upside per intervention period, and found that the volume used did not change significantly from one intervention period to the next though there were some differences by product. Participants who did not return all of their bottles were excluded from the calculations. In intervention period 1, 38 participants used an average of 293.61mL (70.05); in period 2, 38 participants used an average of 290.53 (71.20); and in period 3, 38 participants used an average of 289.03mL (74.64). When analyzed by formulation, the 38 participants using H1 applied an average of 300.79mL (75.81); the 38 participants using Hopigel® applied an average of-270.13mL (71.24); and the 38 participants using the WHO gel formulation applied an average of 302.24mL (63.72) over the intervention period. As volume is a surrogate for compliance, these results could provide some further insight into the link between tolerability, acceptability and compliance.

Lastly, the study conditions of rubbing ABHR gel on hands 20 times in a row do not accurately simulate high-use environments. When participants reapply gel in such a sequential manner, without washing or touching anything in between applications, the emollients and thickening agents build up on hands in a way they would not in a clinical environment. Therefore, some of the elements of acceptability that were exacerbated with continuous repeated use may not have been relevant with normal exposure.

In conclusion, there were no significant differences in tolerability between the three gel formulations tested. Although we aimed to replicate high-use scenarii that can be seen in

healthcare, the results are not directly applicable to care situations, and further study is needed to assess the tolerability and acceptability in healthcare settings. We observed a great variability in participants' reactions to the different formulations tested. Even though H1 had the highest overall acceptability and was preferred most often, there were also a number of participants who strongly preferred the other formulations. These results indicate that formulation preference is quite personal and polarizing. Further study is needed to demonstrate how different high quality ABHRs compare in clinical settings, whether this strong polarization of preference carries over to healthcare workers, and whether preference is associated with improved hand hygiene compliance. If yes, it is clearly important to give healthcare workers a choice between different high-quality formulations to ensure maximum acceptability and thereby enhance patient safety.

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Tables

Table 1: Comparison of three alcohol-based handrub gel formulations: participant characteristics; N=39

		Number	Percentage
Type of skin			
	very fair with freckles	4	10.26%
	fair +/- freckles	10	25.64%
	light brown	13	33.34%
	brown	8	20.51%
	dark brown	1	2.56%
	black	3	7.69%
Activities that can affect hand condition			
	Activities	7	17.95%
	No activities	32	82.05%
Use of hand creme			
	Never	9	23.08%
	Rarely	11	28.20%
	Sometimes, depending the season	10	25.64%
	Once per day	4	10.26%
	Several times a day	5	12.82%
Contact dermatitis			
	Yes	7	17.95%
	No	32	82.05%
Atopic dermatitis			
	Yes	1	2.56%
	No	38	97.44%
Previous adverse event resulting from exposure to ABHR			
	Yes	2	5.13%
	No	37	94.87%

*ABHR : alcohol-based handrub

Table 2: Change in skin tolerability from baseline following repeated application of three alcohol-based handrub gel formulations; randomized-crossover study, N= 39 participants

Difference in redness by result (before/after)										
Product	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**Total**
H1	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)	34 (89.47%)	1 (2.63%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	38 (100.00%)
Hopigel®	1 (2.63%)	0 (0.00%)	0 (0.00%)	3 (7.69%)	35 (89.74%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	39 (100.00%)
WHO gel formulation	0 (0.00%)	0 (0.00%)	1 (2.63%)	2 (5.26%)	34 (89.47%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	38 (100.00%)
Difference in scaliness by result (before/after)										
Product	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**Total**
H1	0 (0.00%)	1 (2.63%)	5 (13.16%)	10 (26.32%)	18 (47.37%)	3 (7.89%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	38 (100.00%)
Hopigel®	1 (2.56%)	1 (2.56%)	7 (17.95%)	10 (25.64%)	17 (43.59%)	2 (5.13%)	1 (2.56%)	0 (0.00%)	0 (0.00%)	39 (100.00%)
WHO gel formulation	0 (0.00%)	1 (2.63%)	4 (10.53%)	6 (15.79%)	26 (68.42%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	38 (100.00%)
Difference in fissures by result (before/after)										
Product	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**Total**
H1	0 (0.00%)	0 (0.00%)	1 (2.63%)	0 (0.00%)	37 (97.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	38 (100.00%)
Hopigel®	0 (0.00%)	0 (0.00%)	1 (2.56%)	1 (2.56%)	37 (94.87%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	39 (100.00%)
WHO gel formulation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	37 (97.37%)	1 (2.63%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	38 (100.00%)

Footnote to Table 2 : changes from baseline condition as assessed by trained observers are indicated for redness, scaliness and fissures

Table 3: Differences in tolerability assessed by observers and through self-evaluation and in acceptability of the three alcohol-based handrub gel formulations; mixed-effects model analysis, randomized-crossover study, N= 39 participants

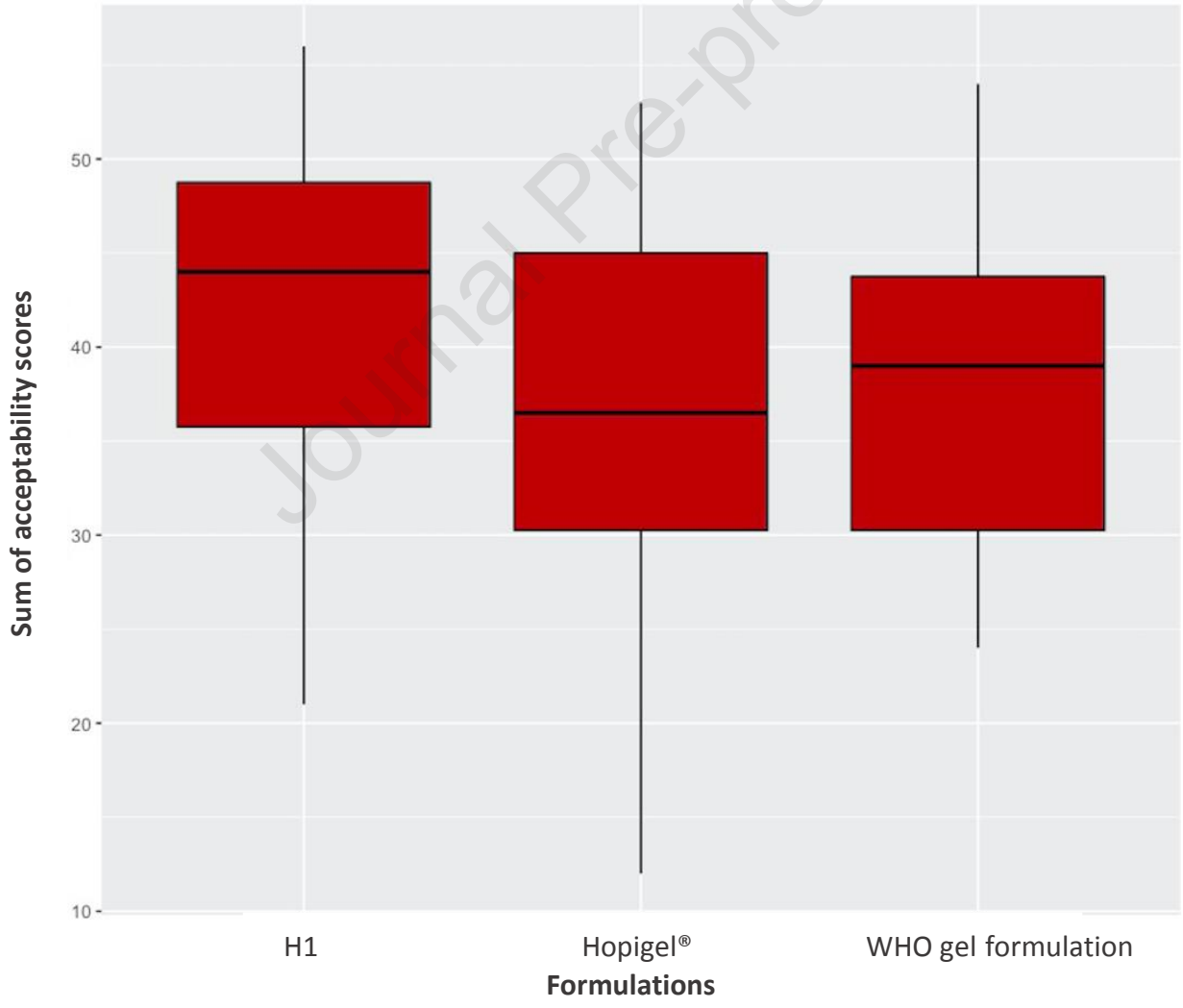
		H1 - Hopigel®		H1- WHO gel formulation		WHO gel formulation - Hopigel®	
		Estimate (95% CI)	P-value	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Observer evaluation	Redness	-0.13 (- 0.4 - 0.14)	0.775	-0.03 (- 0.3 - 0.24)	1	-0.1 (-0.36 - 0.16)	1
	Scaliness	-0.25 (- 0.75 - 0.25)	0.742	0.03 (- 0.47 - 0.53)	1	-0.28 (-0.78 - 0.22)	0.581
	Fissures	-0.05 (- 0.15 - 0.05)	0.695	0.01 (- 0.09 - 0.12)	1	-0.06 (-0.17 - 0.04)	0.466
Self-evaluation	Apparence	0.25 (- 0.26 - 0.77)	0.748	0.23 (- 0.29 - 0.76)	0.889	0.02 (- 0.50 - 0.54)	1
	Integrity	0.25 (- 0.32 - 0.83)	0.902	0.11 (- 0.47 - 0.69)	1	0.14 (-0.43 - 0.72)	1
	Hydratation level	0.61 (- 0.15 - 1.37)	0.179	0.43 (- 0.34 - 1.21)	0.576	0.18 (- 0.58 - 0.94)	1
	Sensations	0.44 (- 0.11 - 0.98)	0.179	0.41 (- 0.13 - 0.96)	0.228	0.02 (- 0.51 - 0.56)	1
	Total Score	1.72 (- 0.17 - 3.61)	0.098	1.53 (- 0.39 - 3.45)	0.186	0.19 (- 1.7 - 2.08)	1
Acceptability	Color	-0.08 (- 0.58 - 0.41)	1	-0.16 (- 0.66 - 0.34)	1	0.08 (-0.42 - 0.57)	1
	Smell	1.44 (0.42 - 2.46)	0.003	0.36 (- 0.66 - 1.38)	1	1.08 (0.06 - 2.09)	0.040
	Texture	0.97 (0.01 - 1.93)	0.052	1.69 (0.73 - 2.65)	0.0001	-0.71 (-1.67 - 0.25)	0.244
	Irritation	0.67 (- 0.15 - 1.48)	0.169	0.24 (- 0.57 - 1.05)	1	0.43 (-0.39 - 1.24)	0.659
	Drying effects	0.67 (- 0.34 - 1.69)	0.354	0.11 (- 0.9 - 1.12)	1	0.56 (-0.45 - 1.58)	0.571
	Ease of use	0.8 (- 0.05 - 1.65)	0.081	0.87 (0.02 - 1.72)	0.050	-0.07 (-0.92 - 0.78)	1
	Speed of drying	-0.002 (- 0.93 - 0.94)	1	0.26 (- 0.68 - 1.20)	1	-0.26 (-1.20 - 0.68)	1
	Application	0.46 (- 0.43 - 1.35)	0.686	0.55 (- 0.34 - 1.45)	0.435	-0.1 (-0.99 - 0.8)	1
	Addition	5.08 (0.33 - 9.83)	0.037	4 (- 0.75 - 8.75)	0.145	1.08 (-3.67 - 5.83)	1

Table 4: Participant designation of "best" and "worst" alcohol-based handrub gel formulation tested; randomized-crossover study, N= 39 participants

	Best-n (%)	Worst-n(%)
H1	19 (50.00)	11 (28.95)
Hopigel ®	14 (36.84)	14 (36.84)
WHO gel formulation	5 (13.16)	13 (34.21)

Figure

Figure: Total of scored elements of acceptability for each of the alcohol-based handrub gel formulations tested; randomized-crossover study, N= 39 participants



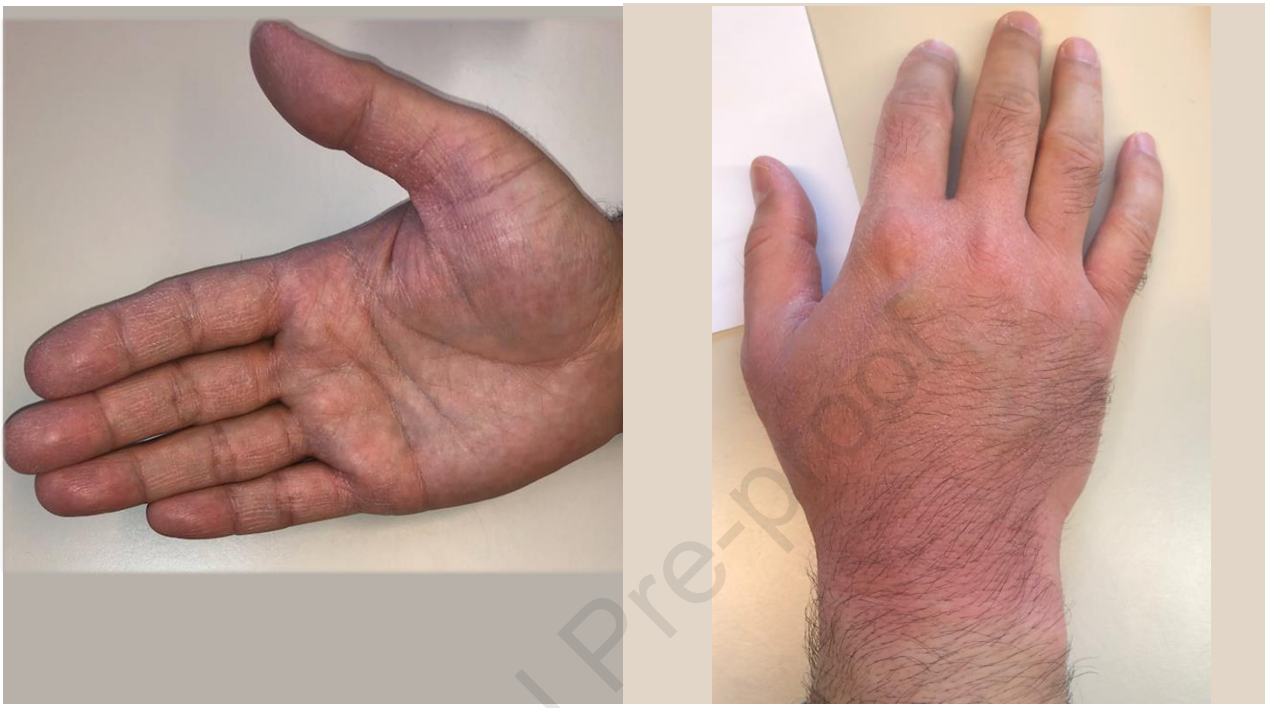
Supplementary electronic material (Appendix)

Appendix 1: Participant questionnaire
(see supplementary document)

Appendix 2: Evaluation of three alcohol-based handrub gel formulations; randomized crossover study. Results of Friedman test for observer-evaluated tolerability, self-evaluated tolerability, and acceptability

	Variable	P-value
Tolerability as assessed by observer	Redness	0.273
	Scaliness	0.250
	Fissures	0.097
Tolerability as assessed by participant	Apparence	0.180
	Integrity	0.809
	Hydration level	0.106
	Sensations	0.118
	Total Score	0.043
Acceptability	Color	0.640
	Smell	0.022
	Texture	0.001
	Irritation	0.148
	Drying effect	0.183
	Ease of use	0.051
	Speed of drying	0.477
	Application	0.245
	Addition	0.140

Appendix 3a: Adverse event to Hopigel®, redness, oedema, scaliness, pain. Reaction subsided over a few days.



Appendix 3b: Wrinkling of skin after 20 applications of H1 following a prolonged hot shower. Reaction subsided quickly, and did not occur again after handrubbing the next day.

Appendix 3c: Texture of Hopigel® after 20 applications

Appendix 3d: Texture of the WHO gel formulation after 20 applications