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Review

Efficacies of the original and modified World Health Organization-recommended hand-rub formulations

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SUMMARY

The World Health Organization (WHO) hand-rub formulations have been in use around the world for at least the past 10 years. The advent of coronavirus disease 2019 (COVID-19) has further enhanced their use. We reviewed published efficacy data for the original and modified formulations. Only efficacy data according to the European Norms (EN) were found. The bactericidal efficacy of the original formulations was, under practical conditions, partly insufficient (EN 1500, only effective in 60 s; EN 12791, efficacy too low in 5 min). The first modification with higher alcohol concentrations improves their efficacy as hygienic hand rub (effective in 30 s). The second (0.725% glycerol) and third (0.5% glycerol) modification improves their efficacy for surgical hand preparation (effective in 5 and 3 min). The original and second modified formulations were tested and demonstrate activity against enveloped viruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 30 s. The ethanol-based formulation is also active against some non-enveloped test viruses in 60 s (suspension tests, EN 14476). In-vivo data on the formulations would provide a more reliable result on the virucidal efficacy on contaminated hands but are currently not available. Nevertheless, the most recent modifications should be adopted for use in healthcare.

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Introduction

Hygienic hand antisepsis is one of the most important measures to prevent healthcare-associated infections caused by micro-organisms such as bacteria, fungi, and viruses. Guidelines published by the US Centers for Disease Control and Prevention and by the World Health Organization (WHO) emphasize the performance of hand hygiene procedure with alcohol-based products [1,2]. Easy access to a fast-acting hand rub with a proven antimicrobial efficacy is a key requirement for hand hygiene in healthcare. The efficacy requirements and test methods, however, vary between countries and continents [3].

The emergence and worldwide spread of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first identified in Wuhan, China, since mid December 2019 has resulted in a major threat to many healthcare systems. Besides personal protective equipment, appropriate hand hygiene is considered an essential step to stop the transmission of SARS-CoV-2 by hands. The shortage of commercially available hand disinfectants in the beginning of the pandemic has focused attention globally on two hand-rub formulations recommended by the WHO in 2009 for local production in
countries and regions with limited resources and a lack of clean water [2,4].

The ingredients of WHO formulation I are 80% v/v ethanol, 1.45% v/v glycerol, and 0.125% v/v hydrogen peroxide (H₂O₂), whereas WHO formulation II contains 75% v/v isopropanol, 1.45% v/v glycerol and 0.125% v/v H₂O₂. Glycerol is added as a humectant to increase the acceptability of the product, and hydrogen peroxide is incorporated to help eliminate contaminating spores [2]. Both formulations can be used for hygienic hand treatment and surgical hand antiseptic. The efficacy requirements and test protocols, however, are completely different. Hygienic hand-rubbing aims to reduce transient hand flora (e.g. *Escherichia coli*, EN 1500) whereas surgical hand antiseptic should primarily reduce the resident hand flora (EN 12791). It is mentioned in the WHO recommendation that the two formulations meet the European efficacy requirements for hygienic hand treatment but without a description of the applied volume and the duration of application, whereas the efficacy requirements for surgical hand preparation were not met in 5 min which is common practice in healthcare in many countries [2]. That is why different efforts have been made in the past to improve the efficacy of both formulations [5–8]. Especially in the coronavirus disease 2019 (COVID-19) shortage situation, healthcare workers were no longer sure which formulation had sufficient bactericidal efficacy for hygienic hand rubbing in 30 s, surgical hand antiseptic in 1.5 or 3 min, and against SARS-CoV-2 in 30 s. The aim of our review is therefore to provide an overview on all published efficacy data obtained with the original WHO-recommended hand-rub formulations and various modifications.

### Results

Nine studies were found with original data on the efficacy of the WHO-recommended hand rubs and three modified formulations. The general bactericidal and yeasticidal activity in suspension of these formulations has so far not been described.

### Search strategy and selection criteria

A Medline search has been done on June 8th, 2020. The following terms were used: WHO-recommended hand rub (six hits) and World Health Organization hand rub (69 hits). Publications were included and results were extracted given they provided original data on the efficacy against bacteria, yeasts, or viruses both in suspension tests and in controlled experiments under practical conditions for hygienic or surgical hand preparation. Reviews were not included, but screened for any information within the scope of this review. Some experiments on the virucidal activity in suspension were performed according to EN 14476 at test concentrations of 80% or 97% due to the addition of virus suspension and soil load. In the EN 14476, testing with a concentration of 97% is only allowed if testing with a concentration of 80% does not reveal sufficient virucidal activity. In case of conflicting results in this review, the concentration of 97% was considered to be more relevant because this mixture is closer to the concentrations used under practical conditions.

### Ethanol-based formulation

The original ethanol-based formulation contains 80% v/v ethanol (~73.5% w/w), 0.125% hydrogen peroxide, and 1.45% glycerol. The efficacy requirement of EN 1500 for hygienic hand antiseptic is not fulfilled with 3 mL in 30 s, but only with two consecutive applications of 3 mL in 30 s, resulting in an applied volume of 6 mL for a total of 60 s [5]. The efficacy requirement of EN 12791 for surgical hand preparation is not fulfilled within 5 min [6,9]. The first modification was to increase the isopropanol concentration to 80% w/w. This modified formulation fulfilled the efficacy requirement of EN 1500 for hygienic hand antiseptic with 3 mL in 30 s, but not enough for surgical hand preparation within 5 min [6,7]. The additional reduction of the glycerol concentration further improved the efficacy for surgical hand preparation so that the modified hand rub with 80% w/w ethanol and 0.725% glycerol was effective in 5 min and the hand rub with 80% w/w ethanol and 0.5% glycerol was effective in 3 min (Table I) [7,8].

The original formulation and its second modification showed consistently virucidal activity (reduction factor >4; inactivation of ≥99.99%) in 30 s against murine norovirus (MNV) as surrogate of human norovirus and various enveloped viruses including SARS-CoV-2 [10–13]. Adenovirus type 5 was inactivated at an 80% concentration within 30 s but the 97% concentration failed with an exposure time >2 min [10,11]. The inactivation of poliovirus was successful in 60 s with a 97% concentration but required more than 5 min with an 80% concentration (Table I) [10,11].

### Isopropanol-based formulation

The original isopropanol-based formulation contains 75% v/v isopropanol (~67.8% w/w), 0.125% hydrogen peroxide, and 1.45% glycerol. The efficacy requirement of EN 1500 for hygienic hand antiseptic is not fulfilled with 3 mL in 30 s, but only with two consecutive applications of 3 mL in 30 s, resulting in an applied volume of 6 mL for a total of 60 s [5]. The efficacy requirement of EN 12791 for surgical hand preparation is not fulfilled within 5 min [6,9]. The first modification was to increase the isopropanol concentration to 75% w/w. This modified formulation fulfilled the efficacy requirement of EN 1500 with 3 mL in 30 s but was still not effective enough for surgical hand preparation within 5 min [6,7]. The additional reduction of the glycerol concentration further improved the efficacy for surgical hand preparation so that the modified hand rub with 75% w/w isopropanol and 0.725% glycerol was effective in 5 min and the hand rub with 75% w/w isopropanol and 0.5% glycerol was effective in 3 min [7,8]. The original formulation and its second modification were active in 30 s against enveloped viruses including SARS-CoV-2 [10–13]. Against non-enveloped viruses the original formulation inactivated adenovirus type 5 in 2 min, but had rather poor virucidal activity against MNV and poliovirus [10] (Table II).

### Discussion

The two alcohol-based WHO-recommended hand-rub formulations for hygienic and surgical hand preparation were published in 2009 specifically for local production in developing countries where access to commercial products is difficult or
| Variable                                      | Original WHO formulation I | 1<sup>st</sup> modified formulation I | 2<sup>nd</sup> modified formulation I | 3<sup>rd</sup> modified formulation I | References |
|-----------------------------------------------|---------------------------|----------------------------------------|--------------------------------------|--------------------------------------|------------|
| **Composition**                               |                           |                                        |                                      |                                      |            |
| Ethanol                                       | 80% v/v<sup>a</sup>       | 80% w/w                                | 80% w/w                              | 80% w/w                              |            |
| Glycerol                                      | 1.45%                     | 1.45%                                  | 0.725%                               | 0.5%                                 |            |
| Hydrogen peroxide                             | 0.125%                    | 0.125%                                 | 0.125%                               | 0.125%                               |            |
| **Antimicrobial efficacy**                    |                           |                                        |                                      |                                      |            |
| Bactericidal activity (suspension test; EN 13727) | No data                  | No data                                | No data                              | No data                              |            |
| Yeasticidal activity (suspension test; EN 13624) | No data                  | No data                                | No data                              | No data                              |            |
| Activity against enveloped viruses (suspension test; EN 14476) | Active against: BVDV (30 s) HCV (30 s) SARS-CoV-2 (30 s) | No data                              | Active against: ZIKV (30 s) EBOV (30 s) SARS-CoV (30 s) MERS-CoV (30 s) influenza A virus (30 s) BCoV (30 s) MVA (30 s) HCV (30 s) SARS-CoV-2 (30 s) | No data | [10–13] |
| Activity against non-enveloped viruses (suspension tests with 80% concentration of test product; EN 14476) | Active against: adenovirus type 5 (30 s) MNV (30 s) Insufficient activity against: poliovirus (300 s; RF 2.2–2.5 log<sub>10</sub>) | No data                              | Active against: adenovirus type 5 (30 s) MNV (30 s) Insufficient activity against: poliovirus (300 s; RF 2.8 log<sub>10</sub>) | No data | [10–13] |
| Activity against non-enveloped viruses (suspension tests with 97% concentration of test product; EN 14467) | Active against: poliovirus (60 s) | No data                              | Active against: MNV (30 s) poliovirus (60 s) Insufficient activity against: adenovirus type 5 (120 s; RF 3.6 log<sub>10</sub>) | No data | [10–13] |
| Bactericidal efficacy for hygienic hand disinfection (EN 1500) | Insufficient efficacy (3 mL for 30 s) Sufficient efficacy (2 mL for 2 × 30 s) Insufficient efficacy (1.5, 3 and 5 min) | Sufficient efficacy (3 mL for 30 s) No data | No data | Sufficient efficacy (5 min) | [5] |
| Bactericidal efficacy for surgical hand preparation (EN 12791) | Insufficient efficacy (5 min) | Sufficient efficacy (5 min) | Sufficient efficacy (5 min) | Sufficient efficacy (3 min) | [6-9] |

BVDV, bovine viral diarrhoea virus; HCV, hepatitis C virus; ZIKV, Zika virus; EBOV, Ebolavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; BCoV, bovine coronavirus; MVA, modified vaccinia virus Ankara; MNV, murine norovirus; RF, reduction factor.

<sup>a</sup> Equivalent to 73.5% w/w.
Table II
Antimicrobial efficacy with corresponding exposure/application times of the WHO-recommended isopropanol-based hand rub and three modified formulations for hygienic and surgical hand preparation

| Variable | Original WHO formulation II | 1st modified formulation II | 2nd modified formulation II | 3rd modified formulation II | References |
|----------|-----------------------------|-----------------------------|----------------------------|-----------------------------|------------|
| Composition | Isopropanol | 75% v/v\(^a\) | 75% w/w | 75% w/w | 75% w/w | |
| Glycerol | 1.45% | 1.45% | 0.725% | 0.5% | |
| Hydrogen peroxide | 0.125% | 0.125% | 0.125% | 0.125% | |
| Antimicrobial efficacy | Bactericidal activity | No data | No data | No data | No data | |
| | Yeasticidal activity | No data | No data | No data | No data | |
| | Activity against enveloped viruses (suspension test; EN 14476) | Active against: BVDV (30 s) HCV (30 s) SARS-CoV-2 (30 s) | No data | Active against: ZIKV (30 s) EBOV (30 s) SARS-CoV (30 s) MERS-CoV (30 s) influenza A virus (30 s) BCoV (30 s) MVA (30 s) HCV (30 s) SARS-CoV-2 (30 s) | No data | [10–13] |
| | Activity against non-enveloped viruses (suspension tests with 80% concentration of test product; EN 14476) | Active against: Adenovirus type 5 (120 s) Insufficient activity against: MNV (120 s; RF 2.8 log\(_{10}\)) poliovirus (300 s; RF 0.5 log\(_{10}\)) | No data | No data | No data | |
| | Bactericidal efficacy for hygienic hand disinfection (EN 1500) | Sufficient efficacy (2 × 3 mL for 2 × 30 s) Insufficient efficacy (3 mL for 30 s) | Sufficient efficacy (3 mL for 30 s) | No data | No data | [5] |
| | Bactericidal efficacy for surgical hand preparation (EN 12791) | Insufficient efficacy (1.5, 3 and 5 min) | Sufficient efficacy (5 min) | Sufficient efficacy (5 min) | Sufficient efficacy (3 min) | [6–9] |

BVDV, bovine viral diarrhoea virus; HCV, hepatitis C virus; ZIKV, Zika virus; EBOV, Ebolavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; BCoV, bovine coronavirus; MVA, modified vaccinia virus Ankara; MNV, murine norovirus; RF, reduction factor.

\(^a\) Equivalent to ~67.8% w/w.
impossible, or commercial products are simply too expensive [2]. As a result of the current COVID-19 pandemic, a global shortage of commercial products has led to these two formulations now being produced in industrialized countries worldwide, which normally have a very strict regime for the approval and marketing of such products. This includes, for example, proof of microbicidal efficacy according to the test regulations applicable in the respective countries [4].

In Europe the existing standards use a step-by-step approach to testing efficacy of hand hygiene products. First, the new formulation is evaluated in vitro in suspension tests for demonstrating bactericidal (EN 13727), yeasticidal (EN 13624), or virucidal (EN 14476) activity. In a second step, the bactericidal efficacy of a new formulation is tested in vivo under practical conditions on the hands of volunteers according to the European Norm EN 1500 for hygienic hand preparation or EN 12791 for surgical hand preparation. Interestingly, the bactericidal or fungicidal in-vitro efficacy of the WHO-recommended hand-rub formulations and their modifications has, to our knowledge, never been investigated and no published data were found. This may be due to the fact that these WHO-recommended formulations never had to go through the process of official approval as biocidal products in Europe, as they were originally intended as an ‘emergency solution’ for non-European developing countries. Nevertheless, a bactericidal activity can be assumed for the ethanol-based hand rub based on data with a similar formulation based on 80% w/w ethanol in 15 s [14]. So far only some in-vitro data are available on the virucidal activity of both the original and modified WHO formulations [10–13]. This is due to the fact that there are still no in-vivo tests available in Europe to verify efficacy against viruses on the hands of volunteers although an ASTM protocol without efficacy requirements has been described and used by investigators (ASTM E 1838-2) [15].

For both original WHO-recommended alcohol-based hand-rub formulations it was shown that they did not meet the European efficacy standards under practical conditions according to EN 12791 [9]. Even prolongation of the duration of application from 3 min to 5 min, the longest exposure for surgical hand preparation allowed by the norm, did not result in a positive outcome [5,9]. Under these conditions or with these negative results, a formulation for surgical hand preparation would not be allowed in European hospitals. But the WHO expert group thought that the microbicidal activity of surgical antiseptics is an ongoing issue for research. Due to the lack of epidemiological data there was, and still is, no indication that the efficacy of n-propanol as a reference in EN 12791 finds a clinical correlate although n-propanol was reported to be the most effective single alcohol against the resident skin flora [16,17]. It was and is the consensus opinion of the WHO expert group that the choice of n-propanol might be inappropriate as the reference alcohol for the validation process. Additionally, only a few formulations for hand antisepsis incorporate n-propanol.

We only found efficacy data according to the European efficacy tests. To our knowledge, WHO alcohol-based hand-rub formulations have never been tested with results published according to the US Food and Drug Administration (FDA) ASTM efficacy standards applicable in the USA.

Since it is difficult to change a European standard and its criteria, many attempts have been made to improve the efficacy of the two WHO-recommended formulations by modifying the composition of the hand rubs step by step. Increasing the alcohol concentration of both formulations by ~7% by using weight instead of volume percent concentrations in a first step and later, in a second step, reducing the glycerol content from 1.45% to 0.725% rendered both hand-rub formulations non-inferior to the reference alcohol n-propanol of EN 12791, and therefore suitable for surgical hand preparation in 5 min according to European requirements [5,7]. These modified WHO formulations were also used by WHO in a before—after intervention cohort study, between July 2013 and December 2015, at five African hospitals [18]. Improvement was observed across all perioperative prevention practices and a significant effect on the overall SSI risk was observed.

Very recently, modifications of both WHO hand-rub formulations containing 80% (w/w) ethanol, 0.125% (v/v) hydrogen peroxide, and 0.50% (v/v) glycerol (WHO I) and 75% (w/w) isopropanol, 0.125% (v/v) hydrogen peroxide, and 0.50% (v/v) glycerol (WHO II) were shown to fulfil the most stringent available in-vivo test method for efficacy testing of products for surgical hand preparation, EN 12791, in 3 min [8]. Glycerol is known to decrease the bactericidal effect of 80% ethanol, 75% isopropanol and 60% n-propanol (all w/w) [19]. The reason for the effect is unknown [19].

Since it is useful to have the same alcohol-based hand-rub formulation in the surgical setting and in other medical areas, especially when there is a product shortage, let us take a look at the efficacy of WHO-recommended hand-rub formulations for hygienic hand treatment.

A hand rub for hygienic hand preparation must firstly inactivate a large part of the clinically relevant transient flora, which may consist of bacteria, yeasts, and viruses. Unfortunately, the bactericidal efficacy of the original WHO-recommended formulations was not sufficient for hygienic hand rub according to EN 1500 in 30 s, which is the common duration of application in most hospitals. A sufficient bactericidal efficacy could only be achieved in 60 s, whereby a necessary exposure time of 1 min per hand disinfection does not contribute to increase the compliance with hand hygiene measures. When modified WHO formulations with increased alcohol concentrations of 80% w/w ethanol or 75% w/w isopropanol were used the requirements of the European efficacy testing norm EN 1500 could be fulfilled in 30 s [5].

All data obtained with the original and the second modified formulations demonstrated a sufficient virucidal activity in 30 s against a variety of enveloped viruses including SARS-CoV-2 [10–13]. The ethanol-based hand-rub formulation was also active against MNV in 30 s. Data obtained with other non-enveloped viruses are conflicting and depend on the hand-rub concentration used for testing. The regular testing with the EN 14476 is done with an 80% concentration. Both the original ethanol-based hand rub and the second modified formulation failed to inactivate poliovirus within 5 min whereas both formulations were effective against poliovirus in 1 min when tested at a 97% concentration. With adenovirus type 5 the results were different. Both the original ethanol-based hand rub and the second modified formulation were effective in 30 s (80% concentration) but the second modified formulation failed to inactivate adenovirus type 5 within 2 min (97% concentration). The reason for the failure of the 97% concentration to inactivate this virus is unknown and is the subject of ongoing in-vitro studies. Although an 80% concentration is typically used to support efficacy claims originated in the suspension assay, we...
consider the 97% concentration to be closer to the use of a hand rub in clinical practice and would therefore prefer to rely on data obtained with a 97% concentration in case of conflicting results. Nevertheless, in vivo tests are considered the preferred methods to evaluate how alcohol-based hand rubs will perform in the real world [20,21]. Ideally the test method includes a suitable positive control (reference disinfection) and clinically relevant efficacy requirements [2].

Although it has already been shown in 2013 how WHO handrub formulations could be improved to meet both European standards for efficacy requirements (EN 1500 and EN 12791), and although these modified formulations have even been used by WHO itself between 2013 and 2015 in a multi-centre study published in 2018, these modifications have not yet been officially approved by WHO [18]. One of the arguments stated was the necessary application duration of 5 min for surgical hand preparation. This duration of application does not correspond with common practice in hospitals in Europe where 3 min or perhaps only 1.5 min are usual. New efficacy data obtained with the third modification of both formulations (reduction of glycerol to 0.5%) provide evidence for sufficient efficacy for surgical hand preparation in 3 min [8]. A second argument was the lack of data on acceptance and tolerability for modified formulations with lower glycerol content. In a study published in 2019, Menegueti et al. showed that a modified WHO formulation containing only 0.5% glycerol led to better ratings of skin tolerance than the original WHO formulation containing 1.45% or a modification containing 0.75% glycerol [22]. The higher concentration of alcohols may increase the risk of skin dryness or skin irritation [23]. The increase of ~7%, however, is quite low suggesting that the overall risk of skin dryness and irritation will not be significantly different from the original formulations. The cost for production of the original formulation is overall low but may increase with a higher concentration of alcohol despite a lower concentration of glycerol [24]. Overall, this important formulating step may now allow the WHO to approve these modified formulations.

Neither of the alcohol-based hand-rub formulations recommended by WHO meets any European efficacy requirements but they are now used worldwide for both hygienic and preoperative hand preparation in the healthcare sector. Based on the results of this literature review, we recommend the preferred use of modified WHO formulations as proposed by Suchomel et al. [8]. Lowering the glycerol concentration to 0.5% might improve availability of these alcohol-based formulations especially in areas with limited supplies of glycerol. Although the criteria for use as a product regulated by the US FDA differ from the EN requirements, these results could also be of interest to US healthcare providers as data according ASTM standards are still not available, neither for the original WHO-recommended alcohol-based hand rubs, nor for one of the described modifications [25].

Conflict of interest statement

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