12WHO-recommended handrub formulations

12.1. General remarks

To help countries and health-care facilities to achieve system change and adopt alcohol-based handrubs as the gold standard for hand hygiene in health care, WHO has identified formulations for their local preparation. Logistic, economic, safety, and cultural and religious factors have all been carefully considered by WHO before recommending such formulations for use worldwide (see also Part I, Section 14).

At present, alcohol-based handrubs are the only known means for rapidly and effectively inactivating a wide array of potentially harmful microorganisms on hands.[60,221,329,484–487]

WHO recommends alcohol-based handrubs based on the following factors:

1. evidence-based, intrinsic advantages of fast-acting and broad-spectrum microbicidal activity with a minimal risk of generating resistance to antimicrobial agents;
2. suitability for use in resource-limited or remote areas with lack of accessibility to sinks or other facilities for hand hygiene (including clean water, towels, etc.);
3. capacity to promote improved compliance with hand hygiene by making the process faster and more convenient;
4. economic benefit by reducing annual costs for hand hygiene, representing approximately 1% of extra-costs generated by HCAI (see also Part III, Section 3);[488–490]
5. minimization of risks from adverse events because of increased safety associated with better acceptability and tolerance than other products (see also Part I, Section 14).[491–498]

For optimal compliance with hand hygiene, handrubs should be readily available, either through dispensers close to the point of care or in small bottles for on-person carriage.[335,485]

Health-care settings currently using commercially-available handrubs should continue to use them, provided that they meet recognized standards for microbicidal efficacy (ASTM or EN standards) and are well accepted/tolerated by HCWs (see also Implementation Toolkit available

at http://www.who.int/gpsc/en/). It is obvious that these products should be regarded as acceptable, even if their contents differ from those of the WHO-recommended formulations described below. WHO recommends the local production of the following formulations as an alternative when suitable commercial products are either unavailable or too costly.

12.1.1. Suggested composition of alcohol-based handrub formulations for local production

The choice of components for the WHO-recommended handrub formulations takes into account cost constraints and microbicidal activity. The following two formulations are recommended for local production with a maximum of 50 litres per lot to ensure safety in production and storage.

Formulation I

To produce final concentrations of ethanol 80% *v/v*, glycerol 1.45% *v/v*, hydrogen peroxide (H_2O_2) 0.125% *v/v*.

Pour into a 1000 ml graduated flask:

a. ethanol 96% *v/v*, 833.3 ml
b. H_2O_2 3%, 41.7 ml
c. glycerol 98%,14.5 ml

Top up the flask to 1000 ml with distilled water or water that has been boiled and cooled; shake the flask gently to mix the content.

Formulation II

To produce final concentrations of isopropyl alcohol 75% *v/v*, glycerol 1.45% *v/v*, hydrogen peroxide 0.125% *v/v*:

Pour into a 1000 ml graduated flask:

a. isopropyl alcohol (with a purity of 99.8%), 751.5 ml
b. H_2O_2 3%, 41.7 ml
c. glycerol 98%, 14.5 ml

Top up the flask to 1000 ml with distilled water or water that has been boiled and cooled; shake the flask gently to mix the content.

Only pharmacopoeial quality reagents should be used (e.g. *The International Pharmacopoeia*) and not technical grade products.

12.1.2. Method for local production

12.1.2.1. Volume of production, containers

- **10-litre** preparations: glass or plastic bottles with screwthreaded stoppers can be used.
- **50-litre** preparations: large plastic (preferably polypropylene, translucent enough to see the liquid level) or stainless steel tanks with an 80 to100 litre capacity should be used to allow for mixing without overflowing.

The tanks should be calibrated for the ethanol/isopropyl alcohol volumes and for the final volumes of either 10 or 50 litres. It is best to mark plastic tanks on the outside and stainless steel ones on the inside.

12.1.2.2. Preparation

1. The alcohol for the chosen formulation is poured into the large bottle or tank up to the graduated mark.
2. H_2O_2 is added using the measuring cylinder.
3. Glycerol is added using a measuring cylinder. As the glycerol is very viscous and sticks to the walls of the measuring cylinder, it can be rinsed with some sterile distilled or cold boiled water to be added and then emptied into the bottle/tank.
4. The bottle/tank is then topped up to the corresponding mark of the volume (10-litre or 50-litre) to be prepared with the remainder of the distilled or cold, boiled water.
5. The lid or the screw cap is placed on the bottle/tank immediately after mixing to prevent evaporation.
6. The solution is mixed by gently shaking the recipient where appropriate (small quantities),or by using a wooden, plastic or metallic paddle. Electric mixers should not be used unless “EX” protected because of the danger of explosion.
7. After mixing, the solution is immediately divided into smaller containers (e.g. 1000, 500 or 100 ml plastic bottles). The bottles

should be kept in quarantine for 72 hours. This allows time for any spores present in the alcohol or the new or re-used bottles to be eliminated by H_2O_2.

12.1.2.3. Quality control

If concentrated alcohol is obtained from local production, verify the alcohol concentration and make the necessary adjustments in volume to obtain the final recommended concentration. An alcoholmeter can be used to control the alcohol concentration of the final use solution; H_2O_2 concentration can be measured by titrimetry (oxydo-reduction reaction by iodine in acidic conditions). A higher level quality control can be performed using gas chromatography[499] and the titrimetric method to control the alcohol and the hydrogen peroxide content, respectively. Moreover, the absence of microbial contamination (including spores) can be checked by filtration, according to the European Pharmacopeia specifications.[500]

For more detailed guidance on production and quality control of both formulations, see the "WHO-recommended hand antisepsis formulation - guide to local production" (Implementation Toolkit available at http://www.who.int/gpsc/en/).

12.1.2.4. Labelling of the bottles

The bottles should be labelled in accordance with national guidelines. Labels should include the following:

- Name of institution
- Date of production and batch number
- Composition: ethanol or isopropanol, glycerol and hydrogen peroxide (% *v/v* can also be indicated) and the following statements:
- WHO-recommended handrub formulation
- For external use only
- Avoid contact with eyes
- Keep out of reach of children
- Use: apply a palmful of alcohol-based handrub and cover all surfaces of the hands. Rub hands until dry. Flammable: keep away from flame and heat.

12.1.2.5. H_2O_2

While alcohol is the active component in the formulations, certain aspects of other components should be respected. All raw materials used should be preferably free of viable bacterial spores. The low concentration of H_2O_2 is incorporated in the formulations to help eliminate contaminating spores in the bulk solutions and excipients[501,502] and is *not* an active substance for hand antisepsis. While the use of H_2O_2 adds an important safety aspect, the use of 3–6% of H_2O_2 for the production might be complicated by its corrosive nature and by difficult procurement in some countries. Further investigation is needed to assess H_2O_2 availability in different countries as well as the possibility of using a stock solution with a lower concentration.

12.1.2.6. Glycerol

Glycerol is added to the formulation as a humectant to increase the acceptability of the product. Other humectants or emollients may be used for skin care, provided that they are affordable, available locally, miscible (mixable) in water and alcohol, non-toxic, and hypoallergenic. Glycerol has been chosen because it is safe and relatively inexpensive. Lowering the percentage of glycerol may be considered to further reduce stickiness of the handrub.

12.1.2.7. Other additives to the formulations

It is strongly recommended that no ingredients other than those specified here be added to the formulations. In the case of any additions, full justification must be provided together with documented safety of the additive, its compatibility with the other ingredients, and all relevant details should be given on the product label.

In general, it is not recommended to add any bittering agents to reduce the risk of ingestion of the handrubs. Nevertheless, in exceptional cases where the risk of ingestion might be very high (paediatric or confused patients), substances such as methylethylketone and denatonium benzoate[503]*)* may be added to some household products to make them less palatable and thus reduce the risk of accidental or deliberate ingestion. However, there is no published information on the compatibility and deterrent potential of such chemicals when used in alcohol-based handrubs to discourage their abuse. It is important to note that such additives may make the products toxic and add to production costs. In addition, the bitter taste may be transferred from hands to food being handled by individuals using handrubs

containing such agents. Therefore, compatibility and suitability, as well as cost, must be carefully considered before deciding on the use of such bittering agents.

A colorant may be incorporated to differentiate the handrub from other fluids as long as such an additive is safe and compatible with the essential components of the handrubs (see also Part I, Section 11.3). However, the H_2O_2 in the handrubs may tend to fade any colouring agent used and prior testing is recommended.

No data are available to assess the suitability of adding gelling agents to the WHO-recommended liquid formulations, but this could increase potentially both production difficulties and costs, and may compromise antimicrobial efficacy.[203,325]

The addition of fragrances is not recommended because of the risk of allergic reactions.

All handrub containers must be labelled in accordance with national/international guidelines.

To further reduce the risk of abuse and to respect cultural and religious sensitivities, product containers may be labelled simply as "antimicrobial handrubs" (see Part I, Section 17.4).

12.1.2.8. Use of proper water for the preparation of the formulations

While sterile distilled water is preferred for making the formulations, boiled and cooled tap water may also be used as long as it is free of visible particules.

12.1.3. Production and storage

Manufacture of the WHO-recommended handrub formulations is feasible in central pharmacies or dispensaries. Whenever possible and according to local policies, governments should encourage local production, support the quality assessment process, and keep production costs as low as possible. Special requirements apply for the production and stock piling of the formulations, as well as for the storage of the raw materials.

Because undiluted ethanol is highly flammable and may ignite at temperatures as low as 10°C, production facilities should directly dilute it to the above-mentioned concentration (Section 12.1.1). The flash points of ethanol 80% (*v/v*) and isopropyl alcohol 75% (*v/v*) are 17.5°C and 19°C,

respectively,(Rotter M, personal communication) and special attention should be given to proper storage in tropical climates (see also Part I, Section 23.6.1). Production and storage facilities should be ideally air-conditioned or cool rooms. Open flames and smoking must be strictly prohibited in production and storage areas. Pharmacies and small-scale production centres supplying the WHO-recommended handrub formulations are advised not to manufacture locally batches of more than 50 litres at a time. For safety reasons, it is advisable to produce smaller volumes and to adhere to local and/or national guidelines and regulations. The production should not be undertaken in central pharmacies lacking specialized air conditioning and ventilation. National safety guidelines and local legal requirements must be adhered to for the storage of ingredients and the final product.

12.1.4. Efficacy

It is the consensus opinion of the WHO expert group that the WHO-recommended handrub formulations can be used both for hygienic hand antisepsis and for presurgical hand preparation.

12.1.4.1. Hygienic handrub

The microbicidal activity of the two WHO-recommended formulations was tested by a WHO reference laboratory according to EN standards (EN 1500) (see also Part I, section 10.1.1). Their activity was found to be equivalent to the reference substance (isopropanol 60 % *v/v*) for hygienic hand antisepsis.

12.1.4.2. Presurgical hand preparation

Both WHO-recommended handrub formulations were tested by two independent reference laboratories in different European countries to assess their suitability for use for pre-surgical hand preparation, according to the European Standard EN 12791. The results are reported in Part I, Section 13.5.

12.1.5. Safety standards

With regard to skin reactions, handrubbing with alcohol-based products is better tolerated than handwashing with soap and water (see also Part I, Section 14).

In a recent study conducted among ICU HWs, the short-term skin tolerability and acceptability of the WHO-recommended handrub formulations were significantly higher than those of a reference product[504]. Lessons learnt about acceptability and tolerability of the WHO-recommended formulations in some sites where local production has taken place are summarized below (Section 12.2).

12.1.6. Distribution

To avoid contamination with spore-forming organisms,[338] disposable bottles should preferably be used although reusable sterilizable bottles may reduce production costs and waste management. To prevent evaporation, containers should have a maximum capacity of 500 ml on ward and 1 litre in operating theatres, and possibly fit into a wall dispenser. Leakage-free pocket bottles with a capacity of no more than 100 ml should also be available and distributed individually to HCWs, but it should be emphasized that the use of these products should be confined to health care only. The production or re-filling unit should follow norms on how to clean and disinfect the bottles (e.g. autoclaving, boiling, or chemical disinfection with chlorine). Autoclaving is considered the most suitable procedure. Reusable bottles should never be refilled until they have been completely emptied and then cleansed and disinfected.

Cleansing and disinfection process for reusable handrub bottles: empty bottles should be brought to a central point to be reprocessed using standard operating procedures. Bottles should be thoroughly washed with detergent and tap water to eliminate any residual liquid. If they are heat-resistant, bottles should be thermally disinfected by boiling in water. Whenever possible, thermal disinfection should be chosen in preference to chemical disinfection, since chemical disinfection might not only increase costs but also needs an extra step to flush out the remains of the disinfectant. Chemical disinfection should include soaking the bottles in a solution containing 1000 ppm of chlorine for a minimum of 15 minutes and then rinsing with sterile/cooled boiled water.[505] After thermal or chemical disinfection, bottles should be left to dry completely upside-down, in a bottle rack. Dry bottles should be closed with a lid and stored, protected from dust, until use.

12.2. Lessons learnt from local production of the WHO-recommended handrub formulations in different settings worldwide

Since the Guide to Local Production has been disseminated through the WHO complementary sites platform and pilot sites, many settings around the world have undertaken local production of the two WHO-recommended formulations.

A web-based survey (http://www.surveymonkey.com) was carried out to gather information on the feasibility, quality control and cost of local production, and the acceptability and tolerability of the formulations by HCWs in different countries. Questions were designed to collect information on issues such as training and numbers of personnel involved in production, the source and cost of each component, quality control of each component and the final product, equipment used for production, adequacy of facility for preparation and storage, and finally distribution and end use. There were also open-ended questions on lessons learnt related to each item. Responses were obtained from eleven sites located in Bangladesh, Costa Rica, Egypt, Hong Kong SAR, Kenya, Mali, Mongolia, Pakistan (two sites), Saudi Arabia, and Spain.

12.2.1. Production facilities and personnel

Production of a WHO-recommended handrub formulation took place at the pharmacy of the health-care facility itself in Egypt, Kenya, Mali, Mongolia, the two sites in Pakistan, and Spain. In Bangladesh, Costa Rica, Hong Kong SAR, and Saudi Arabia, either private commercial or government companies were asked to manufacture the product; in these countries, it is intended that the production will supply numerous health-care settings.

The quantity of handrub produced ranged from 10 litres to 600,000 litres per month. Qualified pharmacists were involved in the production at all sites. However, in the case of local production at the hospital level and also in some large-scale production facilities (e.g. in Bangladesh), this task was added to the regular workload as economic constraints did not permit to dedicate a staff member only for this reason. Other categories of workers were also required for the production, but varied in numbers and qualifications. The facilities for preparation and storage were considered adequate by all but two sites (in Mali and one in Pakistan). Adequate ventilation and temperature control and fire safety signs were also available at most sites.

12.2.2. Procurement of components

All sites, except for the one in Bangladesh and the two located in Pakistan, produced the WHO-recommended formulation I, based on ethanol, mostly because of easier procurement (from local suppliers in most cases) and lower cost. In some cases, ethanol was derived from sugar cane or wheat. In Pakistan, isopropyl alcohol was used because, although cheaper, ethanol is subject to licensing restrictions and to strict record-keeping. Glycerol was procured by local suppliers in most cases while hydrogen peroxide had to be imported in five sites.

12.2.3. Equipment

Procurement of the equipment for production was relatively easy and not particularly expensive in most sites. Either plastic or stainless steel containers were used for mixing except in Egypt where glass containers were used. In contrast, finding adequate dispensers for the final product use was more problematic. In Kenya and Mali, it was not possible to purchase suitable dispensers in the country and they were donated by Swiss institutions. For HCWs, 100 ml pocket bottles are in use in Hong Kong SAR, Mali, Mongolia and Pakistan; 500 ml wall-mounted dispensers are also available in Egypt, Hong Kong SAR, Kenya, Mongolia, Pakistan and Spain. Bangladesh has been using 100 ml glass bottles and 500 ml plastic bottles, Costa Rica 385 ml bottles and Saudi Arabia 1 litre bottles or bags. For long-term sustainability, container moulds of both bottles and caps, for final use may have to be made locally which may represent a very high initial cost. Pakistan was successful in enlisting the support of a private sector company in making bottles using new moulds. Bangladesh too identified local suppliers who are able to make the desired plastic dispensers.

The cleaning and recycling process proposed by WHO has been put in place and is working well in six sites. Methods used for disinfection varied and included treatment with chlorine or alcohol.

12.2.4. Quality control

The quality control of alcohol concentrations in the final product was regularly performed by alcoholmeter in all sites but one. Hydrogen peroxide was quality checked at six sites (Bangladesh, Costa Rica, Mali, Mongolia, Pakistan, and Saudi Arabia).

Multiple samples from seven sites (Costa Rica, Egypt, Hong Kong SAR, Mali, Mongolia, Pakistan, and Saudi Arabia) were sent to the University of

Geneva Hospitals, Geneva, Switzerland, for more sophisticated quality checks by gas chromatography[499] and the titrimetric method to control the alcohol and the hydrogen peroxide content. Initial results from four sites showed either higher or lower alcohol and/or H_2O_2 concentrations, but the product was eventually declared to conform to acceptable ranges in all sites. Quality was shown to be optimal also for three types of formulations made in Saudi Arabia in which either a fragrance or special humectants were added to the WHO formulation I. Interestingly, samples from Mali, which were kept in a tropical climate without air conditioning or special ventilation, were in accordance with the optimal quality parameters in all samples even 19 months after production. The site located in Bangladesh was able to perform gas chromatography and titrimetry for quality control locally and reported optimal results for all tests.

12.2.5. Costs

Cost calculation of the local production of the WHO-recommended handrub formulations at the different sites has been quite complex in the attempt to consider several aspects such as the cost of raw materials and dispensers, the recycling process (when applicable), and production staff salaries. The cost of imported items was linked to the US$ and fluctuated markedly. Cost also varied according to the supplier and the pack sizes. The cost of equipment (if any) to enable the facility to start production was not considered in the cost calculations of the examples below because it varied considerably based on local needs and sources.

The production cost (including salaries but not the dispenser) per 100 ml was US$ 0.37 and US$ 0.30 for formulation I in Kenya and Mali respectively and US$ 0.30 for formulation II in Bangladesh. In Pakistan and Hong Kong SAR, the cost including the pocket bottle was US$ 0.44 per 100 ml of formulation II, and US$ 0.50 per 100 ml of formulation I, respectively. Prices of some commercially-available handrubs may be much higher and vary greatly: US$ 2.50–5.40 for a 100 ml pocket bottle; prices of gels can be as high as US$ 8 for a 100 ml pocket bottle. Effective actions to facilitate local procurement of some raw ingredients for the production of the WHO-recommended handrub formulations would lead very likely to a further reduction of the overall cost of the end product.

Studies are necessary to evaluate the cost-effectiveness of the local production of the WHO-recommended handrub formulation in the course of a hand hygiene promotion campaign. As an example, in 2005 the cost of an alcohol-based hand rinse originally developed by the pharmacy of the

University of Geneva Hospitals and currently commercially marketed, was € 0.57 for a 100 ml pocket bottle, € 1.74 for a 500 ml bottle, and € 3.01 for a 1000 ml bottle. A study performed in this institution on the cost implications of a successful hand hygiene campaign showed that the total cost of hand hygiene promotion, including the provision of the alcohol-based handrub, corresponded to less than 1% of the costs associated with HCAI.[490]

12.2.6. Issues raised by the survey

Several issues related to the expertise and time availability of personnel involved in production were identified by the survey participants. These included the request for additional training in production aspects for pharmacists, the need for existing staff to take on responsibilities in addition to their primary roles, decisions to include production as part of the job description of hospital pharmacists, and the question of remuneration for these additional responsibilities.

Some participants emphasized that more attention needs to be paid to the requirements for preparation and storage facilities, especially if production has to be scaled up to peripheral hospitals. A purpose-built production area with proper humidity and temperature control according to the recommendations for good manufacturing practices is a prerequisite for production. Several items of equipment were inadequate in some facilities, particularly for scaling up. Clearer guidance on large-scale production would be beneficial and WHO is exploring practical solutions to resolve this issue.

There were also lessons learnt related to the procurement of raw ingredients. Sub-standard materials are available on the market and it is important to select local sources with care. It would be important to have specific recommendations on the chemical grade of the component and acceptable manufacturers. However, actual requirements need to be considered when taking decisions on quantities to be purchased and specific attention should be paid to the risk of shortages of supplies, especially in remote areas.

In some cases, the possibility of theft and accidental ingestion of the alcohol-based handrub made it difficult to obtain support from hospital administrators.

The survey showed that in many hospitals the facilities and the equipment for quality control are inadequate, especially as far as testing for hydrogen

peroxide is concerned. However the centralization of high-level quality control at the University Hospitals of Geneva overcame these obstacles and provided timely and very helpful support. Nevertheless, the availability of this service may be reduced with the expansion of local production to more sites around the world. Indeed, the fact that some samples failed to meet the standard required concentrations indicated the importance of the quality check, and it would be very important to identify other reference laboratories able to perform it.

Tolerability and acceptability information were available from four sites (Bangladesh, Hong Kong SAR, Pakistan and Saudi Arabia) where, in general, the WHO-recommended formulations were well appreciated by HCWs. In Hong Kong SAR and Pakistan, the WHO-recommended formulations were preferred to the product previously in use because of better tolerability. Hair bleaching and one case of dermatitis were the rare adverse effects reported. Issues related to the unpleasant smell of the final product were raised by HCWs from all four sites, but were not a major obstacle to adoption. No religious issues related to the alcohol content were identified in the survey.

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