(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☒ No ☐

This application comes from within the WHO itself and builds on long-standing activities aimed to highlight the burden of health-care associated infections (HCAI) and on the general awareness of the need for infection prevention and control that the current outbreak of Ebola virus disease has induced.

Health-care workers’ hands are the most frequent means of transmitting HCAI pathogens. Hand hygiene and use of alcohol-based hand rub (ABHR) reportedly leads to significant reduction of HCAI in both adults and pediatrics. The WHO Report on the Burden of Endemic HCAI Worldwide states that implementation of best hand hygiene practices at the bedside is crucial as a global solution.

In England, 8.2% of patients admitted to hospital develop HCAI (Hospital Infection Society 2007). HCAI cause 5,000 deaths and cost £930 million annually (National Audit Office 1998). In the USA, an estimated 5% of patients develop HCAI, at a cost of 4.5 billion USD per year. This translates into an estimated two million cases of HCAI per annum, accounting for nearly 100,000 deaths (Klevens 2007). In Canada, an estimated 220,000 HCAI occur each year, with 8,000 related deaths (Zoutman 2003).

The Application does not report data from developing countries. However, it is stated that studies of hand hygiene promotion in relation to preventing HCAI have been conducted in developing countries as Armenia, Costa Rica, Mali, Pakistan.

Infection control experts are working to identify and correct factors that contribute to these rates. Although hand hygiene has long been regarded as the most effective preventive measure (Teare 1999), several studies over the past few decades have demonstrated that compliance with hand hygiene recommendations is poor and interventions are not effective long term. [Gould DJ et al. Interventions to improve hand hygiene compliance in patient care. Cochrane Library 2010].

(2) Have all important studies that you are aware of been included in the application?

Yes ☒ No ☐

The application mainly refers to WHO guidelines and related documents, in particular:

- WHO Guidelines on Hand Hygiene in Health Care, 2009
• Interim Infection Prevention and Control Guidance for Care of Patients with Suspected or Confirmed Filovirus Haemorrhagic Fever in Health-Care Settings, with Focus on Ebola, 2014

The Applicant has provided a link to a list of relevant publications [http://www.who.int/gpsc/journals_articles/en/] including systematic reviews that are cited in chapter 8 but not other important contributions that were considered in this assessment report. These latter include:
• Macinga DR, et al. The relative influences of product volume, delivery format and alcohol concentration on dry-time and efficacy of alcohol-based hand rubs BMC Infectious Diseases 2014, 14:511

The application does not accurately link statements to evidence-based publications.

(3) **Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?**

Yes ☒ for efficacy  No ☒ for effectiveness

The CDC Guideline of 2002 carefully addressed the antimicrobial and antiviral activity of alcohols and the several factors that affect their efficacy, including the type, concentration and volume of alcohol used, contact time, and whether the hands are wet when the alcohol is applied.

The systematic reviews of Picheansathian et al. of 2004 compared the effectiveness of different alcohol-based solutions for hand hygiene. The authors concluded that at equal concentrations, N-propanol is the most effective alcohol of those commonly used and ethanol the least. Isopropanol 90% is as effective as Npropanol 60% in antimicrobial activity. Ethanol-based formulations should contain at least 70% ethanol (v/v). It is noteworthy that, when expressed as percent by volume (v/v) instead of percent by weight (w/w), the alcohol content of solutions can be affected by temperature, specific gravity, and reaction concentration. For example, 70% alcohol by weight is equivalent to 76.8% by volume if prepared at 15ºC, or 80.5% if prepared at 25ºC [CDC Guideline, 2002].
More recently (2014) Macinga et al. investigated the influence of product volume, delivery format, and alcohol concentration on dry-time and antimicrobial efficacy of ABHR foams, gels, and rinses and concluded that application volume is the primary driver of ABHR dry-time and efficacy, whereas delivery format does not significantly influence either. Although products with greater alcohol concentration dry more quickly, volumes required to meet EN 1500 standards (see WHO Guidelines 2009, p.25) can take longer than 30 s to dry, even when alcohol concentration is as high as 90%.

In their review about the ‘Role of hand hygiene in healthcare-associated infection prevention’ [Journal of Hospital Infection, 2009; 73:305-315] Allegranzi and Pittet argue that there is convincing evidence that improving hand hygiene can reduce infection rates. This conclusion is based on 23 studies published between 1977 and 2008, almost all reportedly showing a temporal association between improved hand hygiene practices and reduced infection and cross-transmission rates. All these studies but one were observational. Only 12 included ABHR, most often along with other promotional and/or educational interventions. In nine studies there was a reduction in HCAI rate, which the authors recognize as the ultimate outcome. This result could not be achieved in the other three studies including the sole controlled cross-over study, which however was criticized for some shortcomings. Allegranzi and Pittet note that in many countries, the evidence from studies on hand hygiene effectiveness has been convincing enough to motivate governments to invest resources in hand hygiene national and subnational campaigns. However, the authors continue - this evidence mainly reflects findings from interventions implemented in healthcare settings in developed countries. Looking at procurement opportunities, ABHR products are available only in South Africa in the African continent and in China, India, and Japan in the Asian Pacific region. Allegranzi and Pitt conclude that further research is needed to evaluate the relative efficacy of each key element of multimodal strategies, to assess their implementation feasibility in settings with limited resources, and to gather information on successful solutions allowing adaptation.

As for compliance, the 2010 update of the Cochrane systematic review by Gould et al. included four studies reporting indicators of hand hygiene compliance and proxy indicators such as product use. Microbiological data were recorded in one study. Hand hygiene compliance increased for one of the studies where it was measured by direct observation instead of the less reliable product use, but the results from the other study were not conclusive. Product use increased in the two studies in which it was reported, with inconsistent results reported for one initiative. MRSA incidence decreased in the one study reporting microbiological data. The authors concluded that “the quality of intervention studies intended to increase hand hygiene compliance remains disappointing. Although multifaceted campaigns … appear to have an effect, there is insufficient evidence to draw a firm conclusion. There remains an urgent need to undertake methodologically robust research to explore the effectiveness of soundly designed and implemented interventions to increase hand hygiene compliance”.

In their research paper of 2008 Picheansathian and Coll. report that after implementing a hand hygiene promotion program in a neonatal intensive care unit of a university hospital in Thailand, compliance with hand hygiene among nursing personnel improved significantly from 6.3% before the program to 81.2% 7 months after the programme.
However, hospital infection rate did not decrease after the intervention but remained high at 18.4 episodes/100 patients. The authors mention that this also occurred in two previous studies (Simmons B et al. Infection Control and Hospital Epidemiology 1990; 11: 589–594; and Salemi C. et al. Infection Control and Hospital Epidemiology 2002; 23: 32–35).

In conclusion, while we are pretty confident about which ABHR products and how should be used and about their microbiological efficacy, there are inconsistent findings supporting their effectiveness in terms of reduction of HCAI rate. According to most of the literature in this field, the last update of the Cochrane systematic review and the Applicant itself, there is no consistent evidence that ABHR promote hand hygiene compliance or reduce HCAI.

(4) Is there evidence of efficacy in diverse settings and/or populations?

Yes ☑ No ☐

It is important to define the utility of the hygiene program in different clinical and geographical setting, including experience as in emergency humanitarian situations (medical camp, epidemic events).

The history of hand hygiene is closely linked to the pediatric population and hand hygiene in children has been studied most often in the neonatal intensive care units.

In their review of 2009 Allegranzi and Pittet took into consideration studies conducted in adult and neonatal intensive care units, medical intensive care units, adult intermediate care units, newborn nurseries, neurosurgery units, orthopedic surgical units, urology units and even hospital-wide studies. However, the authors recognized that evidence about efficacy and effectiveness of ABHR mainly reflects findings from interventions implemented in healthcare settings in developed countries. As mentioned in section (3), ABHR products are available only in a few African and Asian countries.

(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☐ No ☑ refers to the 2nd Q

According to the CDC Guideline the drying effect of alcohol can be reduced or eliminated by adding 1%–3% glycerol or other skin conditioning agents. Alcohol-based rinses or gels containing emollients cause substantially less skin irritation and dryness than the soaps or antimicrobial detergents tested.

Even well-tolerated alcohol hand rubs containing emollients may cause transient stinging sensation at the site of cuts or abrasions. ABHR preparations with strong fragrances may be poorly tolerated by people with respiratory allergies. Allergic contact dermatitis or contact urticaria syndrome caused by hypersensitivity to alcohol or various additives present in certain ABHR occurs only rarely (CDC Guideline).
ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☒ No ☐

In general these products for hand hygiene could be used everywhere by healthcare professionals with a minimum of 20-30 second of application. WHO provides a range of tools to 1) educate on use of product; 2) raise awareness to the times when product should be used; 3) monitor usage of products/hand hygiene in practice; 4) manufacture ABHR in hospital pharmacies or other facilities for local use.

When ABHR is made locally according to the instructions provided by the WHO (see section (9)), quality assurance is required which needs alcoholmeters on site or the ability to send a sample of the product to an approved facility.

Alcohols are flammable. Flash points of ABHR range from 21°C to 24°C, depending on the type and concentration of alcohol. As a result, ABHR should be stored away from high temperatures or flames.

Since alcohols are volatile, containers should be designed so that evaporation is minimized and initial concentration is preserved.

Contamination of alcohol-based solutions has seldom been reported.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☒

The main ingredients listed by WHO as constituting effective ABHR products are Ethanol (96%), Hydrogen peroxide (3%), Glycerol (98%), Sterile distilled or boiled cold water, Isopropyl alcohol (99.8%).

Ethanol is listed in both the US & EU pharmacopeia as a medicine ingredient. In addition, in the US, ABHR are regulated by FDA as OTC drugs. However, the Applicants recognize that ABHR are not currently registered as medical products in all countries. In Canada and Australia, ABHR are defined as “natural health products” or “therapeutic goods” respectively.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☒ No ☐

- WHO Guidelines on Hand Hygiene in Health Care First Global Patient Safety Challenge Clean Care is Safer Care (2009)
(9) Please comment briefly on issues regarding cost and affordability of this medicine.

Commercial ABHR are produced mainly in the USA and Europe, and exist in health care in most developed countries. The implementation toolkit accompanying the 2009 WHO Guidelines on Hand Hygiene in Health Care includes a Guide to Local Production to manufacture ABHR in hospital pharmacies or other facilities for local use. Local production has been carried out in many healthcare settings worldwide and was reportedly monitored and evaluated by WHO in several sites. No major procurement, production, and storage obstacles were encountered and long-term stability at tropical temperatures was up to 19 months. The final products complied with quality control standards and had good skin tolerability at low cost (less than US $0.50 per 100 mL). Estimates from the UK suggest that even a reduction of just 0.1% in the rates of HCAI, achieved through the implementation of ABHR at the point of care, is highly likely to be cost saving over a five year period (WHO Guidelines, 2009).

(10) Any additional comments?

This reviewer concurs with Allegranzi and Pittet that research in this field is a challenging activity since methodological and ethical concerns make it difficult to conduct adequately sized randomized controlled trials that could establish the relative importance of hand hygiene in the prevention of HCAI. In addition, it is recognized that HCAI surveillance is a very resource- and time-consuming activity requiring rigorous and standardized methods, and therefore is seldom available on a regular and reliable basis. However, it is also agreed that demonstration of the effectiveness of strategies to improve hand hygiene on the ultimate outcome of HCAI rate is crucial in both motivating healthcare workers’ behavioral change and securing an investment in this preventive measure by policy-makers and healthcare managers. The effectiveness of ABHR in terms of HCAI reduction appears to be still controversial. Another controversial issue is how significant should be the hand hygiene compliance increase following the intervention in order to be considered satisfactory.

(11) Please summarise the action you propose the Expert Committee takes.

This reviewer endorses the WHO public health recommendation to use ABHR. It is also acknowledged that full global adoption remains challenging. Including ABHR in the EML might help promote their use and facilitate accessibility to these products. However, considering ABHR as medicines could be seen as an arbitrary stretching of their role. The basic logic itself should support their extended use. Much HCAI is spread by direct contact and it is logical to suppose that hand hygiene can interrupt the chain of infection. The established microbiological efficacy of ABHR should be enough to support this basic assumption. On the contrary, the current inconsistent findings about ABHR effectiveness in
terms of compliance promotion and HCAI reduction could make someone argue against their inclusion in the main EML.

Therefore, this reviewer is of the opinion that

- the WHO should keep promoting the use of ABHR products and instigate comparative clinical trials of their microbiological efficacy and effectiveness in terms of better compliance and prevention/reduction of HCAI in different clinical and geographical settings;
- in the meantime, ABHR might be placed in the Complementary List.