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Review

Efficacy of ethanol against viruses in hand disinfection

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Ethanol is used worldwide in healthcare facilities for hand rubbing. It has been reported to have a stronger and broader virucidal activity compared with propanols. The aim of this review was to describe the spectrum of virucidal activity of ethanol in solution or as commercially available products. A systematic search was conducted. Studies were selected when they contained original data on reduction of viral infectivity from suspension tests (49 studies) and contaminated hands (17 studies). Ethanol at 80% was highly effective against all 21 tested, enveloped viruses within 30 s. Murine norovirus and adenovirus type 5 are usually inactivated by ethanol between 70% and 90% in 30 s whereas poliovirus type 1 was often found to be too resistant except for ethanol at 95% (all test viruses of EN 14476). Ethanol at 80% is unlikely to be sufficiently effective against poliovirus, calicivirus (FCV), polyomavirus, hepatitis A virus (HAV) and foot-and-mouth disease virus (FMDV). The spectrum of virucidal activity of ethanol at 95%, however, covers the majority of clinically relevant viruses. Additional acids can substantially improve the virucidal activity of ethanol at lower concentrations against, e.g. poliovirus, FCV, polyomavirus and FMDV although selected viruses such as HAV may still be too resistant. The selection of a suitable virucidal hand rub should be based on the viruses most prevalent in a unit and on the user acceptability of the product under frequent-use conditions.

Introduction

Ethanol is widely used in hand rubs, gels, and foams for hand hygiene in healthcare settings [1–7]. The World Health Organization has even listed ethanol at 80% (v/v) as an essential medicine in the category 'alcohol-based hand rub' [8]. Since 1994 the US Food and Drug Administration considers ethanol between 60% and 95% as generally safe and effective for hand rubbing, although the safety aspect has been under review again since 2015 [9]. Recent studies indicated that there may be a risk from systemic absorption and long-term exposure. The aim of the new proposed rule is to demonstrate systemic safety under daily and long-term use [10]. The spectrum of antimicrobial activity of a hand rub used in healthcare must include bacteria and yeasts according to EN 14885; virucidal activity, however, is not mandatory [11]. However, ∼5% of all healthcare-associated infections are caused by viruses, so virucidal activity of hand rubs has relevance in some units with a high prevalence of viral disease and during viral outbreaks [12]. The European terminology allows three different claims on virucidal activity: 'active against enveloped viruses'; 'limited spectrum virucidal activity' which includes enveloped viruses, adenoviruses, noroviruses and rotaviruses; and 'virucidal activity' which includes all viruses relevant in human medicine [13]. Numerous studies have been published on the virucidal activity of ethanol solutions and products but the spectrum of virucidal activity of ethanol has so far not been described in detail. The aim of this review is therefore to describe the spectrum of virucidal activity of ethanol *in vitro*

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and *in vivo*. In addition, the European claims are evaluated regarding specific viruses that may not be covered by the test viruses selected for a specific claim.

Methods

A systematic literature search was conducted via the National Library of Medicine (PubMed) on October 10th, 2016, and updated on June 22nd, 2017, using the following terms: virucidal activity alcohol (85 hits), virucidal activity ethanol (41 hits), virucidal efficacy alcohol (38 hits), virucidal efficacy ethanol (22 hits), alcohol-based hand rub virus (22 hits), alcohol-based hand rub viruses (19 hits), ethanol-based hand rub virus (three hits), ethanol-based hand rub viruses (one hit), ethanol virucidal disinfectant (50 hits), ethanol-based sanitizer virucidal (four hits), alcohol-based sanitizer virucidal (three hits), virus inactivation ethanol hand (15 hits), virus inactivation ethanol hands (16 hits) and virus inactivation alcohol hand (24 hits). In addition, studies deemed suitable for this review were also included. Data were extracted from the publications and were selected when they provided original data on reduction of viral infectivity in suspension tests (49 studies) and on contaminated hands (17 studies). A solution or product was considered sufficiently effective against a virus in a suspension test when it achieved ≥ 4 $\log_{10}$ reduction or the limit of detection was reached. There was no minimum criterion for the limit of detection so that solutions or products could have passed in an assay, although the initial viral titre may have been low or the cytotoxicity of the product may have been high, resulting in an overall low $\log_{10}$ reduction of viral infectivity. Studies were not included when they provided data on the reduction of viral infectivity on inanimate surfaces or used other methods to determine efficacy (e.g. reduction of viral RNA).

Results

The concentrations of ethanol are described in w/w and were sometimes determined by calculation when they were originally in v/v. Some studies, however, did not specify whether the ethanol concentration was by volume or weight. In these cases, the ethanol concentration is described without w/w.

Efficacy against enveloped viruses

Ethanol has been shown to be effective against various enveloped viruses [14]. Beginning at a concentration of 42.6% (w/w) ethanol is effective within 30 s against SARS coronavirus, MERS coronavirus, ebolavirus, influenza A virus including the human type H3N2, the avian type H3N8 and human type H1N1, influenza B virus, HIV, HBV, vacciniavirus, duck hepatitis B virus, togavirus, pseudorabies virus, Newcastle disease virus, bovine viral diarrhoea virus, zikavirus, herpes simplex viruses type 1 and 2 and RSV [5,14–35]. Ethanol is effective at 73.6% (w/w) against HCV in 15 s and 30 s but not at 40% [16,35,36].

Efficacy against non-enveloped viruses in suspension tests

EN 14476 allows determining a partial activity against non-enveloped viruses described as 'limited spectrum virucidal activity' tested with adenovirus type 5 and murine norovirus. A hand rub with limited spectrum virucidal activity is considered to be effective against enveloped viruses, adenovirus, norovirus, and rotavirus. In a first step, data from suspension tests according to the test principle of EN 14476 are reviewed for those viruses covered by the claim of 'limited spectrum virucidal activity'. These viruses have particular clinical importance as outbreak viruses. In 2016 a total of 1444 nosocomial outbreaks have been notified in Germany with 76.0% being caused by noroviruses and 6.4% being caused by rotaviruses [37].

Adenovirus

Ethanol as a solution has largely sufficient activity in 30 s against adenovirus type 5 (test virus of EN 14476) at concentrations between 45% (w/w; contains additional active ingredients) and 95% (w/w) although one study indicates sufficient activity only in 1 min with 77% (w/w) ethanol [3,30,35,38,39]. Ethanol at 70% (w/w) as a gel was sufficiently active in 2 min [3].

Adenovirus type 2 is less susceptible. Ethanol needs 2 min at 55% (w/w) and 85% (w/w) [5,21]. In 30 s, ethanol at 62.4% (w/w) was not sufficiently effective [40]. Ethanol at 50% required a 10 min exposure time to be effective [14]. The combination of ethanol 73.6% (w/w) and peracetic acid (0.2%), however, was effective in 30 s [41].

Data with other adenoviruses do not provide a clear picture. Ethanol at 72.5–77% (w/w) was effective in 60 s against adenovirus type 7 but not against adenovirus type 8 [42].

Rotavirus

Gels based on 85% ethanol (w/w) or the combination of 62.4% (w/w) ethanol with additional citric acid were effective against rotavirus in 30 s as well as a hand rub based on 55% ethanol (w/w), 0.7% phosphoric acid and three other alcohols [5,21,40].

Norovirus

Today, the murine norovirus (MNV), a gastrointestinal tract virus, is widely used to determine the activity against noroviruses. Ethanol at concentrations between 62.4% (w/w) and 85.8% (w/w) is usually effective against MNV in 30 s or 1 min [30,35,38,43–45]. Lower concentrations were less effective. A gel based on 53.2% (w/w) ethanol was only effective in 1 h [46]. According to one study, ethanol at 42.6% (w/w) reduced MNV in 1 min by 0.3 $\log_{10}$ and in 5 min by 0.4 $\log_{10}$ [44]. In another study, ethanol at 42.6% (w/w) reached $\sim$3 $\log_{10}$ reduction in 30 s whereas ethanol at 24.7% (w/w) or 8% (w/w) is ineffective within 3 min [43].

In the past, the feline calicivirus (FCV) was often used as a surrogate for human noroviruses although it is a respiratory tract virus. FCV is difficult to inactive by ethanol. Ethanol solutions at 42.5% and 62.4% (both w/w) were effective at 3 min; ethanol at 73.6% (w/w) required 5 min [47]. Formulations with 72.5% ethanol (w/w) did not reach a 4 $\log_{10}$ reduction in 60 s [42]. A solution based on 77% ethanol (w/w) showed only little activity against FCV in 60 s ($<$1 $\log_{10}$) [42]. Even after 5 min the efficacy was still insufficient ($<$2 $\log_{10}$) [39]. A hand rub based on $>$85.8% (w/w) ethanol was almost ineffective in 30 s ($<$1 $\log_{10}$) [30]. Finally, ethanol at 42.6%, 62.4%, and 85.8% (all w/w) revealed insufficient efficacy in 5 min with the highest $\log_{10}$ reduction of 2.6 [44].

Whenever different types of acid are added, ethanol in hand rubs has been described to be effective in 30 s at 45%, 50.2%, 55%, 62.4%, and 67.9% (all w/w) [21,30,40,48]. Malic acid at 0.35% has also been reported to improve the efficacy of ethanol against FCV to some extent [49].

Enteroviruses

EN 14476 allows determining a full virucidal activity (test viruses: adenovirus type 5, murine norovirus, and poliovirus type 1). In a second step, data from suspension tests according to the test principle of EN 14476 are reviewed for enteroviruses that should be covered by the claim 'virucidal activity'.

Coxsackievirus

Data on the efficacy of ethanol against coxsackievirus are conflicting. Ethanol at 72.5–92.4% (w/w) has been reported to be effective against coxsackievirus B5 within 60 s and also against coxsackievirus B1 within 10 min but not against coxsackievirus A7 [42,50]. Higher ethanol concentrations (85–90%) are effective against coxsackievirus B3 in 15–60 s [51].

Echovirus

The efficacy of ethanol against echoviruses is rather good. One study shows that ethanol at 92.4% (w/w) is effective against echovirus 11 in 20 s [52]. Another study found a $\log_{10}$ reduction $\geq$3 within 1 min for ethanol at 92.4% (w/w) against the same virus, whereas ethanol at 67.9% (w/w) was almost ineffective (<1 $\log_{10}$) at the same exposure time [53]. Against echovirus 6 ethanol was effective at 50% within 10 min [14].

Human enterovirus 71

Against the human enterovirus 71 ethanol had only little activity at 62.4% (w/w) and 67.9% (w/w) within 10 min (<1 $\log_{10}$). At 79.6% (w/w) a 3.21 $\log_{10}$ reduction was achieved in the same exposure time, and at 92.4% (w/w) the $\log_{10}$ reduction was 5.78 [54].

Poliovirus

All formulations with ethanol up to 80% (w/w) and without acid were not sufficiently effective in up to 5 min against poliovirus type 1 when tested under standard conditions with 80% product proportion in the suspension (Table I). When the product proportion is increased in the suspension test to 97%, some formulations with 73.5% or 80% ethanol (w/w) were effective within 1 min. One formulation with 95% (w/w) ethanol was effective in 30 s. Gels were mostly less effective compared to solutions.

The addition of various types of acids can substantially improve the activity of ethanol against poliovirus type 1 so that the formulations are often sufficiently effective in 30 s (Table II).

Poliovirus type 2 is somewhat less susceptible to ethanol compared to poliovirus type 1 [57].

Rhinovirus

A hand rub based on 55% ethanol (w/w), 0.7% phosphoric acid, and three other alcohols was effective in 30 s [21].

Other non-enveloped viruses

In a third step, data from suspension tests according to the test principle of EN 14476 are reviewed for other non-enveloped viruses that should be covered by the claim 'virucidal activity'.

Hepatitis A virus

A gel based on 54.2% ethanol (w/w) showed no effect at all (0 $\log_{10}$) against hepatitis A virus (HAV) after 30 s [40]. Ethanol at 80% or 95% (both w/w) was not sufficiently effective within 2 min [58]. A hand rub based on 80% ethanol showed only little reduction of viral infectivity within 30 s (0.47), but it was higher after 2 min ($\geq$2.2 $\log_{10}$) [24]. When 0.7% phosphoric acid and three other alcohols are added to ethanol at 55% (w/w) the formulation was effective against HAV in 30 s [21]. Ethanol at 62.4% (w/w) with additional 0.25% citric acid, however, was not sufficiently effective in 30 s with 1.75 $\log_{10}$ [40].

Table I
Efficacy of different formulations based on ethanol without additional acids in suspension tests against poliovirus type 1

Ethanol concentration (w/w)	Viscosity (type of product)	Exposure time	Mean $\log_{10}$ reduction	Reference
62.4%[a]	Solution (S)	1 min	2.3	[55]
		5 min	1.0	[55]
		10 min	5.0	[55]
70%	Gel (C)	3 min	0–0.87[b]	[3]
	Solution (C)	3 min	0.75–3.25[c]	[3]
73.5%[a]	Solution (F)	0.5 min	0.9	[35]
	Solution (S)	1 min	2.9	[55]
	Solution (F)	1 min	2.2	[35]
	Solution (F)	2 min	2.0	[38]
	Solution (F)	2 min	2.8	[35]
	Solution (F)	3 min	3.1	[35]
	Solution (S)	5 min	2.9	[55]
	Solution (F)	5 min	2.2	[38]
	Solution (F)	5 min	3.5	[35]
	Solution (S)	10 min	5.4	[55]
	Solution (S)	30 min	<4	[41]
73.5%[a,d]	Solution (F)	30 s	3.4	[38]
		1 min	4.5	[38]
78.8%[a]	Solution (S)	30 s	0.4	[39]
		1 min	1.3	[39]
		5 min	2.9	[39]
80%	Solution (F)	2 min	2.0	[38]
		5 min	2.8	[38]
80%[d]	Solution (F)	30 s	3.1	[38]
		1 min	4.2	[38]
85%	Gel (C)	3 min	4.25	[5]
85.7%[a]	Solution (S)	1 min	1.6	[55]
	Solution (S)	5 min	1.2	[55]
	Solution (S)	10 min	1.7	[55]
95%	Solution (C)	30 s	$\geq$4	[30]
100%	Solution (S)	1 min	1.5	[55]
		5 min	2.3	[55]
		10 min	2.3	[55]

(C), commercially available product; (F), formulation with auxiliary agents or additional active agents; (S), solution of ethanol.
[a] Determined by calculation (originally in v/v).
[b] Four experiments.
[c] Three experiments.
[d] Tested in suspension with 97% product proportion.

Table II
Efficacy of different formulations based on ethanol with additional acids in suspension tests against poliovirus type 1

Ethanol concentration (w/w)	Type of acid	Viscosity (type of product)	Exposure time	Mean log_{10} reduction	Reference
45%	Phosphoric acid	Solution (C)	30 s	≥4	[30]
55%[a]	0.7% phosphoric acid	Solution (C)	30 s	≥4	[21]
			1 min	≥4	[21]
62.4%[b]	0.25% citric acid	Gel (C)	30 s	3.5	[40]
69.39%[c]	0.2% citric acid, 0.2% uric acid	Solution (F)	1 min	4.0	[56]
73.5%[b]	0.2% peracetic acid	Solution (F)	30 s	≥4	[41]
78.8%[b]	0.1% citric acid, 1% lactic acid	Solution (F)	30 s	≥4	[39]

(C), commercially available product; (F), formulation with auxiliary agents or additional active agents.
[a] With three additional alcohols.
[b] Determined by calculation (originally in v/v).
[c] With one additional alcohol.

Foot-and-mouth disease virus

The infectivity of the foot-and-mouth disease virus (FMDV) was insufficiently reduced by ethanol between 55.2% and 72.5% (both w/w) within 5 min [59]. Hand rubs with 70–75.2% ethanol (w/w) and additional phosphoric acid (0.6%) or 50% (w/w) ethanol and additional citric acid (0.5%), however, were effective within 30 s [59].

Polyomavirus

Ethanol has only little activity against polyomavirus SV 40, an additional test virus that was chosen due to its resistance to alcohols by experts for the German test method to determine virucidal activity [60]. A gel based on 85% ethanol (w/w) revealed sufficient activity in 15 min [5]. A hand rub based on 78.2% (w/w) ethanol had insufficient activity within 10 min (~2 log_{10}) [57]. When 0.7% phosphoric acid and three other alcohols are added to ethanol at 55% (w/w) the formulation was able to reduce infectivity sufficiently in 60 s [21]. Ethanol at 73.6% (w/w) in combination with 0.2% peracetic acid was effective in 30 s [41].

Parvovirus

Ethanol has almost no virucidal activity against parvovirus. At 80% ethanol the infectivity of the canine parvovirus was reduced in 5 min only by 0.1 log_{10} [24].

Virucidal activity on hands

Some data can be found for the enveloped influenza A virus. A gel based on 61.5% ethanol completely reduced viral infectivity of the H1N1 influenza A virus after one application [61]. The formulations with ethanol between 54.2% and 58.1% (both w/w) ethanol effectively reduced viral infectivity of the same virus within 30 s by 3.25–3.35 log_{10} [62].

First results with non-enveloped viruses were reported in 1978. One millilitre of a solution based on 70% ethanol reduced rhinovirus on hands by 1.5 log_{10} [63]. Table III shows data obtained for ethanol-based formulations with current methods for various non-enveloped viruses. Overall, the majority of non-enveloped viruses can only be reduced partially by ethanol-based formulations. Exceptions are rotavirus and MNV for which most data indicate sufficient activity. When ethanol is combined with different types of acids the efficacy on hands can be improved substantially with HAV as an exception (Table IV).

Non-quantitative data were found in addition for rhinovirus. When hands artificially contaminated with rhinovirus were treated with 1.5 mL ethanol (65%) once or twice, rhinovirus was no longer be detected on 13 of 15 hands or 13 of 16 hands, respectively [70]. A similar result was described after the application of 1.5 mL ethanol (83%) [70].

Discussion

The evidence for sufficient activity of ethanol against enveloped viruses is very broad. Hand rubs must fulfil the EN 1500 efficacy requirement, hence they often contain ≥80% ethanol when applied for 30 s [4,71]. At this concentration hand rubs have comprehensive activity against different types of enveloped viruses.

Hand rubs with 'limited spectrum virucidal activity' are deemed suitable for inactivation of noroviruses and adenoviruses. Based on data obtained for MNV, hand rubs with 70–90% ethanol are usually effective against norovirus within 30 s. For adenovirus, however, the situation is somewhat different. The EN 14476 test virus (adenovirus type 5) is mostly inactivated by ethanol between 45% and 95% in 30 s. Other types of adenovirus, however, are less susceptible to ethanol such as adenovirus types 2 and 8. Both types of adenovirus have been reported before to have only little susceptibility to other biocidal agents such as povidone iodine or peracetic acid, indicating a general reduced susceptibility [72]. The in-vitro data are supported by the description of an outbreak with adenovirus type 8 which was successfully controlled by various measures including use of a virucidal hand rub [73].

Virucidal activity according to EN 14476 aims to include all enveloped and non-enveloped viruses relevant in human medicine [13]. After reviewing published data, some viral species are unlikely to be sufficiently inactivated by ethanol alone, even at high concentrations: polyomavirus and coxsackieviruses B5 and B1. Other viruses are only sufficiently inactivated by ethanol at 95% such as poliovirus, echovirus 11, human enterovirus, and coxsackievirus B3 (≥85% ethanol). The majority of ethanol-based hand rubs with concentrations up to 90% are therefore likely to yield <4 log_{10} reduction against these viruses, suggesting insufficient efficacy. The addition of acids to the formulation such as phosphoric acid, citric acid, or peracetic acid can substantially improve the virucidal efficacy of ethanol, as shown with adenovirus type 2,

Table III
Mean log_{10} reduction of viral infectivity on artificially contaminated hands or finger tips by treatment of hands with ethanol-based formulations without additional acids

Type of virus	Ethanol concentration (w/w)	Viscosity (type of product)	Application time	Mean log_{10} reduction	Reference
Poliovirus type 1	74.5%	Solution (S)	10 min	1.0[a] 2.5[b]	[57]
	80%	Solution (S)	30 s	0.42	[64]
	80%	Solution (S)	10 min	2.2	[65]
	96.8%	Solution (S)	10 min	3.2	[65]
Poliovirus type 2	74.5%	Solution (S)	10 min	0.2[a] 0.7[b]	[57]
Coxsackievirus B3	74.5%	Solution (S)	10 min	1.1[a] 2.9[b]	[57]
Coxsackievirus B4	74.5%	Solution (S)	10 min	1.3[a] 3.0[b]	[57]
Echovirus type 9 strain Hill	74.5%	Solution (S)	10 min	0.7[a] 2.6[b]	[57]
Echovirus type 9 strain Barty	74.5%	Solution (S)	10 min	1.3[a] 2.2[b]	[57]
Polyomavirus SV 40	74.5%	Solution (S)	10 min	0.9[a] 1.8[b]	[57]
Murine norovirus	54.1%[c]	Gel (C)	20 s	2.8	[66]
	54.1%[c]	Gel (C)	30 s	3.5	[66]
	62.4%[c]	Solution (S)	30 s	4.69	[43]
	68%[c]	Solution (S)	30 s	0.91	[40]
	67.8%[c]	Solution (S)	20 s	3.0	[66]
	67.8%[c]	Solution (S)	30 s	2.7	[66]
	73.5%[c]	Solution (S)	20 s	1.7	[66]
	>90%	Solution (C)	30 s	3.91	[30]
Human enterovirus 71	68%[c]	Solution (S)	30 s	0.86	[54]
	92.9%[c]	Solution (S)	30 s	4.06	[54]
Rotavirus	70%[d]	Solution (S)	30 s	2.85	[67]
Feline calicivirus	54.1%[c]	Gel (C)	20 s	1.4	[66]
	54.1%[c]	Gel (C)	30 s	2.1	[66]
	62%[d]	Solution (S)	30 s	0.50	[68]
	62%[d]	Solution (S)	2 min	0.55	[68]
	62.4%[c]	Solution (S)	30 s	3.78	[47]
	62.4%[c]	Solution (S)	30 s	0.68	[21]
	67.8%[c]	Solution (S)	20 s	1.5	[66]
	67.8%[c]	Solution (S)	30 s	2.2	[66]
	70%	Solution (S)	30 s	2.66	[69]
	70%	Solution (S)	30 s	2.62	[69]
	70%	Solution (S)	30 s	1.18	[69]
	70%	Solution (S)	30 s	1.45	[69]
	70%	Solution (S)	30 s	1.33	[69]
	75.1%	Solution (C)	30 s	0.93	[69]
	80%	Solution (C)	30 s	1.34	[69]
	85.7%[c]	Solution (S)	30 s	2.84	[47]
	95%	Solution (C)	30 s	1.90	[69]
	99.5%[d]	Solution (S)	30 s	1.00	[68]
	99.5%[d]	Solution (S)	2 min	1.30	[68]

(C), commercially available product; (S), solution of ethanol.
[a] Hand test.
[b] Finger test.
[c] Determined by calculation (originally in v/v).
[d] No information on v/v or w/w.

Table IV
Mean $\log_{10}$ reduction of viral infectivity on artificially contaminated hands or finger tips by treatment of hands with ethanol-based formulations containing additional acids

Type of virus	Ethanol concentration (w/w)	Viscosity (type of product)	Application time	Mean $\log_{10}$ reduction	Reference
Adenovirus type 5	62.4%[a]	Gel (C)[b]	15 s	≥3.16	[40]
			30 s	≥3.12	[40]
Poliovirus type 1	55%	Solution (C)[b]	30 s	3.04	[21]
			1 min	3.13	[21]
	62.4%[a]	Gel (C)[c]	30 s	2.98	[40]
Murine norovirus	45%	Solution (C)[b]	30 s	3.94	[30]
	55%	Solution (C)[b]	30 s	3.91	[30]
	62.4%[a]	Gel (C)[c]	30 s	2.48	[40]
Hepatitis A virus	62.4%[a]	Gel (C)[c]	30 s	1.32	[40]
Rotavirus	62.4%[a]	Gel (C)[c]	15 s	≥4.32	[40]
			30 s	≥3.84	[40]
Feline calicivirus	55%	Solution (C)[b]	30 s	2.38	[21]

(C), commercially available product.
[a] Determined by calculation (originally in v/v).
[b] Additional phosphoric acid.
[c] Additional citric acid.

poliovirus type 1, polyomavirus, HAV, FMDV, and FCV. Although the efficacy is better, the dermal tolerance is likely to be worse. Post-marketing surveillance of an ethanol-based hand rub with phosphoric acid revealed frequent and significant skin lesions among the users [74]. Improved formulations, however, may have better user acceptability [75,76]. It would be beneficial in any case to look at the user acceptability of a virucidal hand rub locally before healthcare workers are asked to use it [77].

A European work item (WI 00216088) exists with the aim of measuring the virucidal activity on hands artificially contaminated with murine norovirus. Ethanol, probably at 70%, has been selected as the reference alcohol. Ethanol as an alcohol has a superior efficacy against non-enveloped viruses compared with the propanols. Against MNV, for example, most studies indicate that iso-propanol is considerably less effective compared with ethanol [43,44,46]. Against FCV iso-propanol has overall only poor virucidal activity [44,47]. And enteroviruses have been reported to be more or less resistant to iso-propanol at various concentrations within 10 min [14,51,54,55,78].

A look at the efficacy data of ethanol against non-enveloped viruses, however, shows that MNV is one of the most susceptible non-enveloped viruses. In addition, ethanol at 70% would not be considered to be virucidal according to EN 14476 due to the insufficient activity against poliovirus. A non-virucidal reference alcohol may therefore be found in the future as a positive control for the phase 2, step 2 test for virucidal efficacy on hands, which may reduce the credibility and acceptance of the upcoming standard. Perhaps it will be an option to select MNV for a phase 2, step 2 test to support 'limited spectrum virucidal activity' and another more resistant non-enveloped virus to support virucidal activity under practical conditions.

In conclusion, the spectrum of virucidal activity of ethanol at high concentrations covers the majority of clinically relevant viruses. Additional acids can substantially improve the virucidal activity against, for example, poliovirus, FCV, polyomavirus, and FMDV, although selected viruses such as HAV may still be too resistant. The selection of a suitable virucidal hand rub should be based on the most prevalent viruses in a unit and on the user acceptability of the product under frequent-use conditions.

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None declared.

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References

[1] Goroncy-Bermes P. Hand disinfection according to the European Standard EN 1500 (hygienic handrub): a study with gram-negative and gram-positive test organisms. Int J Hyg Environ Health 2001;204:123–6.
[2] Goroncy-Bermes P, Koburger T, Meyer B. Impact of the amount of hand rub applied in hygienic hand disinfection on the reduction of microbial counts on hands. J Hosp Infect 2010;74:212–8.
[3] Kampf G, Ostermeyer C, Werner H-P, Suchomel M. Efficacy of hand rubs with a low alcohol concentration listed as effective by a national hospital hygiene society in Europe. Antimicrob Resist Infect Control 2013;2:19.
[4] Kramer A, Rudolph P, Kampf G, Pittet D. Limited efficacy of alcohol-based hand gels. Lancet 2002;359:1489–90.
[5] Kampf G, Rudolf M, Labadie J-C, Barrett SP. Spectrum of antimicrobial activity and user acceptability of the hand disinfectant agent Sterillium Gel. J Hosp Infect 2002;52:141–7.
[6] Macinga DR, Shumaker DJ, Werner HP, Edmonds SL, Leslie RA, Parker AE, et al. The relative influences of product volume, delivery format and alcohol concentration on dry-time and efficacy of alcohol-based hand rubs. BMC Infect Dis 2014;14:511.
[7] Kampf G, Marschall S, Eggerstedt S, Ostermeyer C. Efficacy of ethanol-based hand foams using clinically relevant amounts: a cross-over controlled study among healthy volunteers. BMC Infect Dis 2010;10:78.
[8] World Health Organization. WHO model list of essential medicines. Geneva: WHO; 2015.
[9] Department of Health and Human Services; Food and Drug Administration. Tentative final monograph for health care antiseptic products; proposed rule. Fed Reg 1994;59:31401–52.

[10] Department of Health and Human Services; Food and Drug Administration. Safety and effectiveness of healthcare antiseptics. Topical antimicrobial drug products for over-the-counter human use; proposed amendment of the tentative final monograph; reopening of administrative record; proposed rule. Fed Reg 2015;80:25166–205.

[11] EN 14885:2015. Chemical disinfectants and antiseptics. Application of European standards for chemical disinfectants and antiseptics. Brussels: CEN (Comité Européen de Normalisation); 2015.

[12] Aitken C, Jeffries DJ. Nosocomial spread of viral disease. Clin Microbiol Rev 2001;14:528–46.

[13] EN 14476:2013. Chemical disinfectants and antiseptics. Virucidal quantitative suspension test for chemical disinfectants and antiseptics used in human medicine. Test method and requirements (phase 2, step 1). 2013.

[14] Klein M, Deforest A. Antiviral action of germicides. Soap Chem Spec 1963;39:70–2.

[15] Rabenau HF, Kampf G, Cinatl J, Doerr HW. Efficacy of various disinfectants against SARS coronavirus. J Hosp Infect 2005;61:107–11.

[16] Siddharta A, Pfaender S, Vielle NJ, Dijkman R, Friesland M, Becker B, et al. Virucidal activity of World Health Organization-recommended formulations against enveloped viruses, including Zika, Ebola, and emerging coronaviruses. J Infect Dis 2017;215:902–6.

[17] Eggers M, Eickmann M, Kowalski K, Zorn J, Reimer K. Povidone-iodine hand wash and hand rub products demonstrated excellent in vitro virucidal efficacy against Ebola virus and modified vaccinia virus Ankara, the new European test virus for enveloped viruses. BMC Infect Dis 2015;15:375.

[18] Groupe V, Engle CC, Gaffney PE. Virucidal activity of representative antiinfective agents against influenza A and vaccinia virus. Appl Microbiol 1955;3:333–6.

[19] Jeong EK, Bae JE, Kim IS. Inactivation of influenza A virus H1N1 by disinfection process. Am J Infect Control 2010;38:354–60.

[20] Kampf G, Steinmann J, Rabenau H. Suitability of vaccinia virus and bovine viral diarrhea virus (BVDV) for determining activities of three commonly-used alcohol-based hand rubs against enveloped viruses. BMC Infect Dis 2007;7:5.

[21] Kramer A, Galabov AS, Sattar SA, Döhner L, Pivert A, Payan C, et al. Virucidal activity of a new hand disinfectant with reduced ethanol content: comparison with other alcohol-based formulations. J Hosp Infect 2006;62:98–106.

[22] Martin LS, Meoougal JS, Loskoski SL. Disinfection and inactivation of the human T lymphotropic virus type III/lymphadenopathy associated virus. J Infect Dis 1985;152:400–3.

[23] Spire B, Barre-Sinoussi F, Montagnier L. Inactivation of lymphadenopathy associated virus by chemical disinfectants. Lancet 1984;2:899–901.

[24] van Engelenburg FA, Terpstra FG, Schuitemaker H, Moorer WR. The virucidal spectrum of a high concentration alcohol mixture. J Hosp Infect 2002;51:121–5.

[25] van Bueren J, Larkin DP, Simpson RA. Inactivation of human immunodeficiency virus type 1 by alcohols. J Hosp Infect 1994;28:137–48.

[26] Bond WXV, Favero MS, Petersen NJ, Ebert JW. Inactivation of hepatitis B virus by intermediate to high-level disinfectant chemicals. J Clin Microbiol 1983;18:535–8.

[27] Kobayashi H, Tsuzuki M, Koshimizu K. Susceptibility of hepatitis B virus to disinfectants or heat. J Clin Microbiol 1984;20:214–6.

[28] Bingel KF, Hermann C. Die experimentelle Desinfektion des Vakzinevirus als Grundlage für die klinische Pockenimpfung. Med Welt 1966;2:76–82.

[29] Grossgebauer K. Zur Desinfektion der mit Pocken kontaminierten Hand. Gesundheitswes Desinfekt 1967;59:1–12.

[30] Steinmann J, Paulmann D, Becker B, Bischoff B, Steinmann E, Steinmann J. Comparison of virucidal activity of alcohol-based hand sanitizers versus antimicrobial hand soaps in vitro and in vivo. J Hosp Infect 2012;82:277–80.

[31] Rabenau HF, Rapp I, Steinmann J. Can vaccinia virus be replaced by MVA virus for testing virucidal activity of chemical disinfectants? BMC Infect Dis 2010;10:185.

[32] Sauerbrei A, Schacke M, Gluck B, Bust U, Rabenau HF, Wutzler P. Does limited virucidal activity of biocides include duck hepatitis B virucidal action? BMC Infect Dis 2012;12:276.

[33] Bucca MA. The effect of various chemical agents on eastern equine encephalomyelitis virus. J Bacteriol 1956;71:491–2.

[34] Cunningham CH. The effect of certain chemical agents on the virus of Newcastle disease of chicken. Am J Vet Res 1948;9:195–7.

[35] Steinmann J, Becker B, Bischoff B, Paulmann D, Friesland M, Pietschmann T, et al. Virucidal activity of 2 alcohol-based formulations proposed as hand rubs by the World Health Organization. Am J Infect Control 2010;38:66–8.

[36] Ciesek S, Friesland M, Steinmann J, Wedemeyer H, Manns MP, Steinmann J, et al. How stable is the hepatitis C virus (HCV)? Environmental stability of HCV and its susceptibility to chemical biocides. J Infect Dis 2010;201:1859–66.

[37] Robert Koch-Institut. Infektionsepidemiologisches Jahrbuch meldepflichtiger Krankheiten für 2016. 2017. Berlin.

[38] Steinmann J, Becker B, Bischoff B, Magulski T, Steinmann J, Steinmann E. Virucidal activity of Formulation I of the World Health Organization's alcohol-based handrubs: impact of changes in key ingredient levels and test parameters. Antimicrob Resist Infect Control 2013;2:34.

[39] Okunishi J, Okamoto K, Nishihara Y, Tsujitani K, Miura T, Matsuse H, et al. Investigation of in vitro and in vivo efficacy of a novel alcohol based hand rub, MR06B7. Yakugaku Zasshi 2010;130:747–54.

[40] Macinga DR, Sattar SA, Jaykus LA, Arbogast JW. Improved inactivation of nonenveloped enteric viruses and their surrogates by a novel alcohol-based hand sanitizer. Appl Environ Microbiol 2008;74:5047–52.

[41] Wutzler P, Sauerbrei A. Virucidal efficacy of a combination of 0.2% peracetic acid and 80% (v/v) ethanol (PAA-ethanol) as a potential hand disinfectant. J Hosp Infect 2000;46:304–8.

[42] Iwasawa A, Niwano Y, Kohno M, Ayaki M. Virucidal activity of alcohol-based hand rub disinfectants. Biocontrol Sci 2012;17:45–9.

[43] Paulmann D, Steinmann J, Becker B, Bischoff B, Steinmann E, Steinmann J. Virucidal activity of different alcohols against murine norovirus, a surrogate of human norovirus. J Hosp Infect 2011;79:378–9.

[44] Park GW, Barclay L, Macinga D, Charbonneau D, Pettigrew CA, Vinje J. Comparative efficacy of seven hand sanitizers against murine norovirus, feline calicivirus, and GII.4 norovirus. J Food Prot 2010;73:2232–8.

[45] Tung G, Macinga D, Arbogast J, Jaykus LA. Efficacy of commonly used disinfectants for inactivation of human noroviruses and their surrogates. J Food Prot 2013;76:1210–7.

[46] Belliot G, Lavaux A, Souihel D, Agnello D, Pothier P. Use of murine norovirus as a surrogate to evaluate resistance of human norovirus to disinfectants. Appl Environ Microbiol 2008;74:3315–8.

[47] Gehrke C, Steinmann J, Goroncy-Bermes P. Inactivation of feline calicivirus, a surrogate of norovirus (formerly Norwalk-like viruses), by different types of alcohol in vitro and in vivo. J Hosp Infect 2004;56:49–55.

[48] Shimizu-Onda Y, Akasaka T, Yagyu F, Komine-Aizawa S, Tohya Y, Hayakawa S, et al. The virucidal effect against murine norovirus and feline calicivirus as surrogates for human norovirus by ethanol-based sanitizers. J Infect Chemother 2013;19:779–81.

[49] Akasaka T, Shimizu-Onda Y, Hayakawa S, Ushijima H. The virucidal effects against murine norovirus and feline calicivirus F4 as surrogates for human norovirus by the different additive concentrations of ethanol-based sanitizers. J Infect Chemother 2016;22:191–3.

[50] Drulak M, Wallbank AM, Lebtag I, Werboski L, Poffenroth L. The relative effectiveness of commonly used disinfectants in inactivation of coxsackievirus B5. J Hygiene 1978;81:389–97.

[51] Moldenhauer D. Quantitative evaluation of the effects of disinfectants against viruses in suspension experiments. Zentralbl Bakteriol Mikrobiol Hyg B 1984;179:544–54.
[52] Drulak M, Wallbank AM, Lebtag I. The relative effectiveness of commonly used disinfectants in inactivation of echovirus 11. J Hygiene 1978;81:77–87.
[53] Kurtz JB. Virucidal effect of alcohols against echovirus 11. Lancet 1979;1:496–7.
[54] Chang SC, Li WC, Huang KY, Huang YC, Chiu CH, Chen CJ, et al. Efficacy of alcohols and alcohol-based hand disinfectants against human enterovirus 71. J Hosp Infect 2013;83:288–93.
[55] Tyler R, Ayliffe GAJ, Bradley C. Virucidal activity of disinfectants: studies with the poliovirus. J Hosp Infect 1990;15:339–45.
[56] Ionidis G, Hubscher J, Jack T, Becker B, Bischoff B, Todt D, et al. Development and virucidal activity of a novel alcohol-based hand disinfectant supplemented with urea and citric acid. BMC Infect Dis 2016;16:77.
[57] Schürmann W, Eggers HJ. Antiviral activity of an alcoholic hand disinfectant: comparison of the in vitro suspension test with the in vivo experiments on hands, and on individual fingertips. Antiviral Res 1983;3:25–41.
[58] Wolff MH, Schmitt J, Rahaus M, König A. Hepatitis A virus: a test method for virucidal activity. J Hosp Infect 2001;48:S18–22.
[59] Harada YU, Lekcharoensuk P, Furuta T, Taniguchi T. Inactivation of foot-and-mouth disease virus by commercially available disinfectants and cleaners. Biocontrol Sci 2015;20:205–8.
[60] Schwebke I, Eggers M, Gebel J, Geisel B, Glebe D, Rapp I, et al. Prüfung und Deklaration der Wirksamkeit von Desinfektionsmitteln gegen Viren zur Anwendung im humanmedizinischen Bereich: Stellungnahme des Arbeitskreises Viruzidie beim Robert Koch-Institut. Bundesgesundheitsblatt 2017;60:353–63.
[61] Grayson ML, Melvani S, Druce J, Barr IG, Ballard SA, Johnson PD, et al. Efficacy of soap and water and alcohol-based hand-rub preparations against live H1N1 influenza virus on the hands of human volunteers. Clin Infect Dis 2009;48:285–91.
[62] Larson EL, Cohen B, Baxter KA. Analysis of alcohol-based hand sanitizer delivery systems: efficacy of foam, gel, and wipes against influenza A (H1N1) virus on hands. Am J Infect Control 2012;40:806–9.
[63] Hendley JO, Mika LA, Gwaltney Jr JM. Evaluation of virucidal compounds for inactivation of rhinovirus on hands. Antimicrob Agents Chemother 1978;14:690–4.
[64] Davies JG, Babb JR, Bradley CR, Ayliffe GAJ. Preliminary study of test methods to assess the virucidal activity of skin disinfectants using poliovirus and bacteriophages. J Hosp Infect 1993;25:125–31.
[65] Steinmann J, Nehrkorn R, Meyer A. Two in vivo protocols for testing virucidal efficacy of handwashing and hand disinfection. Zentralbl Hyg Umweltmed 1995;196:425–36.
[66] Sattar S, Ali M, Tetro JA. In vivo comparison of two human norovirus surrogates for testing ethanol-based handrubs: the mouse chasing the cat! PLoS One 2011;6, e17340.
[67] Bellamy K, Alcock R, Babb JR, Davies JG, Ayliffe GA. A test for the assessment of "hygienic" hand disinfection using rotavirus. J Hosp Infect 1993;24:201–10.
[68] Lages SLS, Ramakrishnan MA, Goyal SM. In-vivo efficacy of hand sanitisers against feline calicivirus: a surrogate for norovirus. J Hosp Infect 2008;68:159–63.
[69] Kampf G, Grotheer D, Steinmann J. Efficacy of three ethanol-based hand rubs against feline calicivirus, a surrogate for norovirus. J Hosp Infect 2005;60:144–9.
[70] Turner RB, Fuls JL, Rodgers ND. Effectiveness of hand sanitizers with and without organic acids for removal of rhinovirus from hands. Antimicrob Agents Chemother 2010;54:1363–4.
[71] Suchomel M, Kundi M, Pittet D, Weinlich M, Rotter ML. Testing of the World Health Organization recommended formulations in their application as hygienic hand rubs and proposals for increased efficacy. Am J Infect Control 2011;40:328–31.
[72] Sauerbrei A, Sehr K, Brandstadt A, Heim A, Reimer K, Wutzler P. Sensitivity of human adenoviruses to different groups of chemical biocides. J Hosp Infect 2004;57:59–66.
[73] Chaberny IE, Schnitzler P, Geiss HK, Wendt C. An outbreak of epidemic keratoconjunctivtis in a pediatric unit due to adenovirus type 8. Infect Control Hosp Epidemiol 2003;24:514–9.
[74] Kampf G, Reichel M. Gehäufte Hautirritationen durch ein viruzides Händedesinfektionsmittel mit hohem Phosphorsäuregehalt. Arbeitsmed Sozialmed Präventivmed 2010;45:546–7.
[75] Stauffer F, Griess M, Pleininger G, Zhumadilova A, Assadian O. Acceptability and tolerability of liquid versus gel and standard versus virucidal alcohol-based hand rub formulations among dental students. Am J Infect Control 2013;41:1007–11.
[76] Conrad A, Grotejohann B, Schmoor C, Cosic D, Dettenkofer M. Safety and tolerability of virucidal hand rubs: a randomized, double-blind, cross-over trial with healthy volunteers. Antimicrob Resist Infect Control 2015;4:37.
[77] Larson E, Girard R, Pessoa-Silva CL, Boyce J, Donaldson L, Pittet D. Skin reactions related to hand hygiene and selection of hand hygiene products. Am J Infect Control 2006;34:627–35.
[78] Eggers H-J. Experiments on antiviral activity of hand disinfectants. Some theoretical and practical considerations. Zentralbl Bakteriol 1990;273:36–51.