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Hygienic hand antiseptics: Should they not have activity and label claims against viruses?

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Enteric and respiratory viruses are among the most frequent causes of human infections, and hands play an important role in the spread of these and many other viral diseases. Regular and proper hand hygiene by caregivers and food handlers in particular is essential to decontaminate hands and potentially interrupt such spread. What would be considered a proper decontamination of hands? Handwashing with regular soap and water is often considered sufficient, but what of hygienic handwash and handrub antiseptic products? Are they more effective? The evidence suggests that some clearly are. Activity against bacteria may not reflect the ability of hygienic hand antiseptics to deal with viruses, especially those that are nonenveloped. In spite of the acknowledged importance of hands as vehicles for viruses, there is a lack of suitable regulatory mechanism for handwash or handrub products to make claims of efficacy against viruses. This is in contrast with the ability of general-purpose disinfectants to make antiviral claims, although transmission of viruses from surfaces other than those of reusable medical devices may play only a minor role in virus transmission. This review discusses the (1) recent information on the relative importance of viruses as human pathogens, particularly those causing enteric and respiratory infections; (2) the survival of relevant viruses on human hands in comparison with common gram-negative and gram-positive bacteria; (3) the potential of hands to transfer or receive such contamination on casual contact; (4) role of hands in the spread of viruses; (5) the potential of hygienic measures to eliminate viruses from contaminated hands; (6) relative merits of available protocols to assess the activity of hygienic hand antiseptics against viruses; and (7) factors considered crucial in any tests to assess the activity of hygienic hand antiseptics against viruses. In addition, this review proposes surrogate viruses in such testing and discusses issues for additional consideration by researchers, manufacturers, end-users, and regulators. (Am J Infect Control 2002;30:355-72)

Regular and proper hygienic hand antisepsis, although widely recognized as crucial in infection control,[1] continues to present many challenges. The 3 essential elements it requires to achieve the desired outcome are the following: (1) an effective topical agent, (2) a proper procedure with which to use it, and (3) regular compliance in its use. If just one of these is missing, the effectiveness of hand decontamination in infection control is likely to be compromised.

Compliance depends largely on the individual. The institution, professional bodies,[1,2] and government agencies[3] provide guidance on proper procedures for hand antisepsis. However, these 2 factors alone may not achieve the intended objective if the product in use is ineffective. Therefore, relevant government agencies review label claims for the protection of patients, clients, and health care providers alike. The US Food and Drug Administration (FDA) is in the process of formalizing this issue with regard to claims for bactericidal activity[4] of topicals.

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Activity of such products against vegetative bacteria does not indicate effectiveness against viruses, fungi, and protozoa. The cells of fungi and protozoa are larger than those of vegetative bacteria, suggesting that at least their physical removal from skin may be equal to that of bacteria. In contrast, viruses present a special challenge as a result of their much smaller size, compact nature, and ability to survive on human skin. This suggests that the ability of viruses to persist on hands may depend partially on their ability to "hide" within the crevices on the skin surface. This may also make it more difficult to dislodge them by simple handwashing.

Terms and scope of the review

The significance of regular and proper handwashing by caregivers and food handlers for infection control is incontrovertible. However, the use of formulated handwashes or handrubs may reduce the risk of spread of viruses. Topicals are used as surgical scrubs and preoperative skin preparations, where the targets are both transient and resident microflora of the skin, and as hygienic handwashing or antiseptic agents mainly to eliminate transient microorganisms.

Not only can hands carry viruses but they are often considered the preeminent means of their transmission. The importance of viruses as human pathogens is also well recognized.[5] Although some handwash or handrub products, notably those containing a high proportion of alcohol, have demonstrated efficacy against many viruses in experimental settings,[6] there is a general lack of effort to formulate hygienic handantiseptics against viruses, test them for their virus-eliminating potential, and an absence of suitable regulations to prepare and review label claims for such activity. When such products are tested for activity against viruses, it is often with inappropriate methodology and use of viruses that may be unsafe or irrelevant in hand antisepsis.[7] It is also important to note that many marketed topical formulations are not more effective against viruses than unmedicated soap and water.[8] However, little incentive exists for the development of improved virucidal antiseptics because of the lack of a means to register label claims for effective products. In contrast, general purpose disinfectants, which may be less important than hand antiseptics in intrepreting the spread of viral infections, can make label claims against viruses. It is difficult to know whether the major obstacle to more effective virucidal topicals is lack of regulations, the lack of demand for regulation by manufacturers or users, or both. Other complicating factors are the high cost of testing and the lack of accepted standard methods to examine virucidal activity of topicals.

Although there is no intent to negate the value of handwashing, there is plenty of evidence from experimental literature to suggest that some handwash agents, notably products formulated with alcohol as a major active ingredient,[19] outperform soap and water against many pathogens, including viruses. This article will, therefore, focus solely on germicidal soaps and waterless products formulated for hygienic hand antisepsis rather than handwashing with soap and water.

Terms such as "disinfection" and "antisepsis" often imply the inactivation of pathogens; however, in the field, the reality is a combination of both removal and inactivation, particularly in handwashing. It is difficult to arrive at a neutral term that includes both removal and inactivation of microbial targets and could be used in the debate to determine whether these issues need to be regarded separately in the regulation of topicals. For this purpose, and to try and maintain neutrality early in the debate, the word "eliminate" will be used at various places in this article. "Decontamination" has also been used here to denote the ridding of hands of harmful transient microorganisms with or without their in situ inactivation.

There is rapidly increasing acceptance and use of alcohol-based waterless agents in the United States and Canada for hand antisepsis between traditional handwashings.[10,11] Because the use of such agents does not require any water rinse after treatment, they would be expected to inactivate any transiently acquired pathogens in situ on hands even if they do not substantially remove soil and other debris. Unless otherwise stated, the phrase "hygienic hand antiseptics" in this article includes both traditional water-aided and waterless agents.

The primary focus of this article is on the importance of enteric and respiratory virses, the role of hands in their spread, and the potential benefits of formulating topicals to include activity against viruses. It will also critically assess the methods available for testing topicals against viruses as well as the main conditions and criteria for such testing. Perhaps 2 aspects that will require particular attention in this context are the level of virus-eliminating activity desired in topical agents, and which, if any, viruses should be used as surrogates for human

Table 1. Basic characteristics of viruses causing respiratory, enteric, eye, skin, and other infections in humans

Virus (# of types)	Size and shape	Genome	Envelope	Association with disease
Adenoviruses (>47)	70-90 nm, icosahedral	Double-stranded, linear DNA	No	Fever, rhinitis, pharyngitis, laryngitis, bronchiolitis, tonsillitis, cough, pneumonia, and conjunctivitis. Types 40, 41 can cause acute gastroenteritis.
Astroviruses (>2)	27-30 nm, icosahedral	Single-stranded, positive-sense RNA	No	Acute gastroenteritis
Coronaviruses (3)	120-160 nm, pleomorphic	Single stranded, Linear, positive-sense RNA	Yes	Common colds and perhaps gastroenteritis
Cytomegalovirus (1)	150 nm diameter with an iscosahedral core	Double-stranded, linear DNA	Yes	
Enteroviruses (>70)	27-30 nm, icosahedral	Single-stranded, positive-sense RNA	No	Gastroenteritis, myocarditis, skin rash, meningitis, encephalitis, and polio-like paralysis
Hepatitis A virus (1)	27-30 nm, icosahedral	Single-stranded, positive-sense RNA	No	Infectious hepatitis
Herpesviruses (>8)	150 nm diameter with an iscosahedral core	Double-stranded, linear DNA	Yes	Sores on lips, genital area, fingers, eyes as well as chicken pox; cervical cancer Kaposi's sarcoma, encephalitis, and meningitis
Influenzaviruses (3)	100 nm diameter with helical symmetry	Single-stranded, segmented RNA	Yes	Influenza and pneumonia
Norwalk and related viruses (>6)	27-32 nm, round	Single-stranded, positive-sense RNA	No	Acute gastroenteritis
Papillomaviruses (>60)	40-55 nm, icosahedral	Circular, double-stranded DNA	No	Warts, laryngeal papillomas, cervical cancer
Poxviruses (>10)	230-400 nm with a complex structure	Double-stranded DNA	Yes	Vesicles and pustules on skin
Respiratory syncytial virus (1)	150-300 nm, pleomorphic	Single-stranded, negative-sense, segmented RNA	Yes	Bronchiolitis and pneumonia among infants, children under 1 y of age and the elderly
Rhinoviruses (>100)	27 nm, icosahedral	Single-stranded, positive sense RNA	No	Most frequent cause of the common cold
Rotaviruses (>6)	60-80 nm, icosahedral	Double stranded, segmented RNA	No	Severe diarrhea among children, mild gastrointestinal illness in adults

pathogenic viruses. It is hoped that this critical analysis helps to clarify the topic and stimulate discussion. More information on this and related issues are summarized elsewhere.[6,10,11]

Relative importance of viruses as human pathogens

Viruses are a leading cause of morbidity and mortality in humans.[5] Even mild viral infections can be a heavy burden on the health care system[12-14] and the general economy. Indeed, the relative significance of viruses is increasing as we successfully combat common bacterial diseases, and many ongoing changes in our societies are adding to the importance of viruses as pathogens.[15] Factors that make viruses significant pathogens have been summarized recently.[12] In the continued absence of safe chemotherapy and vaccines, measures such as hand hygiene remain crucial for interrupting the spread of many types of viruses, particularly by caregivers and food handlers.

Several animal viruses[16] can also infect humans,[17] and such zoonotic agents are important when handling domestic or experimental animals. It is also quite likely that human hands can spread viruses between animals.[18] Data from human experiments show the infectious dose of viruses to be as low as one infectious unit.[19]

US data from more than 2 decades ago incriminated viruses in 5% of all cases of nosocomial infections;[20] in pediatric settings the rate was as high as 32%.[21] These figures were most likely underestimations even when gathered because of the general difficulties in the differential clinical and laboratory diagnoses of viral infections. Moreover, many changes in medical and surgical techniques as well as health care practices have occurred in the intervening years without any significant developments in the chemotherapy of viral infections. These factors, when taken together, suggest the effect of viruses as nosocomial pathogens may be greater now.

Table 2. Estimates of the annual incidence of URTIs in the United States*

Etiologic agent	% Illness caused by each agent	No. illnesses caused by each agent per 10,000 population	% Illnesses with consultation	No. illnesses with consultation per 10,000 population
Rhinoviruses	34	8325	17.6	1465
Coronaviruses	14	3428	17.6	603
Influenzaviruses	9	2204	37.9	835
Parainfluenzaviruses	4	979	26.2	257
Respiratory syncytial virus	4	979	55.6	544
Adenoviruses	2	490	43.2	212
Other viruses	2	490	27.8	136
Subtotal	69	16,895		4052
Bacterial	8	1959	48.6	952
Unknown agents or noninfectious	23	5630	21.5	1211
Total	100	24,484		6215

*Adapted from *Epidemiol Infect.*[33]

Table 3. Effect of respiratory tract infections in the elderly

Etiologic agent(s)	% Cases	
	Nicholson et al[34]	Greenberg et al[35]
Rhinoviruses	52	23
Coronaviruses	26	23
Influenzaviruses	10	12
Respiratory syncytial virus	7	12
Parainfluenzaviruses	3	29
Adenoviruses	0.5	0.02
Subtotal	98.5	99.02
Others (chlamydia and mycoplasma pneumoniae)	1.5	Not tested
Total	100	99.02

Of all the viral infections of humans, those of the respiratory and enteric tracts are most common globally. According to the World Health Organization,[22] acute respiratory infections and diarrheal diseases lead to an annual loss of 83 and 73 million years of healthy life, respectively. In 1998 alone these 2 types of infections killed a total of 5.7 million people worldwide.[22] They are also among the most frequent nosocomial pathogens.[21,23] Notwithstanding the difficulties of laboratory diagnosis of viral infections, the most reliable data on the prevalence of respiratory and enteric infections are in the industrialized world. Better surveillance and enhanced application of molecular tests would undoubtedly increase the relative significance of viruses in the etiology of both acute and chronic diseases.

The following is a summary of the relative importance of respiratory, enteric, and other viral infections of humans, evidence for their spread by hands and the role of topicals in interrupting such spread. The basic characteristics of such viruses as they pertain to their potential for spread by hands are summarized in Table 1.

Effect of respiratory viruses on human health

Viruses cause most upper respiratory tract infections (URTI) or "colds" in humans.[24,25] Except in the young and the elderly, URTI are generally mild and self-limiting but can result in considerable economic losses. Also, viral infections can trigger attacks of asthma.[26,27] Close similarities between the clinical presentations of many viral and bacterial infections of the respiratory and enteric tracts could lead to underreporting of viral infections.[28,29] Even milder viral infections can be important predisposing factors to more severe and possibly fatal secondary bacterial infections.[30] Moreover, coinfections of the respiratory tract with a viral and a bacterial agent may lead to atypical clinical presentations, thus masking the role of viruses in such cases. Many viruses do not confer long-term immunity and, consequently, reinfections are common.[31] As is true for other microbial pathogens, induced or acquired immunosuppression enhances a host's susceptibility to viruses.[32]

As shown in Table 2, viruses are incriminated in no less than 69% of acute URTI in the United States.[33] Viruses are particularly significant as etiologic agents of respiratory infections in the young and the elderly. Table 3 is a summary of data from 2 recent studies[34,35] on the relative importance of

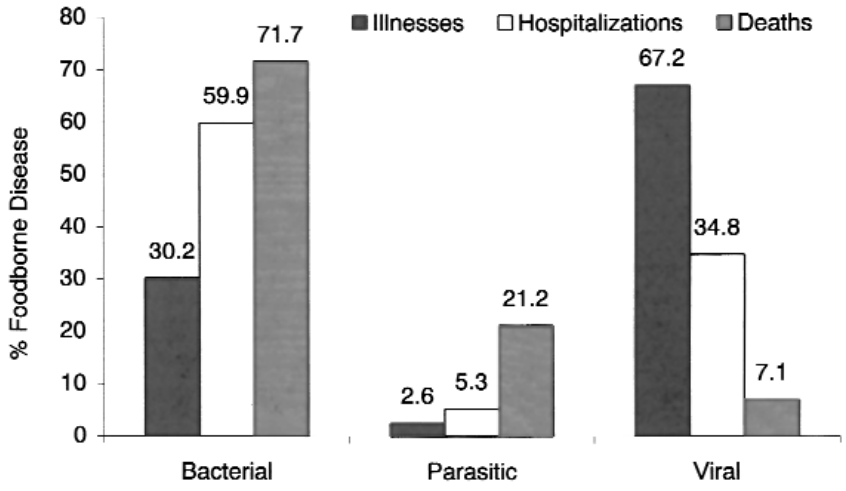

Fig 1. Relative importance of bacterial, parasitic, and viral agents in foodborne disease in the United States. Adapted from Mead et al.[37]

viruses as causes of respiratory infection in the elderly in the United States.

Effect of enteric viruses on human health

Acute gastroenteritis is also among the most common problems of human health throughout the world.[22,31] It kills an estimated 2.2 million children annually.[22] It also has a greater health effect on adults than had been realized before, and data gathered during a period of 17 years (1979-1995) show that, in the United States, at least 450,000 people 20 years of age or older are hospitalized each year for gastroenteritis.[36] As stated above for respiratory viruses, many enteric viral infections also do not give rise to long-term immunity and reinfections are therefore frequent.

During the past 30 years, several viruses have been discovered as the major causes of acute gastroenteritis in humans.[5] In the United States, however, rotaviruses are the most common cause of diarrhea among children and infect virtually every child in the United States and Canada by the age of 4 years. Other relatively recently identified pathogens include the Norwalk group of viruses, the enteric adenoviruses, and astroviruses.

Enteric viruses are a common cause of gastroenteritis in adults as well. Studies on adults hospitalized for gastroenteritis in the United States found 14% of the cases resulted from these viruses, and bacteria were incriminated in less than 9% of the cases.[36] The available information shows that rotaviruses, hepatitis A virus (HAV), and Norwalk-like viruses are the most common enteric viral agents in the United States. According to the Centers for Disease Control (CDC),[37] the average total of cases of viral gastroenteritis is more than 30 million, whereas bacteria and parasites account for nearly 8 million cases of gastroenteritis. This attests to the high significance of viruses in the etiology of acute gastroenteritis. Fig 1 shows the relative importance of bacteria, parasites, and viruses as agents of foodborne disease in the United States.[37] It is not possible to speculate on what proportion of such infections may be spread by hands; however, if improved hand hygiene results in even a small reduction in the number of cases, it would still represent a substantial reduction in the burden on human health.

By definition, enteric viruses are shed in the feces of those infected and enter the body mainly by the mouth,[38] making the "fecal-oral route" the predominant means of their spread and hands a common vehicle in such transmission,[39] directly through inoculation of self or others and indirectly by exposure to articles handled by virus-contaminated hands. This does not, however, preclude a more circuitous route where aerosolized viruses settle and are picked up as hand contaminants through contact[40] or are inhaled and translocated to the throat and swallowed.

Often it is the asymptomatic patients that may present the most risk because failure to recognize an

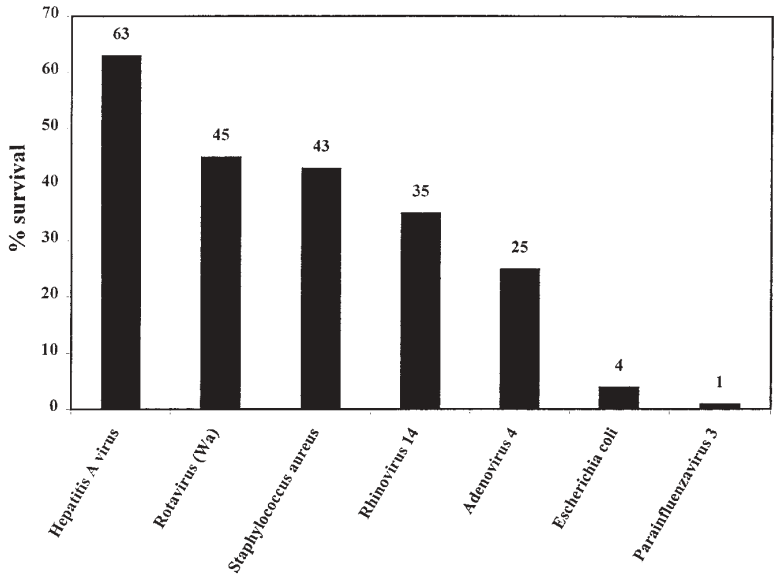

Fig 2. Survival of selected viruses and bacteria on the fingerpads of adult subjects 1 hour after experimental contamination.[114,115]

infection may lead to a breakdown in the barrier protection normally implemented when disease is apparent. Moreover, workers in the health care and allied professions or those employed in food handling may report for work not recognizing that they are infected.

Role of hands in the spread of respiratory, enteric, and other viruses

Rhinoviruses. Rhinoviruses are responsible for most cases of URTI.[41] In the United States, they were incriminated in 52% (121 of 231) of the laboratory-diagnosed cases of URTI in 60- to 90-year-old persons living at home.[36] These viruses can survive on human hands for hours (Fig 2), and experiments with human volunteers have clearly demonstrated the potential of hands to spread rhinoviral colds[42,43] and the ability of hand antiseptics in interrupting such transmission.[25]

Adenoviruses. In addition to URTI, adenoviruses can cause conjunctivitis, hemorrhagic cystitis, pneumonia, and gastroenteritis.[5] Serotypes 40 and 41 primarily affect the gut, contributing to 5% to 20% of hospitalizations of childhood diarrhea in developed countries.[44] Outbreaks of adenoviral infections are not infrequent in settings such as hospitals and day-care centers.[45] Adenoviruses are also a major cause of serious respiratory infections in military recruits, possibly resulting from over-crowding and sharing of facilities.[46] The oral vaccine against adenoviruses used for such people is no longer available with the resultant reemergence of these viruses and possible fatalities resulting from them.[47] In Canada, adenoviruses cause nearly 5% of all laboratory-diagnosed cases of respiratory infections.[48] They can survive on human skin for many hours,[49] suggesting the potential for spread through hands. In fact, the half-life of adenovirus type 4 was found to be nearly 6 hours on ex vivo human skin and approximately 1 hour on disks of stainless steel at the physiologic skin temperature of 32°C.[49]

Nosocomial outbreaks of adenoviral infections are common.[50] That such outbreaks in pediatric respiratory units can be devastating is clearly illustrated by the report of Wesley et al,[51] where hands of attendants are believed to have spread the virus and the case fatality rate in the nosocomially-acquired cases was 91%.

Outbreaks of adenoviral keratoconjunctivitis are a particularly common occurrence in ophthalmology clinics, and quite frequently the virus spread is iatrogenic and involves the hands of health care personnel.[52] Interestingly, Jernigan et al[53] showed that the hands of physician and patients remained culture-positive for the incriminated adenovirus even after washing hands with soap and water and

drying them with a paper towel. Azar et al[54] recovered infectious adenoviruses from the hands of 46% (12 of 26) of the patients with epidemic keratoconjunctivitis and emphasized the potential of virus transfer to hospital personnel through casual hand contact.

Caliciviruses. This group includes several members that are sometimes referred to as small round-structured viruses (SRSV). Human caliciviruses, which cannot be cultured in the laboratory, include the Norwalk agent, which has emerged as the most important cause of acute gastroenteritis, and outbreaks resulting from it occur regularly in communities and institutional settings.[55,56] They are also the most common causes of foodborne disease in the United States,[57-59] accounting for more than 67% of all cases of known etiology, 33% of hospitalization, and 7% of deaths.[37]

A presymptomatic food handler was the most likely source of a foodborne outbreak of acute gastroenteritis resulting from an SRSV that affected nearly 200 people in 4 hospitals served by a central kitchen.[60] SRSV can cause chronic gastroenteritis in children infected with the human immunodeficiency virus (HIV).[61]

Recently, an animal calicivirus has been found to infect humans and cause vesicles on hands,[62] but it is not known if the virus can be spread to other hosts through such infected hands.

Hepatitis A virus. In North America the only hepatitis virus currently relevant to this discussion is HAV; however, if hepatitis E virus was more prevalent, it may also have the capacity to spread through hands. Infection with HAV is common worldwide,[63] and it is the only notifiable foodborne viral infection in Canada and the United States. In many developing countries, HAV is endemic and >90% of children may be infected by 6 years of age.[64] In industrialized countries, improved sanitation and water supply have given rise to large pools of highly susceptible people, increasing the risk of massive common-source outbreaks. In young children HAV is frequently asymptomatic, but transmission to older age groups can result in clinically evident disease. The most common risk factor for HAV infection is contact with another infected person, often in a day-care setting. Food and waterborne outbreaks contribute only 1% to 5% of the total cases reported in any year.[65] In all surveillance studies, no source was identified for 20% to 30% of HAV cases.[65] The vehicles of transmission in foodborne outbreaks of HAV are most often prepared uncooked foods, such as sandwiches or salads, or foods touched by human hands after cooking.[58]

In spite of the availability of vaccines against it, cases of HAV continue to occur in the United States and Canada. HAV can survive for several hours on human hands,[8] and its ability to spread through hands is well recognized.[66] A recent study by Bidawid et al[67] has shown that as much as 9% of infectious HAV on experimentally contaminated hands of adult volunteers could be transferred during a 10-second contact with vegetables that are consumed raw.

In another study of reports of foodborne disease[58] that examined outbreaks rather than total numbers of cases, HAV was more commonly found than the Norwalk group of viruses. Whatever the causative agent, it is apparent that foodborne viral infections not only result in considerable morbidity and some mortality, they also contribute significantly to the societal costs of infectious diseases. In one particular foodborne outbreak of HAV in the United States,[68] there were 43 cases and a possible exposure of 5000 patrons. The high cost of the available vaccines limits their use, and HAV continues to be among the most frequently reported vaccine-preventable diseases in the United States.[69]

According to the CDC, the incidence of HAV infections in the United States has been cyclic during the past several decades, with nationwide epidemics occurring every 10 to 15 years. Between epidemics, HAV infections continue to occur at relatively high levels with a recognized underreporting of cases. For example, in 1993, 24,238 HAV cases were reported to the National Notifiable Diseases Surveillance System of the CDC; these reported cases are estimated to correspond to 75,000 actual cases of hepatitis A and 125,000 HAV infections.

Rotaviruses. Rotaviral infections are the leading causes of severe gastroenteritis in infants and young children worldwide.[70] In the United States rotaviruses cause an estimated 3.9 million infections, with 2.7 million cases of gastroenteritis among children younger than 5 years of age. This results in approximately 500,000 outpatient and emergency visits and 49,000 hospitalizations.[71] The economic effect of rotavirus infections in health care is estimated at $264 million, with overall costs of approximately $1 billion.[71]

Outbreaks of rotaviral infection are common in infants and young children in institutional settings such as hospitals,[72] daycare centers,[73,74] and schools,[75] and hands of caregivers are believed to play an important role in virus spread.[10] Although asymptomatic infections are common, subjects with clinical cases excrete relatively large amounts of infectious virus in their feces, contributing to the ease of virus spread. Fecal excretion of infectious rotavirus can be chronic in those who are immunocompromised.[76] The rapid water loss resulting from rotaviral gastroenteritis can be fatal without intravenous or oral rehydration therapy.

Adults can also be sources of infection, and asymptomatic cases are a recognized problem in spreading human rotaviruses. The frequency of rotavirus infection in contacts also demonstrates the highly contagious nature of these viruses. A vaccine against them was recently introduced and withdrawn soon after because of serious side effects in the vaccinated children.[77]

Since 1991, the National Respiratory and Enteric Virus Surveillance System has prospectively monitored rotavirus activity in the United States.[78] Of the 22,912 specimens tested from July 1997 through June 1998 by antigen-detection and electron microscopy, 5343 (23%) were positive for rotavirus. The most recent analysis of prevalence of rotavirus diarrhea in the United States shows 3.9 million cases in 1998. On average, annual cases of foodborne illness resulting from rotaviruses is estimated to be 39,000, which is 0.3% of all the foodborne illnesses resulting from viruses.[37] Seasonal increases in rotavirus detection were noted throughout the United States, and the period of peak rotavirus activity varied by geographic location. Such seasonal variations are consistent with data collected from other temperate countries[79] and may coincide with or follow climatic conditions favoring rotavirus survival.[80]

Astroviruses. The disease caused by astroviruses is similar to that caused by Norwalk-like viruses, but it is milder than rotaviral gastroenteritis. Chronic diarrhea and shedding of virus may occur in children who are immunocompromised.[81,82] Astroviruses spread mainly via the fecal-oral route. Children younger than 1 year of age are most often affected, although adults can be infected and suffer mild disease. Studies of hospitalized children suggest that astroviruses may account for 3% to 5% of the admissions for diarrhea.[83] Outbreaks of astroviral gastroenteritis have been reported from institutional settings such as nursing homes, hospitals, schools, and daycare centers.[84,85] Fatality resulting from astrovirus infection is low (< 10 deaths per year), and probably < 1% of cases of astroviral infections are foodborne.[86] Hands are believed to play an important role in the nosocomial spread of astroviruses.[84]

Papillomaviruses. There is increasing recognition of the importance of papillomaviruses as human pathogens. Apart from causing warts, they are now known to be involved in certain types of cancers in humans.[87-90] Human papillomaviruses (HPV) are difficult to grow in cell lines or experimental animals, and this limits the knowledge of their ability to survive on human skin and also the action of hand antiseptics against them. However, recent studies on the detection of papillomavirus DNA on the hands of patients with genital warts suggested their potential for spread by hands.[91,92] The analyses of Fairley et al[93] also suggests that hands may play a role in the spread of genital warts. Those who are immunocompromised are particularly prone to infections by papillomaviruses and develop numbers of warts on their hands.[94] Such cases can also be quite refractory to treatment.[94]

Bovine papillomaviruses can be cultured to a limited degree in the laboratory, and xenografts of human skin into athymic mice[95] and cellular rafts[96] can be infected with HPV. The use of such surrogate systems shows some potential to study the survival and inactivation of papillomaviruses on human skin. Another approach is to use the closely related papovaviruses such as SV_{40} as a surrogate for HPV in testing the virucidal activity of topicals.[97]

Enteroviruses. These viruses can also cause nosocomial outbreaks, and hands of caregivers most likely play a role in their spread. The CDC's investigation of an outbreak of aseptic meningitis in parents of children attending daycare centers showed that more frequent handwashing was associated with a lower rate of infection.[98]

Respiratory syncytial virus. Respiratory syncytial virus (RSV) is the most frequent cause of serious respiratory infections in young children,[99] and unlike other enveloped respiratory viruses, the available epidemiologic evidence suggests that hands of caregivers play a significant role in its spread.[99,100] More frequent handwashing by health care personnel in conjunction with cohorting of patients has been found to reduce the nosocomial spread of RSV.[101] In Canada, RSV has been incrimi-

nated in nearly 46% of all laboratory-diagnosed cases of respiratory infections.[48]

Cytomegalovirus. Infections resulting from cytomegalovirus (CMV) are common, and infected young children are often the source of the virus for those in close contact with them. Women of childbearing age in daycare centers and pediatric wards have a higher potential for occupational exposure;[102,103] this virus can damage a developing fetus. Infectious CMV has been isolated from the diapers of infected children and the hands of hospital personnel caring for them but not from environmental surfaces in the same settings.[104] Isolation of CMV from the hands of daycare workers has also been reported.[105]

The ability of CMV to survive on hands is not known, but because it is relatively fragile, it is not likely to survive on skin for more than 5 to 10 minutes. Faix[106] used experimentally contaminated gloved hands and cadaveric skin to show that the virus was highly susceptible to inactivation by even ordinary soap.

Other viruses. Coronaviruses are believed to be responsible for almost 14% of all cases of acute URTI in humans,[33] but their association with acute gastroenteritis remains uncertain. These viruses are generally fragile and their ability to survive on human hands is not known. Also, there is no evidence thus far for their spread through hands.

Parainfluenzaviruses are second only to RSV as etiologic agents of serious respiratory infections in young children.[5] They most likely spread by air, and there is no evidence to suggest the role of hands in their transmission. Limited experimental studies with adult volunteers have found human parainfluenzavirus type 3 to fare quite poorly (Fig 2) on the skin of hands.[107] Among the 3 human influenzaviruses, type A is the predominant cause of respiratory infections and it can also give rise to pandemics from time to time.[5] Although influenzaviruses are also among important causes of respiratory infections in humans and often cause nosocomial outbreaks, there is no convincing evidence for their spread by hands. Like parainfluenzaviruses, they do not survive for more than 5 to 10 minutes on hands.[108]

Zoonotic poxviruses can contaminate or even infect the skin of hands, but such cases are rare and limited mainly to those who are in direct contact with infected animals.[109-111] Adult cases of such infections are believed to have given rise to secondary cases in children.[112]

Shedding of viruses by an infected host

As mentioned above, human pathogenic viruses are not a part of the normal microflora of the body. They are shed for varying periods only by those infected with them. However, a large proportion of those infected with viruses, possibly more than 90%, remain asymptomatic while discharging infectious viruses into their surroundings. This presents a serious problem for infection control because viruses discharged by asymptomatic shedders could cause serious disease in others. This is particularly true in hospitals and nursing homes where there is a pool of highly susceptible people who are debilitated as a result of disease, immunosuppression, or other causes. The large numbers of "silent" cases of viral infection also pose serious difficulties for halting virus spread in other settings where a single infected person may come into direct or indirect contact with a large number of uninfected but susceptible hosts. In this context, daycare is recognized as a setting where viruses are readily transmitted, but indirect virus transmission from food handlers through contaminated food is becoming increasingly important.[58]

The shedding of viruses from infected hosts generally begins before the onset of clinical symptoms and often lasts for several days, occasionally weeks, after recovery. The actual amount of virus discharged varies considerably depending on the type of infecting agent and the stage of the infection. For example, at the peak of rotaviral gastroenteritis, every gram of feces may have more than 10^{11} virions and 10^7 to 10^8 infectious virus particles.[113]

Viruses are always discharged in a body fluid from an infected host, and they cannot replicate unless they infect another susceptible host. The longer a virus can survive outside the body of a host, the higher is its potential for spread by vehicles such as hands. Hands can become contaminated readily—directly by contact with any virus-containing body fluids from self or others, or indirectly by touching or handling virus-contaminated surfaces or objects. The degree of contamination and the area over which it is spread are also key considerations here. Fingers, especially the pads and tips, are the most likely to come into contact during touching of infected people and their body substances as well as other contaminated materials. In addition, these same parts of the hands are the most likely to be inadvertently or deliberately brought into contact with portals of entry for susceptible hosts; self-inoculation from virus-contaminated hands is likely to be frequent.

Virus acquisition by and survival on hands

The main modes and vehicles for the spread of human pathogenic viruses and approaches to interrupting their transmission have been summarized previously.[114]

For hands to spread viral infections, it is necessary that viruses survive long enough to permit transfer to and inoculation of a susceptible host, and this appears to be the case with many viruses.[114] Although virus survival on many types of inanimate surfaces and objects is frequently much longer than on skin,[114] viruses that are particularly sensitive to drying may survive better on the skin than when dried onto surfaces, depending on the ambient relative humidity. For example, human herpes virus type 2, which had a half-life of nearly 2 hours in an ex vivo human skin model, survived less than 30 minutes on stainless steel disks.[115] Fig 2 is a composite of data from several studies on the survival of selected enteric and respiratory viruses on the hands of adults; for comparison, it also shows the figures for *Staphylococcus aureus* and *Escherichia coli*. All the nonenveloped viruses survived as well as, if not better than, *S aureus*, which is a common member of the normal microflora of the human skin. In contrast, the behavior of human parainfluenzavirus type 3 (enveloped) was similar to that of *E coli*.

Role of hands in the spread of viral infections

Human hands could act as vehicles for many types of viruses and, by corollary, regular and proper decontamination of hands could reduce the risk of spread of such infectious agents. However, the link between hands and the spread of viral infections is defined mainly by circumstantial evidence and limited experimental studies with human subjects.[114] This lack of direct evidence is not surprising in view of the general difficulties in working with viruses, the seasonal nature of most viral infections, as well as our inability to distinguish between simultaneous spread of a particular infectious agent by hands and other vehicles in a given setting. Experimental studies have also clearly demonstrated the ease with which virus transfer can occur to and from hands during casual contact.[116] Infectious virus particles have also been recovered from naturally contaminated hands of caregivers, from fomites, and from environmental surfaces that are frequently touched or handled.[114] Only recently have standardized methods become available to test the ability of viruses to survive on human hands, to be transferred to and from hands during casual contact, and the potential of topical agents to rid hands of viruses.[114]

Hands are among the most obvious surfaces to become contaminated; this is true whether the contamination is of self or a caregiver. The nature and extent of such contamination will depend on the site of infection, the degree and nature of the discharge from the host, the personal habits of the infected individual, and the hygienic facilities available. The degree of contamination can vary widely. For example, some enteric viral infections can produce a profuse and almost explosive diarrhea that may be difficult to contain. Addressing such an infection in wards or facilities for bed-ridden or mentally handicapped patients can be quite difficult.

Regular interactions between hands and their surroundings suggests that transfer of contaminating virus can occur readily between the contact points. Such transfer of infectious virus to and from hands upon casual contact with objects or other animate or inanimate surfaces can be demonstrated to occur readily in experimental settings.[114,117,118]

Recent studies have used surrogates to study acquisition and spread of pathogens by hands. The DNA of a cauliflower virus was used to show that hands played an important role in the dissemination of the marker in daycare settings[118] as well as in neonatal intensive care units.[119] The use of a bacterial virus (phiX174) showed that clean hands could readily become contaminated when objects or surfaces with infectious virus on them are touched or handled;[117] the reverse has also been shown to be true.

Transfer of a rhinovirus was observed in 15 of 16 trials in which a plastic surface, contaminated 1 to 3 hours previously, was touched by a volunteer.[42] People with acute rhinovirus colds were shown to deposit infectious rhinovirus particles on objects they touched.[120] Infectious rhinovirus particles could be recovered from fingertips of volunteers who handled objects such as doorknobs previously touched by virus-contaminated (donor) hands, and rhinovirus transfer also has been shown to occur by direct hand-to-hand contact.[43]

Studies with human subjects have also established that self-inoculation with rhinovirus- and rotavirus-contaminated fingers can lead to infection.[121,122] Frequency of contact will also promote virus acquisition and transfer; for example, a caregiver with fre-

Table 4. Relative strengths and weaknesses of methods available to assess the virus-eliminating activity of hygienic hand antiseptics

Test protocol	Comments
Suspension tests	Suspension tests[125] are a poor challenge for products to be used on human skin. They are suitable only for screening formulations.
Inanimate carriers	Although the use of inanimate carriers with dried inocula represents a more stringent challenge to the formulation being tested,[126] the contact time and temperature are often not relevant[127] for hygienic hand antiseptics. Also, the topography of inanimate surfaces may be quite different from that of human skin.
Whole-hand method	Field application of hygienic hand antiseptics can be best simulated in a properly designed whole-hand method,[128] but such methods are inherently more difficult to work with viruses because of the relatively large volumes of inocula required and the eluates to be titrated for infectious virus. Such protocols may be suitable for limited confirmatory testing of hand antiseptics and a standard method is now available for this purpose.[129]
Fingertip method	Although a smaller inoculum volume (20 μL) is placed on each fingertip in this method,[123] the volume (20 mL) of the eluent necessary is too large for proper assessment of infectious virus in it, thus making it subject of some of the limitations of the whole-hand method.
Fingerpad method	This method,[128] which is now a standard of American Society for Testing and Materials,[130] requires only 10 μL of the virus inoculum on each fingerpad. The dried inoculum can be exposed to 1 mL of the test or control solution for desired contact time. Virus can then be eluted in less than 2 mL of an eluent and most of this volume can be titrated for infectious virus. This method is capable of assessing, separately, virus elimination after exposure to the handwash agent, water rinse after treatment, and the drying of washed hands. It can be used with handrub agents as well[131] and can be adapted for use with bacteria, fungi, and protozoa. The results with it have been found to correspond well with the whole-hand method.[128]
Ex vivo tests with human skin	In vivo methods may not be unsuitable when testing experimental actives and high-risk viruses such as HIV and ex vivo protocols based on human skin are possible alternatives.[10]
Animal skin	Human skin is unique in the thickness of its stratum corneum, density of hair follicles and the nature of its sweat glands.[132] However, pieces of skin from animals such as pigs are frequently used in testing the activity of topicals against bacteria,[133] but only limited published information is available on the application of this model to viruses.[134]
Other substrates as carriers	Human cadaveric skin, collagen membranes, cultured corneal fibroblasts,[135] and human skin grown in vitro[136] could also be used as substrates, but they all suffer from a variety of limitations. For example, the barrier integrity of cadaveric skin is compromised,[132] cultured monolayers are too fragile for use in germicidal tests, and collagen membranes are devoid of any of the characteristics of viable skin.

quent contacts among daycare participants may inadvertently transfer viruses from one child to another, simply by hand contact. Although significant numbers of viral particles can be transferred when contamination levels are high, the percentage of virus transferred during experimental contacts has been shown to be fairly low. This suggests that the further along the chain of contacts the susceptible host is from the point of primary contact with the virus, the lower the risk that an infection will result and vice versa.

Testing of handwash and handrub agents against viruses

There has been much progress in recent years in the development and evaluation of standardized protocols to assess the virus-eliminating activity of handwash and handrub agents and details in this regard have been presented before.[6,10,123,124] Table 4 presents a summary of this information.[125-135] Factors that are considered crucial in the design and performance of tests on the virus-eliminating potential of hygienic hand antiseptics are enumerated in Table 5.

ISSUES FOR ADDITIONAL DISCUSSION

Many issues that need clear answers in this context have been discussed before,[6,11] and the following is a listing of the more salient ones. Some of these represent policy matters, whereas others will require additional research data.

Surrogate to test hand antiseptics against viruses

As yet, there are no recognized surrogates for testing topicals against viruses, and this encourages the practice of testing a given formulation against as many viruses as possible and listing them all on the product label. This is particularly true in the United States. Such an approach (1) makes product development unnecessarily expensive and time-consuming, (2) encourages the use of the pathogenic viruses themselves (eg, HIV or hantaviruses) that are unsafe to handle and may cause undue risk of laboratory-acquired infections, (3) results in the listing of easy-to-kill (enveloped) viruses, such as HIV, on product labels

Table 5. Important factors in assessing hygienic hand antiseptics against viruses

Test virus(es) to be used	Test viruses should be selected carefully for their safety to human subjects, ease of cultivation and quantitation, ability to survive on human skin, relative resistance to chemical germicides, and relevance to spread by hands. The use of 1 or more carefully selected viruses as surrogates is highly recommended.
Infectivity assay of test virus(es)	Use of animals should be avoided in such tests and cell culture systems with optimal susceptibility to the test virus(es) are considered ideal. As far as possible, indirect measures of virus infectivity (eg, assaying for viral enzymes) should also be avoided.
Human subjects to be selected for testing	Proper permissions must be obtained before the recruitment of human subjects, and everyone selected must be judged suitable on the basis of standard inclusion and exclusion criteria. Written informed consent must also be obtained from each subject before participation.
Nature and level of soil loading	The presence of a soil load in the virus suspension is considered important to present the test formulation to reflect the fact that in nature viruses are always associated with cellular debris and organic and inorganic substances. The soil load selected must be shown to be harmless to the test virus(es).
Diluent, if required, for the test product	If the test product needs dilution in water before use, and unless some other diluent is to be specified on the product label, water with a standardized (eg, 200 parts per million as $CaCO_3$) level of hardness is recommended. Use of tap water should be avoided in such tests because of wide variations in the quality of tap water both geographically and temporally.
Time used for the initial drying of the inoculum	The virus inoculum must be visibly dry before exposure to the test formulations, but over-drying can lead to excessive losses in virus infectivity. Staggering of the inoculation of the carriers and their randomization would be desirable to increase the level of confidence in the data generated.
Contact between virus and germicide	Contact time should not be longer than 10-20 sec to keep it relevant to the field use of such products.
Neutralization of virucidal activity	Virucidal activity of test formulation must be arrested effectively and immediately at the end of the contact time for a meaningful interpretation of the test data. Any neutralizer selected for the purpose must be shown to be safe for the virus and noncytotoxic for the host cells. Dilution of the virus-germicide mixture at the end to the contact time is often the simplest and "universal" means of arresting the germicidal activity when working with hygienic hand antiseptics.
Procedure for the elimination of cytotoxicity	All eluates and their dilutions must be free from cytotoxicity before any measurement of virus infectivity. Gel-filtration or centrifugation inevitably increases contact time between virus and test germicide.
No. test and control subjects	No. of repeats may be dictated by the requirements of the target regulatory agency. However, we believe that no more than 3-6 subjects would be sufficient to demonstrate the activity of a given formulation against the test virus selected. In this regard, the fingerpad method provides for enough digits in any given test to include the necessary controls as well as 2-4 replicates for tests on the hands of the same subject.
Product lots to be tested	At least 2 product lots must be tested and found to give similar results.
Product performance criterion	Currently, no guidelines are available in this regard. However, the limitations of working with viruses in general and to keep the product performance criteria in line with the levels of viral contamination expected on hands under field situations, a 2 to 3 $\log_{10}$ reduction in virus infectivity after exposure to the test product should be considered a reasonable level of performance.
Essential controls	Need for a host system in working with viruses increases the variety of controls beyond those needed in bactericidal tests. For example, controls must be included to ensure that any non-cytotoxic residue of the test germicide is not interfering with the ability of the virus to infect the host cells.

thus gaining an unjust market advantage, (4) encourages label claims against viruses (eg, influenzaviruses) that may not be amenable to control through the use of chemical germicides, and (5) makes product comparisons difficult because of the use of nonstandardized viral strains and variations in test protocols.

Such testing should be conducted with proper surrogates provided the test conditions are rigorous enough. As shown in Table 6, many types of viruses possess characteristics desired in a surrogate, and 1 or 2 of them can be selected to test hand antiseptics.

Some studies have used viruses naturally found in clinical samples,[43,122] but this approach is unsuitable in standard test protocols because of wide variations in the levels of infectious virus and the soil loading in them. The use of phages[137-139] alone in such testing would not be sufficient for product registration, but it could be an inexpensive and rapid way of screening a large number of potential formulations.

Criterion of a product's potency for registration as a hand antiseptic

In many in vitro carrier tests for germicides, a product must reduce the infectivity titer of the test virus by at least 4 $\log_{10}$ to be considered effective.[10] This is too high a requirement for most hygienic hand antiseptics to meet in in vivo tests with the whole-hand or the fingerpad protocols. Alcohol-based products often achieve virus reduction levels between 2 and 3 $\log_{10}$.[8,128] In contrast, water or soap and water, as well as many other products, may achieve only as much as 1 $\log_{10}$ reduction in virus infectivity.[8,128] Perhaps a level of virus reduction of no less than 1

Table 6. Viruses relevant in hand antisepsis and possible surrogates for testing activity against viruses

Virus	In vitro infectivity assay method	Safe for skin	Survival on hands	Potential for spread by hands	Suitability as a surrogate	Comments
Adenoviruses	Yes	Yes	Good	Yes	Yes	Many types of adenoviruses are safe and relatively easy to work with in the laboratory; however, they may be less resistant to chemical germicides than other nonenveloped viruses, such as hepatitis A and rotaviruses.
Norwalk virus	No	Yes	Unknown	Very high	No	Human caliciviruses cannot be grown in the laboratory, but some animal types, such as feline caliciviruses, can be cultured and could act as surrogates for the Norwalk virus.
Hepatitis A virus	Yes	Yes	Very good	Very high	Possible	Relatively resistant to inactivation by many germicides used as topicals; vaccination of personnel handling the virus is recommended.
Herpesviruses	Yes	No	Poor	High	No	Fragile viruses with low resistance to many chemicals
Papillomaviruses	No	No	Unknown	High	No	Human papillomaviruses cannot be grown in the laboratory, whereas some animal papillomaviruses may be cultured and quantitated with some difficulty; papovaviruses such as simian virus 40 (SV_{40}) as possible surrogates.
Enteroviruses (Coxsackie, echo, polioviruses, and other members)	Yes	Yes	Good	Not known	Possible	Although the vaccine strains of polioviruses are safe, the use of all polioviruses will soon be phased out in view of the anticipated eradication of poliomyelitis; whereas a coxsackie- or echovirus may be used instead, their safety will be a concern.
Poxviruses	Yes	No	Yes	Unknown	No	Generally difficult to work with in the laboratory and also require specialized facilities for handling and containment except for vaccinia virus.
Influenza-viruses	Yes	Yes	Very poor	Unknown	No	Fragile viruses with low resistance to many chemicals.
Respiratory syncytial virus	Yes	Yes	Very poor	High	No	Fragile viruses with low resistance to many chemicals.
Rhinoviruses	Yes	Yes	Very good	High	Yes	Relatively safe and easy viruses to work with in the laboratory.
Rotaviruses	Yes	Yes	Very good	Very high	Yes	Relatively safe and easy viruses to work with in the laboratory.

$\log_{10}$ above that achieved for mechanical removal by water with a standard level of hardness may be considered as appropriate for allowing an effectiveness claim for handwash or other topical products against viruses. The ultimate objective here is the reduction of the risk of disease spread through hands without discouraging compliance with handwashing.

Testing virus elimination by the product alone or by the process of hand decontamination as a whole

Precleaning and rinsing after treatment are integral parts of the disinfection process for semicritical medical devices, but precleaning and rinsing may or may not occur in the chemical disinfection of environmental surfaces. In the case of hygienic handwashing, one normally wets hands with tap water, applies the antiseptic agent, rinses them again in water to wash off the hand antiseptic agent, and then dries them with one of several possible means. Water rinsing after treatment and the drying of washed hands can additionally reduce viruses on washed hands.[128] The fingertip[123,140] and whole-hand[128] methods described earlier determine virus reduction only as a combined action of all the steps in hand antisepsis. Is this appropriate? Does this determine the virus-eliminating potential of a product, or does it assess the efficiency of the handwashing or drying process as a whole? How does this approach then compare the potency of water-aided and "waterless" formulations?

CONCLUDING REMARKS

Globally, viruses cause millions of cases of morbidity and mortality in humans every year and, thus

far, the development of chemotherapy against them has met with limited success. Also, many viral infections of the enteric and respiratory tracts remain refractory to prevention by vaccination. Therefore, controlling their spread through regular and proper hand antisepsis remains crucial. However, the use of formulations without proven activity against viruses may only create a false sense of security with respect to viral illness.[47] There is an urgent need to develop and introduce a suitable regulatory framework to allow reasonable label claims against viruses. This is also necessary to promote innovation to broaden the germicidal spectrum of hand antiseptics while keeping them safe to the user and friendly to the environment.

Transfer of infectious viruses to and from hands can readily occur on contact with other animate and inanimate surfaces,[8,114,117,141] suggesting that touching soiled surfaces with decontaminated hands can recontamination them. Proper disinfection of environmental surfaces[122] and washing hands[114] with certain types of agents can interrupt virus transfer to clean surfaces. It is important that decontamination of hands and environmental surfaces reinforce each other, particularly in hospitals and food handling.

The safety and testing requirements for topicals should fall somewhere in between antiviral drugs and other types of germicides. Even though germicides have been discussed at many forums in the past 2 decades, the issue of topicals and viruses remains essentially unexplored. The FDA's tentative final monograph on topical antimicrobials[4] does not mention viruses at all, whereas the FDA's Center for Food Safety and Nutrition[58] regards enteric viruses as important targets. Regulators, manufacturers, and users alike are seeking information and directions, respectively, for the registration, marketing, and purchase of hygienic hand antiseptics.[142] Therefore, this issue needs to be addressed through research and development and discussed between the stakeholders to bring safe and effective products to the market. It is hoped this article will serve as a springboard for discussions in this regard.

As shown here, the numbers of cases of respiratory and enteric viral infections are high, even for only the reported ones. It must be recognized that simply encouraging testing of hand antiseptics against viruses and establishing label claims against them would not prevent all such infections. The real questions relate to how much disease could be prevented, and how much would need to be prevented before the measure became cost effective for society as a whole. This is a complex issue and many factors need consideration, including the possibility that the young and immunocompromised, with their higher susceptibility to infections,[34] may require more frequent use of germicidal products and, consequently, greater exposure to potentially harmful chemicals in them. The challenge for makers of topicals would be to develop safe but effective alternative virucides, and regulators would be challenged to ensure the proper evaluation of any label claims for virus inactivation or elimination. Materials managers in hospitals may also need to be made aware of potential savings in the overall budget even when spending more on the purchasing of better products for hand hygiene.[143,144]

There continues to be much discussion on the significance of the hands of caregivers and food handlers as vehicles for a variety of infections. There are also renewed efforts to increase awareness of this issue in professionals and the general public alike.[143,144] In spite of its high relevance in infection control, the topic of hand antisepsis lacks the scientific profile necessary to attract funding for quality research. Regulatory agencies continue to demand evidence from clinical outcome studies when such investigations may or may not provide clear-cut data even with the investment of much time and resources.

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