Handwashing: Are Experimental Models a Substitute for Clinical Trials? Two Viewpoints

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CLINICAL RELEVANCE OF EXPERIMENTAL MODELS FOR TESTING EFFICACY OF TOPICAL ANTIMICROBIAL PRODUCTS

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The need for standardized test methodologies for the evaluation of topical antimicrobial products has been formally recognized in the United States by the Food and Drug Administration (FDA), by a Committee for Standardization of Disinfectants in Europe and, subsequently, the Council of Europe. Brief histories of their activities are summarized by Bruch and Larson[1] and by Ayliffe.[2] Most test programs include in vitro evaluation to measure minimum inhibitory concentrations (MIC) of the active ingredient against a battery of standard test organisms as a screening mechanism to demonstrate antimicrobial activity. However, a myriad of variations exist with regard to other aspects of testing.

Some of the variations in test methodology can be explained on the basis of why products are being tested. Indications for use of a product, the frequency and intensity of its use and the desired effect(s) are criteria an investigator considers in developing a test protocol (Table). For example, to measure the effect of a product in the removal of contaminating flora, some protocols include the artificial inoculation of organisms known to be of significance in nosocomial infections, while others evaluate the activity of a product only against the indigenous flora occurring naturally on hands.

Protocols vary not only in terms of what they sample (e.g., artificially inoculated, transient or colonizing flora), but also in terms of how they sample. The most most common sampling protocols are variations on the glove juice/scrub rinse technique and impression plate/hand stamping procedures. In general, the rinse techniques have a high sensitivity and allow quantitative as well as qualitative analysis of organisms harvested. They are, on the other hand, more expensive and require a greater degree of technical expertise. The impression plate methods, although less sensitive, are easy, fast and inexpensive.

While there may be some justification for the need to vary methodology to answer different questions and examine various aspects of an issue, most of the differences in handwashing and scrubbing test protocols today are not because researchers are studying different problems, but rather because the research community simply has not agreed to accept standard testing methods. In the United States, this standardization probably will not occur until the FDA publishes a Final Monograph of the testing of topical antimicrobials. In West Germany and Austria, standardization of testing methods has been achieved. Although particular aspects of these standardized protocols can be challenged and criticized, it is at least possible with such a system to compare results across studies and between test sites. Ayliffe[2] has made a plea and cogent argument for the need for international standardization of a

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Table
Criteria Used to Select Methodology for Testing Topical Antimicrobial Products

Criterion	Examples
Indication for product use	Surgical scrub; patient bathing; healthcare personnel antimicrobial handwash; handwashing in general patient care areas; preoperative patient skin preparation
Frequency/intensity of use	One-time use before surgery; short, but frequent handwashes; surgical scrub protocol
Desired effect	Removal of transient flora only; reductions in colonizing flora; residual activity

small number of reproducible test procedures. Until this is accomplished, we will be unable to determine whether variations in study results are caused by testing differences or the product itself.

It is important, however, to recognize the purposes and limitations of experimental models for testing handwashing products. Models are vital for sorting out various characteristics of an ingredient or formula because only when it is possible to control extraneous variables in a standardized experimental setting can one characterize the extent of antimicrobial activity under a known set of use conditions. Once efficacy in terms of antimicrobial activity has been demonstrated, however, the utility and clinical applicability of such models are limited. The basic question regarding hand hygiene is not "How clean can hands get," but rather, "How much cleanliness is associated with how much reduction in risk of infection?" The answer to this question, of course, varies with a variety of host, environmental and agent factors.

Clearly, the strongest evidence for a causal link between handwashing and infections would be obtained through a randomized clinical trial. But what, really, would such a clinical trial add to the evidence at hand? We would be able to conclude, given a positive association, that handwashing as practiced in the study institution(s), in the study units, according to the study protocol, when one particular product was used, was effective. There would be no end to the recommendations for other studies in other settings using other protocols and products. In other words, I'm not convinced that even the definitive study for which we have been lobbying and waiting would, in fact, influence practice. What we know now from natural experiments, epidemiologic studies and experimental models is that clean hands are associated with reduced risk of contact-spread infection in a variety of settings, including the community and healthcare institutions, and a variety of handwashing products make the hands cleaner, some more than others.

One alternative to a series of expensive clinical trials is to set rational standards for products used based on risk of contact spread and host susceptibility, and to rely on experimental models to verify antimicrobial efficacy of products. If this becomes our stance, some form of standardization for testing becomes even more imperative. I will not comment on the relative merits and applicability of models and protocols currently used for product testing. There is always room for better ways to do things, and standardization should not replace ongoing exploration. But standardization would enhance efficiency and reproducibility of product testing and give us a reliable basis for rational decision making.

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ARE EXPERIMENTAL HANDWASHING MODELS A SUBSTITUTE FOR CLINICAL TRIALS TO ASSESS THE EFFICACY OF HAND DISINFECTANTS?

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In principle, there is no doubt that, whenever possible, the effectiveness of preventive measures against infection should be assessed by their ability to reduce clinical infection, as this is their ultimate purpose. In the case of hand disinfection, however, a clear answer will often not be obtained unless the procedure, including the disinfectant under examination, causes a substantial fall in the frequency of infection. This was observed, for example, by Semmelweis, who succeeded in lowering the maternal infection mortality from an average of 13.7% in 1846 to 1.3% in 1848 by introducing his regimen of hand disinfection in Vienna.[1]

Today, measures of hand hygiene, which cannot be omitted for ethical reasons, are more or less included in most procedures involving direct or indirect patient contact, so that the variation of methods cannot be expected to provoke effects as dramatic as they were in those days.[2] For statistical reasons, the chance to demonstrate a significant difference between proportions (here, infection ratios) not only depends on the size of this difference but also on the size of the infection ratio to be lowered. The smaller the initial infection ratio, the smaller the probability of demonstrating a statistically significant difference.

Today's infection ratios attributable to hand transmission, at least those of hospitals in industrialized countries, are probably much lower than those in the days of Semmelweis.[3] These statistical difficulties may, of course, be compensated for by

increasing the sample size (i.e., the number of observed cases). But, as illustrated by the following example, this number can easily reach a magnitude that makes it difficult to organize a clinical trial.

To demonstrate an unrealistically large fall of 50% in the proportion of hand-transmitted infections from 0.02 (2%) to 0.01 (1%), each of two experimental groups of patients (one attended to by medical staff employing the conventional measures of hand hygiene; the other by staff employing the assumed better method under investigation) would have to include approximately 2,500 patients. This result of a power analysis is based on arcsine transformation[1] of the proportions with a desired level of significance of 5% (directional testing) and a chosen power of statistical test of 90%.[4] In this example, the patient population was assumed homogeneous with respect to susceptibility to infection. This requirement can be very difficult to meet if large sample sizes are required.[5]

Hands are an important, though only one, route of transmission. Therefore, their role for transferring infection in a chosen experimental group of patients has to be defined very carefully before any conclusion can be drawn from the results of a clinical trial. Ideally, the way of transmission by hands also should be "homogeneous," implying that the susceptible body site is the same in all patients and that the attending hand invariably has contact with it.

Thus, in assessing the efficacy of hand disinfectants in clinical trials, the following requirements must be met: sample sizes of experimental groups must be large enough to allow demonstration of statistical significance of the desired difference in infection ratios; patients should be homogeneous in their susceptibility to infection; hands must represent an important route of infection in a given population; and homogeneity of the way of transmission is necessary, implying an obligate contact of the attending hand with the susceptible site of the patient.

From this, it follows that in contrast to Semmelweis' situation, there exist only a few constellations meeting these requirements in today's hospitals, at least in industrialized countries. Semmelweis was confronted with a high initial ratio of lethal infections. The students' hands examining the maternal birth-canal were contaminated with highly pathogenic agents and came into obligate contact with the same and very susceptible body sites of a homogeneous group of patients: parturient but probably otherwise healthy women of comparable socioeconomic status. As, by effectively blocking the most important route of transmission, his precaution caused a dramatic fall in infections and eliminated the main cause of death, the mortality ratios before and after the introduction of Semmelweis' measure differed very much and an effect was easily demonstrable.

Today the practical difficulties to produce evidence for the efficacy of a measure of hand hygiene in terms of lowered infection ratios have provoked the evaluation of several alternative approaches. All of them include bacteriological investigations ("models") as a substitute for clinical trials, but in different ways and using various parameters. All of them are devoid of the possibility of generating information on several accompanying features of the handwashing procedure, such as side effects, acceptability and, consequently, handwashing compliance. It must be realized, however, that testing the antimicrobial effectiveness must be the primary aim, as without this feature, blocking of microbial transmission will be insufficient so that other positive features of the antiseptic measures are meaningless.

Studying the influence of handwashing procedures on the carriage ratio of a potential pathogen or an index organism may accumulate results quicker than infection studies, but they are as tedious and are appropriate only when acquisition usually precedes infection. They have proven useful, for example, in comparing the effect of various measures of hand hygiene on the staphylococcal colonization of newborn infants.[2]

Assessing the antimicrobial activity of an antiseptic in vitro may help to establish its antimicrobial spectrum and consequently eliminate measures that are not worth testing clinically or in more complicated models. Results of these tests, however, can be misleading, because the influence of factors such as the physical, chemical and microecological environment of the skin, mode of application and inactivation of the disinfectant is not included in the tests. In the authors view, this is the case not only in suspension tests but also in tests using carriers of nonbiological material and of (nonliving) human or animal skin sections. These drawbacks may be virtually overcome by employing models that mimic real life conditions using hands of volunteers. According to the purpose for which the antiseptic measure is intended (hygienic or surgical hand disinfection), either models with artificial contamination,[3-6] representing the transient flora, or with clean hands[4,7-9] to test the effect against the resident flora, may be used. All of them assess the reduction of the release of test organisms or resident skin flora as achieved by the procedure under examination.

Only three models,[4,6,7] however, relate this reduction to that obtained with a standard-disinfection performed in parallel by the same volunteers and under similar conditions. In this procedure, each volunteer acts as his or her own control and extraneous influences are nullified so that results obtained in different laboratories or with different volunteers are rendered comparable, which otherwise is not the case.[10] At the same time, the antimicrobial effect of the standard procedure can serve as a yardstick for effectiveness, as is the case in the Vienna model.[5] An antiseptic procedure under

investigation should not be significantly less active than the standard procedure. However, the required extent of the effectiveness of the standard procedure has to be fixed arbitrarily, as there are no epidemiological data indicating how effective a disinfection procedure has to be in order to prevent hand-transmitted infection. Therefore, this question will continue to provoke discussion until sufficient results of clinical trials are available.

Intelligently designed in vivo models can help assess the effectiveness of antiseptic measures to reduce bacterial release from the hands with relatively little expense. Therefore, a range of order of various procedures can easily be established according to their effectiveness. Perhaps in patients with "normal" (low) susceptibility to infection, the differences in this range are not relevant because the dose-response curve is too flat; i.e., a large change of hand-transferred pathogens is answered by a little change of the infection ratio. In highly susceptible patients, however, differences in effectiveness may be reflected much more distinctly in altered infection ratios. Although in vivo models have their place in routinely establishing the "degerming" efficacy of new handwashing procedures, clinical trials are sometimes necessary to find out what this effectiveness means in terms of infection ratios in defined patient populations.

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