MEETING HEALTH CANADA
STANDARDS FOR ALCOHOL-BASED
HAND RUBS EFFICACY:
FORMULATION MATTERS!

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CHANGING GEARS
From Environmental Cleaning to Skin Antiseptics...

Hand Hygiene and Alcohol-Based Hand Rubs
Breaking the Chain of Infection

Our main objective is to reduce infection rates in Health Care settings

- Hand Hygiene
- Environmental Cleaning
- Portal of Entry
- Host Susceptibility
- Infectious Agent
- Reservoir
- Portal of Exit
- Transmission

http://faculty.ccc.edu/tr-infectioncontrol/situation1.htm
Objectives

- Overview Health Canada standards for evaluation of antimicrobial efficacy of healthcare use of hand rubs
- Understanding of the variables that drive antimicrobial efficacy of alcohol-based hand rubs
Agenda

Hand Hygiene & Alcohol-Based Hand Rubs

What are the current methods to evaluate antibacterial efficacy of ABHR in Health Canada?

Which factors influence antibacterial efficacy?
  - alcohol concentration?
  - product formulation?
  - product (alcohol) form?
  - product quantity?

Product Acceptance & Clinical Effectiveness

Conclusions
Leading Health Related Institutions Endorse the Use of Alcohol-Based Hand Rubs

Best Practices for Hand Hygiene

In All Health Care Settings

WHO Guidelines on Hand Hygiene in Health Care

First Global Patient Safety Challenge
Clean Care is Safer Care

Ministry of Health and Long-Term Care
Originally Published May 2000
Revised June 2000
Published and revised December 2010

Provincial Infectious Diseases Advisory Committee (PIDAC)

Participating
CHOCA-Canada Standards and Guidelines Core Committee Chair, Dr. Bronwyn Henry Participants:...
Clinical Effectiveness of ABHR

ABHR use associated with increasing HH compliance and reduction of transmission of Hospital Acquired Infections (HAIs)

**Increased Alcohol Use**

- Hand disinfection
- Handwashing

**Fewer Infections**

- Attack rates of MRSA (new cases per 100 admissions)
- Nosocomial infections (cases per 100 admissions)

Alcohol as a Skin Antiseptic

• The activity of alcohol as a skin antiseptic was first studied at the end of the 1800s
• Studies by Price (1939 and 1950) demonstrated that the ideal concentration for alcohol for skin antisepsis is 70% w/w (surgical antisepsis)
  – Efficacy declines above 90%
  – “70% cheaper than more concentrated solutions”
  – “Spreads more evenly over the skin and evaporates more slowly”
  – “Neither cause skin dryness nor extracts its lipids”

Alcohol actually kills by two separate mechanisms:

1) Damages cell membranes $\rightarrow$ loss of cell integrity
2) Inactivates proteins ("denatures")

• Dual mechanism is very unique to alcohol which acts very rapidly and then evaporates
• Leaves no residual behind after evaporation
• Broad spectrum antimicrobial

*Staphylococcus aureus*

exposed to ABHR
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► Conclusions
Health Canada Guidance Document to Antiseptic Skin Products for Human Use

- Categories of Antiseptic products
  - Personal Domestic & Commercial Use
  - Professional Food Handler
  - Professional Health Care

- Product Efficacy Data
  - Tests Recommendations
    - *in vitro, in vivo*, organisms tests, etc.

- Safety Tests
  - Skin irritation, Sensitization

- Quality Tests

- Claims & Labeling

- Submission Filling Process
Guidance for Professional Health Care Use Products

1-Professional Hygienic Handrub: product used for post-contamination treatment of lightly soiled hands that involves rubbing hands without addition of water, an which is designed for frequent use

2-Professional Hygienic Handwash

3-Surgical Handrub

4-Surgical Handwash

5-Patient preoperative skin preparations
Health Canada Professional Hygienic Handrub
Antimicrobial Efficacy Testing Requirements

*In vitro* (Time-Kill)

*In vivo*

ASTM
International
Standards Worldwide

European Committee for Standardization
Comité Européen de Normalisation
Europäisches Komitee für Normung
Health Canada Standard for *in vitro* Efficacy Tests

Data request on key subset of Bacteria (20), Fungi (2) and Viruses (14)

Minimum Acceptable $\log_{10}$ Reduction:
- Bacterial ($\log_{10}$) = 5 (99.999%)
- Fungi & Viruses ($\log_{10}$) = 4 (99.99%)

Bacteria/
Suspension

Test Product
(80% dilution)

30-Second
Contact Time

Bacteria Log
Reduction
Health Canada *in vivo* Antibacterial Efficacy Tests

**ASTM**

E 1174 (HCPHW)

**In vivo Tests**

**EN 1500**

European Committee for Standardization
Comité Européen de Normalisation
Europäisches Komitee für Normung
ASTM E-1174
Healthcare Personnel Handwash (HCPHW)

- Predicts the reduction of organisms by washing or sanitizing hands after handling contaminated objects.
- Measures reduction of transient organisms after single (application 1) or multiple product uses (application 10).

Health Canada Minimum
$log_{10}$ Acceptable

1st Application: 3 log
10th Application: 3 log

ASTM E 1174
Healthcare Personnel Handwash Overview

1- Hand contamination with a known amount of Serratia marcescens

2- ABHS application

3- Glove Juice Sampling

4- Sample diluted serially and plated

5- Microbial enumeration

Health Canada Minimum log_{10}
Acceptable
1st Application: 3 log
10th Application: 3 log
European *In Vivo* Method: EN 1500

- **Challenge organism:** *Escherichia coli*
  - Product application for defined volume & contact time
  - Typical: 3mL for 30 sec
- The test product is evaluated after a single use compared to an internal reference product (60% isopropyl alcohol)
  - Minimum Acceptable Log$_{10}$ Reduction = 3 logs or to be equal or superior to the reference product
- Must show non-inferiority to internal reference (or achieve 3 log reduction according to Health Canada)

1. Hand contamination with *E. coli*
2. ABHS application
3. Plating using fingerpads
Agenda

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  ▶ product formulation?
  ▶ product (alcohol) form?
  ▶ product quantity?
► Factors Influencing Antiviral Efficacy
► Conclusions
Myth: More Antimicrobial Active Ingredient (more alcohol) Always Means Better Kill
Truth: Alcohol Concentration does not Predict Antimicrobial Efficacy of ABHR

- Application 10 log reductions for various marketed ABHRs using *in vivo* methodology ASTM E 1174 (HCPHW)
- Alcohol concentration does not drive efficacy
- Only 2 products met Health Canada requirements

ABHR with the same alcohol concentration has different efficacy

*Edmonds, S. E., Macinga, D. R. and Mays-Suko, P. Comparative efficacy of commercially available alcohol-based hand rubs and WHO-recommended hand rubs which is more critical, alcohol content or product formulation? Association for Professionals in Infection Control and Epidemiology. 2011.*
ABHR Formulations

• ABHR formulations often contain:
  – Alcohol
  – Water
  – Thickeners
  – Moisturizers
  – Buffering Systems
  – Secondary Actives
  – Surfactants

• Ingredients create specific attributes:
  – Skin tolerance, skin moisturization, aesthetic properties
    (e.g. skin feel, fragrance, etc.)
  – Enable specific delivery formats (rinse, gel, foam)

• May improve or inhibit antimicrobial efficacy of formulations in ASTM 1174 (HCPHW) and EN1500
Increasing alcohol concentration does not correlate to increased efficacy
- 70% formulations outperform higher alcohol formulations

Both gel and foam formulations meet Health Canada requirements

Formulation more important than product form

Edmonds, S. E., Macinga, D. R. and Mays-Suko, P. Comparative efficacy of commercially available alcohol-based hand rubs and WHO-recommended hand rubs which is more critical, alcohol content or product formulation? Association for Professionals in Infection Control and Epidemiology. 2011.
Only Well-formulated 70% Ethanol Products Meet Health Canada *in vivo* Efficacy Test ASTM E1174

- Alcohol concentration does not correlate to efficacy
  - Some 70% formulations outperform higher alcohol formulation
- Alcohol form (gel, foam, rinse) does not correlate to efficacy

**FORMULATION MATTERS**

Comparative Efficacy of Commercially Available Alcohol-Based Hand Rubs and WHO-Recommended Hand Rubs: Formulation Matters accepted for publication at AJIC
Sarah L. Edmonds, MS¹, David R. Macinga, PhD², Patricia Mays-Suko, BS², Collette Duley², Joseph Rutter, BS¹, William R. Jarvis, MD³, James W. Arbogast, PhD¹
Well Formulated ABHR with 70-80% Meet Health Canada in vivo Efficacy Test EN1500

EN 1500: ABHR with 70–80% ethanol meet Health Canada bactericidal efficacy requirements

Test Product
1 application of 3 ml for 30s

Reference Product
2 applications of 3 ml for 30 sec

Error bars = 95% CI

All test products were statistically equivalent to the internal reference standard, meeting EN 1500 requirements. In addition, all products obtained a > 3 log reduction, thus meeting Health Canada bactericidal efficacy requirements.
ABHS with 62-70% Ethanol Meet Health Canada Requirements for EN1500

![Graph showing Log₁₀ Reduction for different alcohol-based hand rubs.](image)

Edmonds, S. E., Macinga, D. R. and Mays-Suko, P. Comparative efficacy of commercially available alcohol-based hand rubs and WHO-recommended hand rubs which is more critical, alcohol content or product formulation? Association for Professionals in Infection Control and Epidemiology. 2011.
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  ► product (alcohol) form?
► Product Acceptance & Clinical Effectiveness
► Conclusions
Recommended ABHR Quantity

“Apply one to two full pumps of product onto one palm; the volume should be such that 15 seconds of rubbing is required for drying”

Focus on dry time

PIDAC Best Practice of Hand Hygiene (2010)

“Apply a palmful of alcohol-based handrub and cover all surfaces of the hands [and] rub hands until dry” Focus on hands coverage

WHO Guidelines on Hand Hygiene in Health Care (2009)

“Ideal volume of product to apply to the hands is not known and may vary for different formulations. However, if hands feel dry after rubbing hands together for 10-15 seconds, an insufficient volume of product likely was applied” Focus on dry time

US CDC Guideline for Hand Hygiene in Health-Care Settings (2002)
Product Application Quantity Matters

- Test method: ASTM E2755
- Test product: ABHR 62%

ABHR efficacy is influenced by product quantity applied to the hands

Quantity required for clinical effectiveness remains unknown

More quantity, more efficacy

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► Conclusions
Product Acceptance & Clinical Effectiveness

• The “best” ABHR are those that achieve a balance of antimicrobial efficacy and acceptance by health care workers

• Product efficacy can be outweighed if products are not accepted
  - Lower compliance may result in increased infection rates

• Characteristics that affect acceptability:
  - Skin performance
    • Irritation, Dry time,
  - Product aesthetic (feel, smell, color, etc.)

• The importance of product acceptability is noted in the CDC, WHO and PIDAC Guidelines for hand hygiene


Conclusions

- Alcohol concentration does not influence efficacy. Increasing alcohol concentration alone is not sufficient to guarantee efficacy.
- Alcohol concentration in excess of 70% is not required for efficacy:
  - Well-formulated 70% ethanol gel and foam ABHR met Health Canada requirements for both ASTM E1174 and EN1500, and had superior performance to products containing higher alcohol concentration.
- Products in both gel and foam formats met Health Canada bactericidal efficacy requirements.
- Product formulation and volume are critical determinant of ABHR efficacy.
- Formulation matters!
THANK YOU

For more information on the science of ABHRs, visit our website at gojocanada.ca/healthcare

INQUIRIES HEALTHCARE@GOJO.COM

CALL: 1-800-321-9647
QUESTION S
Challenges When Using HCPHW Method to Measure ABHR Efficacy

1. Hands are contaminated with a large volume of challenge bacteria.

2. Challenge bacteria remains wet on the hands.

3. Test product applied to wet hands, diluting the alcohol below the level required to achieve maximum kill.

4. Activity of the product declines as hands become wetter.

Average Log₁₀ Reduction

<table>
<thead>
<tr>
<th>Wash</th>
<th>1</th>
<th>3</th>
<th>7</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.0</td>
<td>4.0</td>
<td>3.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Wash 1, 3, 7, 10
No “Magic” Alcohol Concentration will Kill all Viruses

Proper formulation is as important as the choice and level of active ingredient

- Antimicrobial active ingredients are effective when properly formulated*
- Concentration of alcohol does not predict antimicrobial efficacy

Ethanol AV Dose Response

* Numerous Patent References from Industry and FDA Monograph Data
Influence of Formulation on ABHR Efficacy Against Hard to kill (non-enveloped) Viruses

- Alcohol:
  - Broad spectrum kill against bacteria and enveloped viruses
  - Ineffective against spores (*C. difficile*) and most non-enveloped viruses (Norovirus)
Alcohol concentration alone does not dictate efficacy of hand sanitizers against Human Norovirus
ABHR vs. Norovirus

• Alcohol-Based Hand Sanitizers Associated With Norovirus Outbreaks”, Dr. Blaney, from CDC, attempted to identify risk factors for widespread Norovirus outbreaks in long-term care facilities (LTCFs) in New England.
Alcohol Efficacy: Time-Kill Dose Response

- There is a “threshold” concentration when alcohol becomes bactericidal
- Approximately 40% for Gram negative bacteria and 50% for Gram positive bacteria
- Activity does not improve above this level

Recommended Concentration Range for ABHR

![Graph showing Log Reduction vs. % Ethanol (v/v)]
## Comparative Efficacy of Alcohol-Based Hand Rubs Using *in vivo* E 1174 and Health Canada Standards

<table>
<thead>
<tr>
<th>Test Product</th>
<th>Study #*</th>
<th>Test Product Description</th>
<th>Application 1 (\log_{10}) Reduction (95% C.I.)</th>
<th>Application 10 (\log_{10}) Reduction (95% C.I.)</th>
<th>Meets Health Canada Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>1</td>
<td>70% v/v ethanol gel</td>
<td>3.58 (3.34-3.82)</td>
<td>3.50 (3.26-3.74)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>1</td>
<td>70% v/v ethanol foam</td>
<td>3.55 (3.32-3.74)</td>
<td>4.00 (3.26-4.24)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>70% v/v ethanol foam</td>
<td>3.48 (3.34-3.61)</td>
<td>4.41 (4.14-4.69)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>1</td>
<td>90% v/v ethanol gel</td>
<td>3.12 (2.89-3.35)</td>
<td>1.80 (1.57-2.63)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>80% v/v ethanol rinse</td>
<td>3.07 (2.84-3.29)</td>
<td>2.39 (2.17-2.61)</td>
<td>No</td>
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<tr>
<td>WH</td>
<td>1</td>
<td>75% v/v isopropanol rinse</td>
<td>3.12 (2.88-3.36)</td>
<td>2.03 (1.80-2.27)</td>
<td>No</td>
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<tr>
<td>F</td>
<td>2</td>
<td>62% v/v ethanol gel</td>
<td>2.99 (2.77-3.21)</td>
<td>1.97 (1.75-2.19)</td>
<td>No</td>
</tr>
<tr>
<td>G</td>
<td>2</td>
<td>70% v/v ethanol foam</td>
<td>2.83 (2.61-3.05)</td>
<td>1.94 (1.72-2.16)</td>
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</tr>
<tr>
<td>H</td>
<td>2</td>
<td>68% v/v ethanol gel</td>
<td>2.48 (2.26-2.70)</td>
<td>1.31 (1.09-1.53)</td>
<td>No</td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>62% v/v ethanol foam</td>
<td>2.86 (2.64-3.08)</td>
<td>2.71 (2.49-2.93)</td>
<td>No</td>
</tr>
<tr>
<td>J</td>
<td>2</td>
<td>70% v/v ethanol gel</td>
<td>2.88 (2.66-3.10)</td>
<td>2.47 (2.25-2.69)</td>
<td>No</td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>60% / f</td>
<td>3.12 (2.88-3.36)</td>
<td>2.03 (1.80-2.27)</td>
<td>No</td>
</tr>
</tbody>
</table>

### Observations

- **Alcohol concentration does not correlate to efficacy**
  - Some 70% formulations outperform higher alcohol formulation
- **Alcohol form (gel, foam, rinse) does not correlate to efficacy**

FORMULATION MATTERS

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*Note: Log\(_{10}\) Reductions are expressed as the geometric mean reduction with 95% confidence intervals.*
EN1500: Technical Nuances

- **Test method does not reflect in-use conditions**
  - Hands may be wet, diluting alcohol concentration
  - Results biased towards higher-alcohol products

- **No clinical rationale for choice of internal reference**
  - 2 x 3mL application not reflective of clinical practice
  - Prediction of clinical effectiveness?

- **Statistical considerations:** The “tighter” the data, the harder it is to pass
  - You are penalized for going to good labs
Alcohol Concentration: *in vivo* Literature

- **EN1500**
  - Ethanol concentrations equal to or greater than 70% are typically, although not always, needed to meet requirements.

- **HCPHW (ASTM E1174)**
  - Few studies published using E1174.
    - Many products evaluated do not meet FDA Application 10 requirements using typical application volumes.
      - Most tested products contain 60% to 62% ethanol.
    - Literature for U.S. products claim formulations meet FDA HCPHW efficacy requirements.

*Difficult to make conclusions regarding influence of alcohol concentration on product efficacy.*
“No randomized clinical trials or epidemiologic data have demonstrated that the liquid formulations reduce transmission of pathogens to a greater degree than gel formulations”

“The question remains whether a small, albeit statistically significant, difference in efficacy between rinses and gels is clinically significant and, if it is, whether a benefit of gels over rinses in terms of improved skin tolerability may lead to increased compliance that would over-shadow their slight antimicrobial inferiority”
Clinical Effectiveness

- Clinical Effectiveness:
  - Interrupt the spread of pathogens and the acquisition of Healthcare Associated Infections (HAIs)

- Influenced by a number of interdependent variables
  - Product efficacy
    - Formulation
    - Product quantity
  - Healthcare worker compliance (Used properly/at appropriate times)
    - Skin performance
    - Product aesthetics