Antimicrobial Products May Promote Resistance

BY JEFF EVANS
Senior Writer

BETHESDA, MD. — Use of household cleaning products that contain benzalkonium chloride may decrease the susceptibility of bacteria to other antimicrobial ingredients in cleaning products and increase their resistance to antibiotics, according to the results of a randomized, double-blind study.

The study is the first randomized intervention study to assess the relationship between the use of two biocidal ingredients found in household cleaning products—benzalkonium chloride (BZK) and triclosan—and antibiotic resistance in the household setting, Allison E. Aiello, Ph.D., reported at an annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

Consumer antiseptics and disinfectants are products that can prevent infections by killing or inhibiting the growth of microorganisms. Biocidal ingredients in these products often are quaternary ammonium compounds (such as BZK) and triclosan.

Some studies have found triclosan in more than 75% of liquid hand-washing soaps sold in the United States. Triclosan has been used ubiquitously since the 1960s and can be found in some toothpaste and embedded in products such as cutting boards and baby diapers. Triclosan also is known to remain in treated sewage that is recycled for use in agriculture, according to Dr. Aiello of the department of epidemiology at the University of Michigan, Ann Arbor.

In 2000, Dr. Aiello and her coinvestigators provided 238 households with either antibacterial products (floor cleaner with 0.08% BZK, surface cleaner with 2.7% BZK, and liquid hand-washing soap with 0.2% triclosan) or the same products without antibacterial ingredients. They cultured the hands of household members before the study started and then after 1 year. Isolates of bacteria from the cultures were tested to determine the minimum inhibitory concentrations (MICs) of BZK and triclosan on which bacteria can grow.

The investigators defined MICs that were above the median for each biocide as "high" and those equal to or less than the median as "low." The investigators analyzed the general trends and changes over time in all bacterial species combined because they could not compare the same isolates at baseline and at the end of 1 year.

Isolates from households that used antibacterial products had more than double the likelihood of having developed resistance to antibiotics.

In isolates from all bacterial species combined, there were no differences between the groups in susceptibility to BZK at baseline or 1 year.

Dr. Aiello and her colleagues then analyzed of isolates of bacteria from all species with a high MIC for BZK. At baseline, these isolates from either group of households had similar rates of antibiotic resistance or high MICs for triclosan. But, after 1 year, the isolates that came from households using antibacterial cleaning products had more than twice the odds of having developed a high MIC for triclosan than did isolates from households that did not use products with antibacterial ingredients. At 1 year, isolates from households that used antibacterial products also had more than double the likelihood of having developed resistance to antibiotics. A subanalysis showed that gram-negative bacterial isolates from households using antibacterial products had nearly fourfold higher odds of developing antibiotic resistance, compared with gram-negative isolates from households that did not use products with antibacterial ingredients.

"Potential selective pressure may result in coselection of resistance genes for other biocides and antibiotics," Dr. Aiello concluded.

Dr. Aiello and her associates tested all gram-negative bacteria against gentamicin, imipenem, and ciprofloxacin. Certain bacterial species were tested against other types of antibiotics.

No covariates—such as use of a product before enrollment, child day care attendance, or antibiotic use—were associated with susceptibility to BZK or with households that used products containing antibacterial ingredients.

Previous studies have shown that both quaternary ammonium compounds and triclosan can activate efflux pumps in bacteria that transfer plasmids containing resistance genes.

The specific mechanisms of action of quaternary ammonium chlorides are unclear, but they are thought to cause generalized membrane damage. Triclosan is known to act on enoyl-acyl carrier protein reductase, called Fab1. Specific mutations in the DNA coding for this protein are known to create cross-resistance to the experimental antibiotic diazaborine and the tuberculosis drug isoniazid, Dr. Aiello said.

Dr. Aiello had no conflicts of interest to disclose. ■

Expert Outlines Why Universal HPV Vaccination Is Needed

BY DOUG BRUNK
San Diego Bureau

CALGARY, ALTA. — As an epidemiologist whose research focuses on the prevention of cervical cancer, Dr. Eduardo L. Franco spends a lot of his time dispelling baseless arguments and protests from other health care professionals and patients that more research is needed before universal human papillomavirus vaccination can be recommended worldwide.

"Although clinical experience has just passed 6 years, the evidence base is one of the strongest in disease prevention," Dr. Franco said at the annual meeting of the Society of Obstetricians and Gynaecologists of Canada. "The standard of proof is far more rigorous than that used in the evaluation of candidate vaccines of the past. It may be the most scrutinized vaccine by the public and the media concerning need and safety."

The HPV vaccine 'may achieve unprecedented lifelong protection.'

DR. FRANCO

Prophylactic HPV vaccines include a quadrivalent form manufactured by Merck & Co. that was licensed in the United States in June 2006 and a bivalent form manufactured by GlaxoSmithKline Inc. that was submitted to the Food and Drug Administration in March 2007.

Dr. Franco, director of the division of cancer epidemiology at McGill University, Montreal, shared several examples of arguments against HPV vaccination that he encounters, followed by his counterargument for each.

One chief argument he hears is that the vaccine is too costly and unaffordable where it's most needed. However, he said, procurement programs such as the Centers for Disease Control and Prevention's Vaccines for Children Program, the Global Alliance for Vaccines and Immunization, and the Pan American Health Organization's revolving fund should help to lower the cost. "Historically," he added, "prices decline with time since deployment. Competition among manufacturers should force a reduction in prices."

In addition, ongoing studies of more simplified schedules—such as administering two doses instead of three—may affect price.

Other common arguments against HPV vaccination include the following:

► **There are no data on long-term duration of protection.** In fact, to date, studies demonstrate a sustained antibody response with no indication that humoral immunity will wane before 10 years. "Even with lowered antibody titers, postvaccination protection has continued unabated," said Dr. Franco, who also is a professor of epidemiology and oncology at McGill. "We did not wait for such proof before deploying other vaccines."

► **Protection is limited; vaccines cover only two oncogenic types.** In fact, protection is against the two most important types (HPV 16 and 18), which translates into a protective fraction of 70% of all cervical cancers. That protection "is likely to be expanded via cross-protection," he said. "In combination with tailored screening strategies, it may achieve unprecedented lifelong protection."

► **Screening will continue to be needed.** Dr. Franco agreed but said that recent progress on new technologies such as HPV testing with Pap triage "will permit extending screening intervals safely and cost effectively. Proper integration of primary and secondary prevention strategies is likely to reduce costs and improve cervical cancer control."

► **There is a risk of type replacement, which occurred with the pneumococcal vaccine.** In fact, Dr. Franco said, there is no epidemiologic proof that HPV types compete for specific niches. "Several studies have tested this hypothesis," he noted. "The fraction of the population not exposed to HPV 16 or 18 is always high; exposure to HPV 16 or 18 does not constrain the pool of susceptible individuals who could acquire other HPVs."

► **We should not vaccinate preteens and teens; there are no efficacy data on patients aged 9-14 years.** This age group is not at risk for lesions and monitoring them "would be unethical and unproductive," he said. "Immunobridging" studies show that vaccine-induced humoral response in preteens is the highest among all groups, "which is sufficient justification for expectation of benefit," Dr. Franco said.

► **There is no proof yet that vaccination can reduce the risk of invasive cancers.** Dr. Franco counters this notion by pointing out that absence of evidence is not evidence of absence. "Sensible judgment based on understanding of the natural history of HPV infection and cervical cancer indicates that prevention of precancerous lesions is an acceptable end point."

► **There is no cervical cancer epidemic.** He responds to this argument by emphasizing that the health costs, morbidity, and mortality associated with cervical cancer are sufficiently important to justify action. Moreover, he said, the HPV vaccination is likely to exert protection against other neoplastic diseases such as malignant anogenital and oropharyngeal cancer and benign genital warts and laryngeal papillomatosis.

► **More research is needed on safety.** Dr. Franco responds to this argument by noting that the safety data on the HPV vaccine "are among the most well documented for any new vaccine. There was no waiting period for the adoption of other vaccines with lesser standards of proof. Inaction has a high cost in terms of morbidity and mortality that could have been averted."

Dr. Franco disclosed that his entire research program has been funded by the Canadian Institutes of Health Research (CIHR), the National Cancer Institute of Canada, and the National Institutes of Health. He has received a Distinguished Scientist salary award from the CIHR and has served as an occasional adviser to several companies with products related to cervical cancer prevention. ■