

## Special Report: Industry backing muddies infection-control science

Sage Products has been generous to science, and science has been kind to Sage Products.

This happy relationship blossomed more than a decade ago, when Sage funded a study at Rush University Medical Center in Chicago to test the efficacy of the company's new antibacterial wipes on hospital patients.

Researchers published their findings in 2006: Used daily, they said, Sage's wipes, soaked with a powerful germ-killing chemical called chlorhexidine, were more than twice as effective as sponge baths at preventing the spread of vancomycin-resistant *Enterococcus*. That's a group of drug-resistant bacteria that infect thousands of hospital patients every year, killing hundreds.

Shortly after, Rush received a \$1 million donation from the family foundation of Sage's founder, Vincent W. Foglia. The money was earmarked for research by the senior scientist on the study, Dr Robert A. Weinstein, an infectious-disease specialist at Rush.

Since then, Sage has provided funding and millions of dollars in wipes for studies by Weinstein and his colleagues. And in that time, Weinstein and his colleagues have published 11 articles on six trials that endorse daily washing of patients with Sage's patented wipes — an “off-label” use, as the U.S. Food and Drug Administration (FDA) has approved the wipes only for cleaning patients before surgery.

Relationships like the one between Sage and researchers are common in the infection-control business. Such ties have helped propel the popularity of chlorhexidine products in hospitals and other healthcare settings where drug-resistant “superbugs” are a chronic problem. In 2014, sixty-three percent of hospitals surveyed by the federal Centers for Disease Control and Prevention (CDC) said they routinely bathed patients with chlorhexidine.

But as use of chlorhexidine products has grown, so have concerns about their effectiveness and safety — and about the role of industry-backed research in promoting them. The industry money funding chlorhexidine research muddies the message of the results, in the view of many health experts.

Dr Martin Blaser, a professor in New York University's Department of Microbiology and chair of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, said it's still impossible to tell whether washing patients daily with such a potent biocide is wise or effective. Indiscriminate use could trigger resistance in harmful bugs or kill off beneficial bacteria, with dangerous consequences, he said.

“We know antibiotic-resistant infections are out of control. We need something that works,” Blaser said. “But we want to know it works.” Weinstein sits on the same presidential advisory council that Blaser chairs.

### SEVERE REACTIONS

Chlorhexidine's potential risks came to the fore in February, when the FDA issued a warning after registering a jump in reports of allergic reactions, including a couple of deaths, and other adverse events linked to the chemical.

And even chlorhexidine isn't contamination-proof. In 2008 and again last year, Sage issued massive recalls of its chlorhexidine cloths that were tied, ironically, to dozens of infections by *Burkholderia cepacia*, a pathogen that wreaks havoc on hospital patients.

The 2008 recall forced a temporary shutdown of a Sage-funded study, but not before six patients participating in the trial contracted the infection as a result of the contamination. A 2013 article on that study, co-written by Weinstein and published in the *New England Journal of Medicine*, referred to the recall as a "treatment interruption" and concluded that the cloths were safe and effective without mentioning the six *B. cepacia* infections.

References to the infections were removed from the original manuscript "for brevity" and because they didn't directly relate to the wipes' effectiveness in reducing drug-resistant infections, said Dr Michael W. Climo, lead author of the study and a professor at Virginia Commonwealth University.

Despite all the promising study results, the number of hospital-acquired drug-resistant infections has remained stubbornly high.

In 2009, the federal government launched a campaign to reduce bloodstream infections by the notorious superbug methicillin-resistant *Staphylococcus aureus* (MRSA) in hospital patients 25 percent by 2013. That failed. The new goal: Halve infection rates by 2020.

A Reuters analysis of federal data found that after a small decline in the rate of MRSA infections in hospital patients from 2013 to 2014, the rate increased slightly the following year.

The CDC confirmed the increase and said it "is being followed closely" as new data become available. It could be a one-year anomaly in a longer-term decline rather than a meaningful increase, said CDC spokeswoman Melissa Brower.

As Reuters reported last year in its series "The Uncounted," the United States has no reliable means of tracking all superbug infections and deaths. In its own analysis, Reuters found that, taken together, more than a dozen superbugs the CDC has labeled grave threats to public health continue to kill tens of thousands of people every year -- in addition to hundreds of thousands of nonfatal infections.

## BIG SOLUTIONS

Hospitals are understandably eager to find ways to beat back the infections, which waste time, money — and lives. But hospitals tend to "like these mass-produced, one-size-fits-all solutions," said Blaser.

Dr Didier Pittet, director of the World Health Organization's Collaborating Centre on Patient Safety, said that in the United States, "the marketing behind the use of chlorhexidine is huge."

Scientists who receive industry funding insist their research is not swayed by their patrons, and point out that industry funding is essential, absent more support from government.

Weinstein said Sage has had no involvement in his work and hasn't influenced his conclusions.

The \$1 million from the Foglia foundation was used for fellowships and studies, including one involving Sage's wipes, Weinstein said. Foglia, through his foundation's attorney, said that the gift had no strings attached and that Weinstein was directed only "to do the most he could for the most people with this." Weinstein said Sage's support hasn't deterred him from publishing negative results about its products. He has produced one such critique, he said. It involved a small trial at Rush in 2006, which appeared as a brief report in a European journal in 2010. The report said daily bathing with the wipes was no better than soap and water at reducing infections from central-line catheters in a surgical intensive care unit. Weinstein also noted that the CDC co-sponsored many of his studies, "so I had someone looking over my shoulder." From 2000 to 2004, Weinstein served as chair of the Healthcare Infection Control Practices Advisory Committee, which advises the CDC on infection-prevention guidelines.

Besides providing funding and products for studies, companies often pay researchers directly for consulting and speaking engagements. Weinstein said he received a few thousand dollars from Sage but stopped accepting speaker fees a decade ago.

Corporate ties to infection-control research extends beyond chlorhexidine. Manufacturers of diagnostic tests have financially supported scientists whose studies found that testing and treating patients upon hospital admission significantly reduced MRSA infections. Hospital garment makers have helped to fund scientists who found gowns and gloves highly effective in combating MRSA. Researchers involved in those studies have said that the companies were not involved in the trials and that their support did not influence the results.

Europe has been faster to recognize chlorhexidine's potential risks. Studies from the region single out potentially fatal allergic reactions to the chemical as a serious, under-reported threat.

Britain's Medicines & Healthcare Products Regulatory Agency issued a warning about the dangerous reactions, called anaphylaxis, in 2012. The number of adverse events related to chlorhexidine reported to the agency increased from 14 in 2007 to 117 in 2016.

## ADVERSE EVENTS

In the United States, the FDA's chlorhexidine warning in February came after a similar spike in incidents reported to the agency's Federal Adverse Event Reporting

System. Under the system, drug manufacturers are required to report when their products are suspected of causing illness or injury.

A Reuters analysis of FDA data found that chlorhexidine was listed as the primary suspect in an average of 85 adverse events a year reported from 2007 through 2014. Then, in 2015, the number jumped to 183, and then to 226 in 2016. The FDA said that a reported event is not necessarily due to the product, and that the agency does not receive reports for every adverse event that occurs.

Anaphylaxis or shock was cited in the FDA's adverse event reports 120 times. Skin irritation, rashes and burns were mentioned 325 times. The tally included 48 life-threatening events and seven deaths.

About a third of the serious allergic reactions were attributed to ChloroPrep, a pre-surgical chlorhexidine applicator previously marketed by CareFusion and now by Becton, Dickinson & Co.

A spokesman for BD, which acquired CareFusion for \$12.2 billion in 2015, said in an email that adverse events like anaphylaxis are "rare occurrences" compared to the "BILLIONS of uses" of the product since it entered the market in 2000.

In 2014, the U.S. Justice Department announced that CareFusion had paid \$40.1 million to settle allegations that it gave \$11 million in kickbacks to Dr Charles Denham to promote its ChloroPrep applicator. The company admitted no liability.

Denham was co-chair of the safe practices committee of the National Quality Forum, a nonprofit healthcare industry group that endorses standards of care. CareFusion allegedly paid him to influence the organization's 2010 endorsement of an antiseptic formulation for surgical sites that described ChloroPrep's patented mix, according to federal records. After a competitor complained, the National Quality Forum conducted a review and removed the reference to a specific preparation.

Denham in 2015 agreed to pay a \$1 million settlement, without admitting liability, according to federal records. He declined to comment for this article, as did the National Quality Forum. The organization later said it had strengthened its conflict of interest policies and severed its relationship with Denham.

The investigation of CareFusion included allegations that the company generated "enormous growth" in sales by illegally marketing ChloroPrep as a product that could prevent infections, federal records say. The FDA-approved label says only that ChloroPrep reduces the number of bacteria present, not the number of infections.

The BD spokesman said the company acquired CareFusion in 2015, after the settlements. "CareFusion took great care to address the potential concerns raised in the settlement and this continues at BD," he said.

#### WARNING ADDED

In response to the FDA's new guidance on chlorhexidine, Sage will add an allergy warning to labels on its wipes, according to a spokeswoman for Stryker Corp, which acquired Sage Products last year in a deal valuing the company at \$2.78 billion.

Stryker does not break out Sage's sales. It told analysts this year that it expects Sage to continue to show exponential sales growth.

Products like chlorhexidine wipes are big business. Global sales of antiseptics and disinfectants were an estimated \$5.6 billion in 2015, according to BCC Research. And the total is projected to grow about 40 percent to \$7.9 billion by 2020.

Stryker bought Sage from Madison Dearborn Partners, a Chicago private equity firm that had acquired the privately owned company only four years earlier for \$1.06 billion, according to a report by the Illinois Venture Capital Association. Madison Dearborn declined to comment further.

Just before Madison Dearborn's investment, a market analysis predicted healthy growth for medicated wipes, citing Weinstein's "influential" 2006 study and a 2011 Sage-supported study by Brown University researchers.

A few months after the purchase, the 2013 New England Journal of Medicine article, co-written by Weinstein, reported a dramatic decrease in drug-resistant cultures in patients bathed with Sage's wipes. And a few months after that, Weinstein co-wrote a study published by the journal that found Sage's wipes reduced MRSA cultures in intensive care units. The study, known as the "REDUCE MRSA" trial, was at the center of a federal whistleblower lawsuit brought against Sage in 2014.

Cindy V. Salgado claimed Sage fired her from her job as a medical liaison in 2014 after she objected to the company's tactics to market its chlorhexidine wipes. The federal lawsuit, filed in the Southern District of California, accused Sage of spending "a considerable amount of resources" to influence speakers and researchers to promote universal daily bathing of patients.

The FDA approved the wipes only for cleansing skin before surgery. Sage is prohibited from marketing them for off-label uses, including universal daily bathing. It's even required to include a warning on the product label against using the cloths as a "general skin cleanser."

However, Sage is not prohibited from informing medical professionals of scientific studies that tout the virtues of its wipes for off-label uses, leaving it up to the customer to decide whether or not to use them.

The lawsuit alleged that, in exchange for free Sage products for two large studies, Dr Susan S. Huang of the University of California Irvine agreed to arrange for instructions on daily chlorhexidine bathing to be posted on the website of the federal Agency for Healthcare Research and Quality (AHRQ) after publication. A Sage manager then told sales staff to direct customers to the AHRQ website, the lawsuit alleged.

After Stryker acquired Sage last year, the company settled with Salgado. Terms weren't disclosed. Salgado's lawyer declined to comment. In a written statement, Stryker said: "Sage denied and continues to deny the allegations brought forth in the suit." It noted that the federal government did not pursue Salgado's allegations of off-label marketing.

## POSTED BY AGREEMENT

Huang said the instructional "toolkit" was posted on the website as part of an agreement between the researchers and AHRQ. "The allegations about any relationship between the AHRQ toolkit and Sage are entirely false," she said.

A spokeswoman for AHRQ, which provided \$2.4 million for the study, said the agency was unaware of the lawsuit. Posting instructions on the website "was suggested solely by the study investigators and AHRQ," she said. "Sage had no role in the decision."

Weinstein said he wasn't aware of the lawsuit.

Huang said Sage did not supply free wipes for the "REDUCE MRSA" study but has contributed them to another major study she is now leading, with Weinstein as a co-investigator. That study looks at whether daily bathing should be expanded from intensive care units to general medical and surgical floors.

"Unless the government starts to fund some of the larger trials, this is the only way we'd be able to do infection prevention trials," she said. "Almost all involve contributed product."

The "REDUCE MRSA" study was one of the most comprehensive of its kind to date — and continues to be debated in the infection-control community.

The randomized controlled trial was done in partnership with Hospital Corp of America, a for-profit chain of 171 hospitals. The aim was to determine whether daily bathing of all adult intensive care unit patients with Sage's wipes would reduce the incidence of MRSA.

The most impressive finding showed that daily washing reduced by 37 percent the number of patients testing positive for MRSA — including those on whom the bacteria was present but not necessarily a source of active infection.

But that comes with a caveat: Patients bathed daily with the wipes also received a dose of mupirocin, an antibacterial ointment, twice a day for five days. The researchers couldn't say how much one or the other contributed to the outcome.

And the study was inconclusive on the most important question: whether daily washing reduced the number of MRSA bloodstream infections.

## "DOESN'T MAKE THE CASE"

Daily wipedowns, the study said, reduced infections by 44 percent — not just MRSA infections, but all bloodstream infections by "any pathogen," drug-resistant or not.

"It really doesn't make the case," said Dr Kevin Kavanagh, a patient safety researcher whose objections to the study were published in a 2013 article in *Antimicrobial Agents and Chemotherapy*. "When you look at data, the vast majority

of the effect on preventing infections was on the more benign skin bacteria and yeast.”

An editorial in the Journal of the American Medical Association co-authored by Pittet of the World Health Organization said the study failed to adequately document the benefits of daily chlorhexidine use or its risks. “And the risk for promotion of resistance is quite high,” Pittet said in an interview.

Antibiotic-resistant bacteria have shown the ability to develop resistance to chlorhexidine itself, he said.

Recent studies found that *Klebsiella pneumoniae*, a lethal superbug, developed resistance to the antibiotic colistin after being exposed to chlorhexidine in laboratory experiments. Colistin is considered a last line of defense against many drug-resistant infections. In March, a large study published in the Journal of the American College of Surgeons found an increase in wound infections among patients bathed with chlorhexidine prior to a hernia operation, the most common surgery in the United States.

“Coupled with increasing concerns for antimicrobial and possibly even emerging antibiotic resistance related to the widespread use of CHG [chlorhexidine], the indiscriminate use of CHG in absence of supportive evidence should be discouraged,” the authors of that study wrote.

In Europe, healthcare providers place greater emphasis on basic infection-control measures like consistent hand-washing and stringent housekeeping. That behavioral approach recently received dramatic support from a U.S. Veterans Administration initiative paid for with federal funds.

Since 2007, the agency has combined active surveillance of patients for MRSA and strict staff adherence to basic infection-control protocols throughout the VA healthcare system. In January, the agency published a study showing an 80 percent drop in MRSA infections systemwide since the program began.

“The reason we’ve had the success we’ve had is because everybody’s engaged,” said Dr Martin E. Evans, lead author of the study. “Even though it’s more work and more expense, it’s a benefit to the patients.”

Weinstein, the Rush infectious-disease specialist who received Sage support, dismissed the criticisms of the “REDUCE MRSA” study. Plenty of studies show chlorhexidine works, and millions of people are benefiting from reduced risk of infection, he said.

“As long as people are benefiting...you use it,” Weinstein said. “If resistance emerges, well, maybe there’ll be a new product.”

(Reporting by Deborah J. Nelson and Ryan McNeill. Edited by John Blanton.)

