Institution: University of Southampton		
Unit of Assessment: 05 Biological Sciences		
Title of case study: 05-07 Demonstrating the antimicrobial properties of copper and driving its use in healthcare facilities and public spaces to reduce infection.		
Period when the underpinning research was undertaken: 2003 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Bill Keevil Sarah Warnes	Professor of Environmental Healthcare Research Fellow	November 2000 – present April 2008 – June 2016
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Research at the University of Southampton's Environmental Healthcare Unit, within the School of Biological Sciences, has proved the antimicrobial properties of copper alloys by demonstrating their ability to kill a range of harmful pathogens including MRSA and SARS-CoV2. These findings have led to major clinical trials and influence in public health bodies, leading to the installation of antimicrobial copper touch surfaces globally in hospitals, in supermarkets, on public transport and in the world's busiest airport. This research has informed retail strategy, shaped government infection control policy and influenced new international standards that have enabled the commercialisation of products with an antimicrobial claim, resulting in the certification of more than 450 copper-containing antimicrobial products on the market.

2. Underpinning research

Recognised for its antibacterial, antiviral and antifungal properties, copper has a rich history of being exploited for health purposes. Its first recorded medical use can be found in Egyptian books written between 2600 and 2200 BC, which describe the use of copper in sterilising chest wounds and drinking water. It was used to treat skin infections in ancient Greece, cure ailments in ancient China and India, and remains an important component of traditional medicine today.

Research led by Professor Bill Keevil has described the processes through which copper, and its alloys, exhibit their anti-microbial properties, and has demonstrated the metal's efficacy in killing superbugs, viruses and fungal pathogens, especially within clinical environments. Studies began in 2002 through a collaboration with the New York-based Copper Development Association (CDA) [**G1**], looking, for the first time, at whether common copper alloys could kill foodborne pathogens. The research showed that copper alloys killed *Escherichia coli O157* (*E. coli*) [**3.1**] and *Listeria monocytogenes*, thus highlighting the potential of copper surfaces, as an alternative to stainless steel, when addressing risks of cross-contamination during food preparation.

In 2006, the CDA switched the focus of its funding to researching the efficacy of copper surfaces in reducing rates of healthcare-associated infections (HAIs) amid growing awareness of the scale of the threat posed by HAIs to patient safety. Around that time, HAIs were responsible for infections in 1.7 million people, 98,987 deaths and USD35.7bn-45bn in treatment costs each year in the US alone, according to government figures. Studies supervised by Keevil at Selly Oak Hospital in Birmingham demonstrated that copper alloys kill antibiotic-resistant 'superbugs' methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and *Clostridium difficile*. For example, studies showed that two strains of VRE were killed in less than 1 hour on alloys containing 90 per cent copper and *C. difficile* spores died in 24-48 hours when exposed to copper alloys [**3.2**].

In parallel, the CDA started working with the International Copper Association (ICA) in 2005, to obtain official registration of copper alloys as an antimicrobial material with the US Environmental Protection Agency (EPA). Keevil's findings paved the way for the successful development of an EPA-approved antimicrobial surface test assay, for which Keevil provided guidance based on University of Southampton laboratory methods. In 2008 the EPA certified the Cu+ trademark underpinned by these methods. This was a first for a solid material. Since then the trademark has been awarded to 450-plus copper alloys with an antimicrobial touch surface efficacy claim [**5.6**].

During 2012, Keevil and colleagues demonstrated the mechanisms that occur when pathogens land on copper surfaces due to touch, coughs or sneezes. To do this, they developed a 'wet' inoculum challenge assay to simulate cough and sneeze droplets falling onto surfaces, and a 'dry' challenge assay to facilitate rapid drying of a pathogen inoculum onto a surface to simulate hand contact [**3.3**]. These studies showed that copper ions, released from copper surfaces, rapidly inhibit cell respiration, attack the bacterial cell membrane or disrupt the viral coat, and destroy the DNA and RNA inside. This means that no mutation can occur, preventing the microbe from developing resistance to copper [**3.4**]. This disproved research by other groups, who claimed copper does not affect DNA and RNA integrity. Keevil's group showed that transfer of antibiotic resistance genes from resistant bacteria to other bacteria is stopped because the nucleic acids encoding these genes are destroyed [**3.5**]. These destructive properties are enhanced by bacterial metabolism, which generates small amounts of hydrogen peroxide. This reacts with the copper ions to form reactive oxygen, which damages the microbes in multiple areas [**3.6**].

3. References to the research

3.1 Noyce, J.O., Michels, H. and Keevil, C.W. (2006). Use of copper cast alloys to control *Escherichia coli O157* cross-contamination during food processing. *Applied and Environmental Microbiology* **72** (6), 4239-4244. https://doi.org/10.1128/AEM.02532-05

3.2 Weaver, L., Michels, H.T. and Keevil, C.W. (2008). Survival of *Clostridium difficile* on copper and steel: futuristic options for hospital hygiene. Journal of Hospital Infection, **68** (2), 145-151. https://doi.org/10.1016/j.jhin.2007.11.011.

3.3 Warnes, S.L. and Keevil, C.W. (2011). Mechanism of copper surface toxicity in vancomycin-resistant enterococci following 'wet' or 'dry' contact. *Applied and Environmental Microbiology* **77**, 6049-6059. https://doi.org/10.1128/AEM.00597-11.

3.4 Warnes, S.L., Caves, V. and Keevil, C.W**.** (2012). Mechanism of copper surface toxicity in *Escherichia coli* O157:H7 and *Salmonella* involves immediate membrane depolarisation followed by slower rate of DNA destruction which differs from that observed for Gram-positive bacteria. *Environmental Microbiology* **14**, 1730-43. https://doi.org/10.1111/j.1462-2920.2011.02677.x

3.5 Warnes, S.L., Highmore, C.J. and Keevil, C.W. (2012). Horizontal transfer of antibiotic resistance genes on abiotic touch surfaces: Implications for public health. *mBio* 2012;3 e00489-12. https://doi.org/10.1128/mBio.00489-12.

3.6 Warnes, S.L., and Keevil, C.W**.** (2016). Lack of Involvement of Fenton Chemistry in Death of Methicillin-Resistant and Methicillin-Sensitive Strains of Staphylococcus aureus and Destruction of Their Genomes on Wet or Dry Copper Alloy Surfaces. *Applied and Environmental Microbiology* **82**, 2132-2136. https://doi.org/10.1128/AEM.03861-15

Key grants:

G1 During the period 2001 to 2003 the Copper Development Association provided GBP150,000 for Keevil's team to research whether the use of copper and copper alloys for work surfaces inhibits survival of verocytotoxic *E. coli 0157* and *L. monocytogenes*. This was followed by further significant grants including GBP542,000 from the Copper Development Association in 2003, GBP260,000 from the International Copper Association in 2009 and USD820,000 from the ICA, New York between 2010 and 2016.

4. Details of the impact

Background: Translation of research findings into clinical trials

Keevil's early research showing the effectiveness of copper in killing *E. coli*, *Listeria* and superbugs formed the basis of two influential clinical trials led by the Copper Development Association (CDA) in the UK and US:

The UK trial (2010) [**5.1**] was funded by the CDA and based in Selly Oak Hospital – the site of Keevil's studies into superbugs. Keevil was an advisor to the trial and four of his studies were cited as key evidence. The trial reported a 90% reduction in bacterial loading on copper-plated surfaces.

For the US trial (2013) [**5.2**] the CDA obtained funding from the Department of Defense, crediting Keevil's studies in giving them the confidence to undertake a major trial involving three hospitals [**5.3**]. The trial demonstrated a reduction in infection rates of 58% in intensive care units which incorporated copper plating onto the surfaces of six frequently-touched near-patient objects.

Harold Michels, the Vice President of the CDA, stated: "*Professor Keevil's research has not only stimulated others to conduct laboratory research on the antimicrobial properties of copper, but also served as a foundation to those conducting clinical trials. The net result is that he has proven that copper alloys kill numerous microorganisms that cause hospital-acquired infections… Professor Keevil has persistently and enthusiastically advocated for reducing and preventing hospital acquired infections and thus saving lives by the use of copper.*" [**5.3**]

Installation of antimicrobial copper surfaces in hospitals and other healthcare settings

The list below is a snapshot of the nature and extent of global clinical impact of antimicrobial copper surfaces since 2014, as reported by the CDA, following Keevil's studies and the subsequent trials [**5.4**]:

- Kitasato University Hospital, a newly remodelled, 1,000-bed hospital in Japan, installed antimicrobial copper door furniture throughout its internal medicine, dermatology, pharmaceutical, haematology and outpatient facilities, while Hitachi Medical Center in Tokyo installed antimicrobial copper beds and overbed tables in its convalescent wards. These were two of nine Japanese hospitals to incorporate antimicrobial copper into their wards in 2014, according to Australian news source 'Hospital and Healthcare'.
- The Sir Robert Ogden Macmillan Centre, a cancer support and information centre that was opened in 2015, and based at Harrogate, installed antimicrobial copper touch surfaces throughout their facility to maximise patient safety.
- The 774-bed Hamburg Asklepios Clinic, a large hospital in Germany that treats 76,000 residents per year, installed antimicrobial copper as part of a refurbishment in 2015.
- Santiago Public Emergency Hospital, a leading Chilean hospital, in 2015 installed antimicrobial copper bed rails and handles, and replaced door handles, sinks and taps and overbed tables with antimicrobial copper equivalents. This followed a clinical trial in nearby Valparaíso, which cited Keevil's studies.
- South Africa's 'Miracle Trains' – Transnet's Phelophepa I and II – provide mobile healthcare to more than 300,000 people in remote rural communities annually. In 2015 the 18-coach trains were equipped with antimicrobial copper door handles and cupboard doors.
- Grinnell Regional Medical Center, the largest hospital in Iowa serving 40,000 residents, took the decision in 2016 to install antimicrobial copper hardware and components throughout its facility.

Overall, in the two years after the 2013 trial, the CDA recorded 60 hospitals in 20 countries in Europe, South America, Africa, and Asia that had installed antimicrobial copper surfaces and furniture. Installations had predominantly taken place in clinical settings where patients are at high risk for infections, such as ICU rooms, paediatric and neonatal units, and cancer centres. [**5.5**].

In terms of the economic significance, drawing upon the 2013 trial, a health economics assessment by the University of York [**5.6**] found that the cost of replacing the six near-patient objects in a 20-bed intensive care unit can be recouped in less than two months. This translates to a 5-year saving of almost GBP2,000,000 if antimicrobial copper surfaces are fitted during a planned build or refurbishment.

Installation of antimicrobial copper surfaces in public venues, transport infrastructure and commercial settings

Keevil's demonstration of the benefits of antimicrobial copper has led to its use in public settings and transportation. The CDA reported the installation in 2014 of antimicrobial copper drinking fountains in the world's busiest airport, Atlanta (107m passengers in 2018) and antimicrobial copper handrails on Poland's *Solis Urbino* bus (European Bus of the Year, 2017). [**5.7**]

Keevil has a longstanding association with electroplating firm Necon Technologies Ltd, who learned of his research while investigating legionella control through copper silver ionisation. Necon's copper touch surface business, *Copper Cover*, has relied on Bill's validation of their products to bring them to market, including a 2020 test for SARS-CoV2. The pandemic has seen the company coat more than 10,000 commonly touched surfaces in locations such as care homes, hospitals and schools. [**5.8**]

Later in 2020, the UK Department for International Trade (DIT) introduced Keevil to the UK supermarket chain Morrisons, who resultantly commissioned Copper Cover to trial the installation of copper touch surfaces in its staff rooms. Currently 1 in 5 infections are transmitted in supermarkets, and Morrisons serve 12 million customers each week across 494 stores throughout the UK [**5.9**]. The trial has led Morrisons to consider the permanent installation of antimicrobial copper surfaces on common touch points such as door push plates and trolley handles:

Informing government infection control policies in Europe and shaping new international regulatory standards for commercial products with antimicrobial claims

Following the approval of copper as an antimicrobial material by the US Environmental Protection Agency (EPA), which was based on Keevil's research, Poland's National Centre for Quality Assessment in Healthcare (NCQA) revised its accreditation standards for healthcare facilities. This included in 2017, Europe's first official recommendation to incorporate antimicrobial copper touch surfaces as an infection prevention and control measure [**5.10**]. The new accreditation standards provide guidelines concerning the prevention of pathogen transmission by touch. Chapter IX 'Infection Control' states: "*Reduction of microbial transmission should be achieved, inter alia, using frequently-touched surfaces made from metals with antimicrobial properties, such as copper, brass and bronze, as per the US Environmental Protection Agency's registration*."

Lubin Hospital, in South West Poland, subsequently installed copper alloy surfaces in its new operating theatres. In recognition of his contribution, Keevil was invited as the Special Guest at the 'Safe Hospital for the Future' Gala awards event in Warsaw, where he gave the keynote lecture on 'Breaking the Chain of Infection'. The event was attended by senior members of the Polish medical community, including the Polish Deputy Minister of Health and the Director of the World Health Organization (WHO) Office in Poland [**5.7**].

In 2014, Keevil was an invited speaker at a meeting in the French National Assembly in Paris attended by French MPs, WHO officials and the French Patients Association (Le Ligne). At this meeting the introduction of antimicrobial copper alloy surfaces to reduce HAIs in French hospitals was discussed. This led to further successful trials of copper alloy fittings in long-term care facilities in 2018, supported by regional French government and the European Commission, and the decision to draw up a French standard, equivalent to the EPA standard in the US. France's equivalent AFNOR (Standards Commission S95S, N36) adopted the dry method testing method developed at Southampton [**3.1**] to evaluate copper alloy and non-copper products with an antimicrobial surface claim for commercialisation. Keevil attended several AFNOR meetings, following on from the original French National Assembly event, and contributed expert advice based on his research. The new AFNOR standard (NF S90-700) was published in April 2019 and since led to the successful establishment of a new technical committee on *Surfaces with biocidal and antimicrobial Properties* at the International Organization of Standardization (ISO) in June 2020 [**5.11**]. The wet and dry testing methods developed at Southampton [**3.1**] have been translated into standard CEN/ISO test methods by the British Standards Institute [**5.12**].

Commercial impact arising from the government-approved certification of the Cu+ trademark for antimicrobial copper products

Keevil's work has influenced the development of test standards, which the CDA states are *"essential for international competitiveness of companies selling antimicrobial materials such as copper alloys''* [**5.7**]. The new international standards, which regulate the commercialisation of products with an antimicrobial touch surface claim, have resulted in the certification of more than 450 copper-containing antimicrobial products on the market [**5.7**]. This includes a specific product line "KME Plus®" from KME, one of the world's largest manufacturer of copper and copper alloy products. The company increased their revenue from USD1,440,000 in 2014 to

USD1,980,000 in 2019, and directly refer to Keevil's work in their official KME Plus® information brochure [**5.13**].

Health and commercial impact through copper-infused clothing

Copper Clothing Ltd was set up in December 2012 after the founder saw a demonstration by Keevil online showing the speed at which MRSA dies on copper compared to stainless steel. Keevil was commissioned by the company in 2014 to evaluate the antimicrobial properties of copper-impregnated fabrics, in products including bed sheets, pyjamas and socks. This paved the way for further R&D activities in the NHS and direct employment of a doctor at the company. Additionally, research led by Keevil has underpinned developments of their copper-impregnated facemask, with over 250,000 units now sold [**5.14**].

Increasing public awareness of the benefits of antimicrobial copper

Keevil's advocacy of the benefits of antimicrobial copper have gone far beyond his numerous peer-reviewed papers and presentations at high-profile conferences. His proactive engagement with the international media has resulted in widespread coverage. In the UK this includes BBC News channels, the BBC's One Show and Dara Ó Briain's Science Club (19,732 views) while coverage abroad includes Le Figaro and Times of India. It was featured in 35 news stories from 34 outlets and reached an upper bound of two million followers on Twitter. A 2017 article by Keevil in The Conversation, which brought together all Southampton research in this area, reached an audience of 234,210 and was tweeted 487 times and shared on Facebook 14,700 times. Keevil's 2020 Smithsonian Magazine article on 'coppers virus killing powers' was shared over 6,000 times on social media. Over the impact period, coverage of Keevil's combined research reached an estimated hundreds of millions of people, measured by examples of media coverage provided by the CDA [**5.7**].

5. Sources to corroborate the impact

5.1 Casey et al. (2010) Role of copper in reducing hospital environment contamination. *Journal of Hospital Infection* **74**, 72-77 https://doi.org/10.1016/j.jhin.2009.08.018. Cites 4 Keevil studies including [**3.2**] as the demonstration of copper's ability to kill a range of micro-organisms in vitro.

5.2 Salgado et al. (2013) Copper Surfaces Reduce the Rate of Healthcare-Acquired Infections in the Intensive Care Unit. *Infection Control and Hospital Epidemiology* **34,** 479-486 https://doi.org/10.1086/670207

5.3 Supporting statement from Harold Michels, Copper Development Association (CDA).

5.4 Antimicrobial copper installations reported by the CDA (website offline, PDF supplied).

5.5 Installations reported by the CDA were collated in the 2016 ECRI Institute report, *Antimicrobial Copper Surfaces for Reducing Hospital-acquired Infection Risk* https://www.ecri.org/Resources/AHCJ/2016_Resources/Antimicrobial_Copper_Surfaces_for_Reducing_Hospital-acquired_Infection_Risk.pdf

5.6 https://www.york.ac.uk/news-and-events/news/2013/research/antimicrobial-copper/

5.7 Supporting statement from Angela Vessey, Copper Development Association.

5.8 Supporting statement from Managing Director, Necon (https://copper-cover.com).

5.9 Supporting statement from Department for International Trade (DIT).

5.10 ICU report of Polish Health Authority recommending antimicrobial copper in hospitals https://healthmanagement.org/c/icu/pressrelease/polish-health-authority-first-in-europe-to-recommend-antimicrobial-copper-in-hospitals

5.11 AFNOR report approving a new field of technical activity on Surfaces with biocidal and antimicrobial properties.

5.12 Report from BSI.

5.13 KME Plus® Brochure https://www.kme.com/fileadmin/DOWNLOADCENTER/COPPER%20DIVISON/4%20Industrial%20Rolled/1%20Rolled%20Copper%20for%20the%20Industry/KME_Plus_Copper_that_protects_health.pdf

5.14 Supporting statement from CEO, Copper Clothing Ltd.