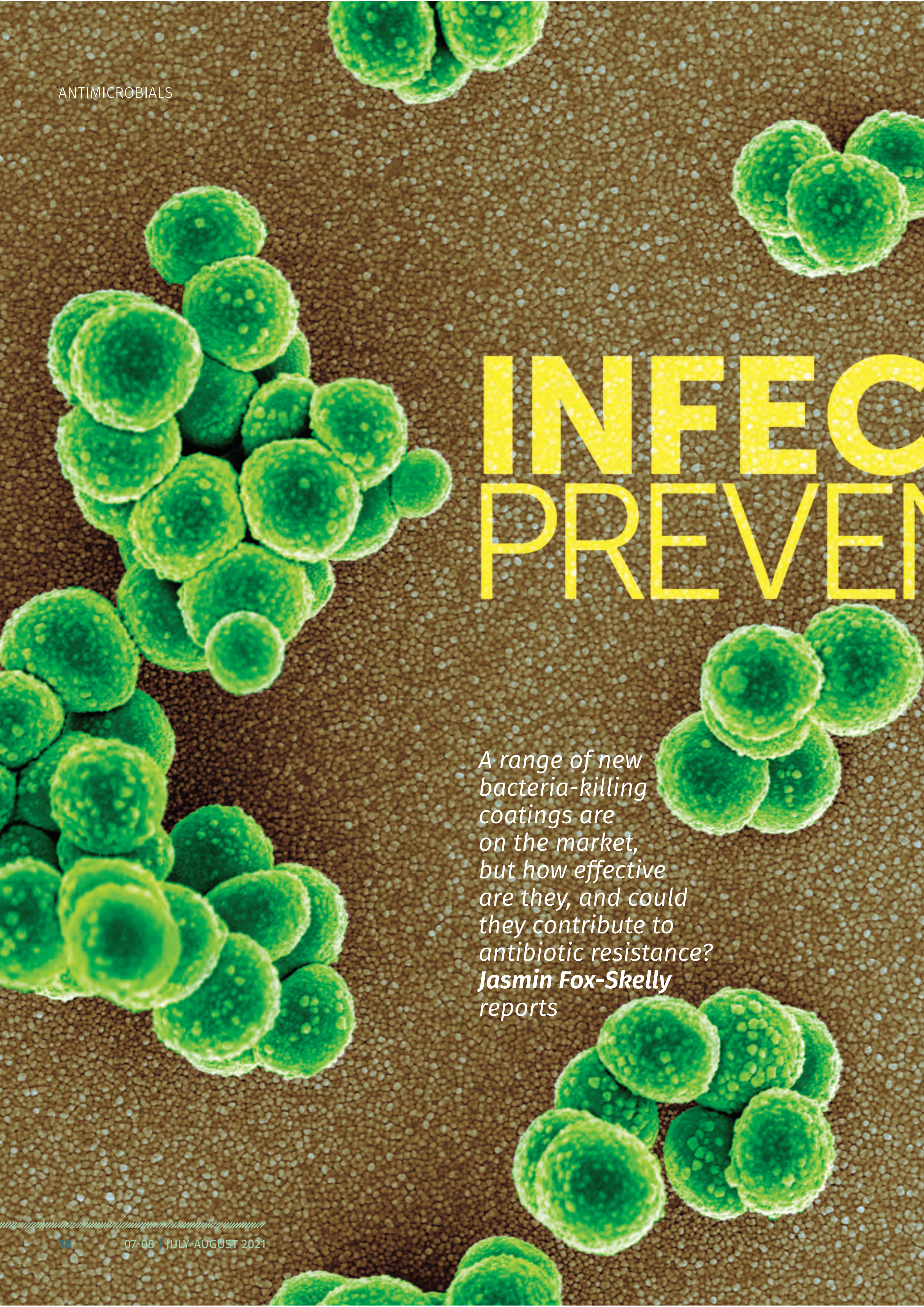

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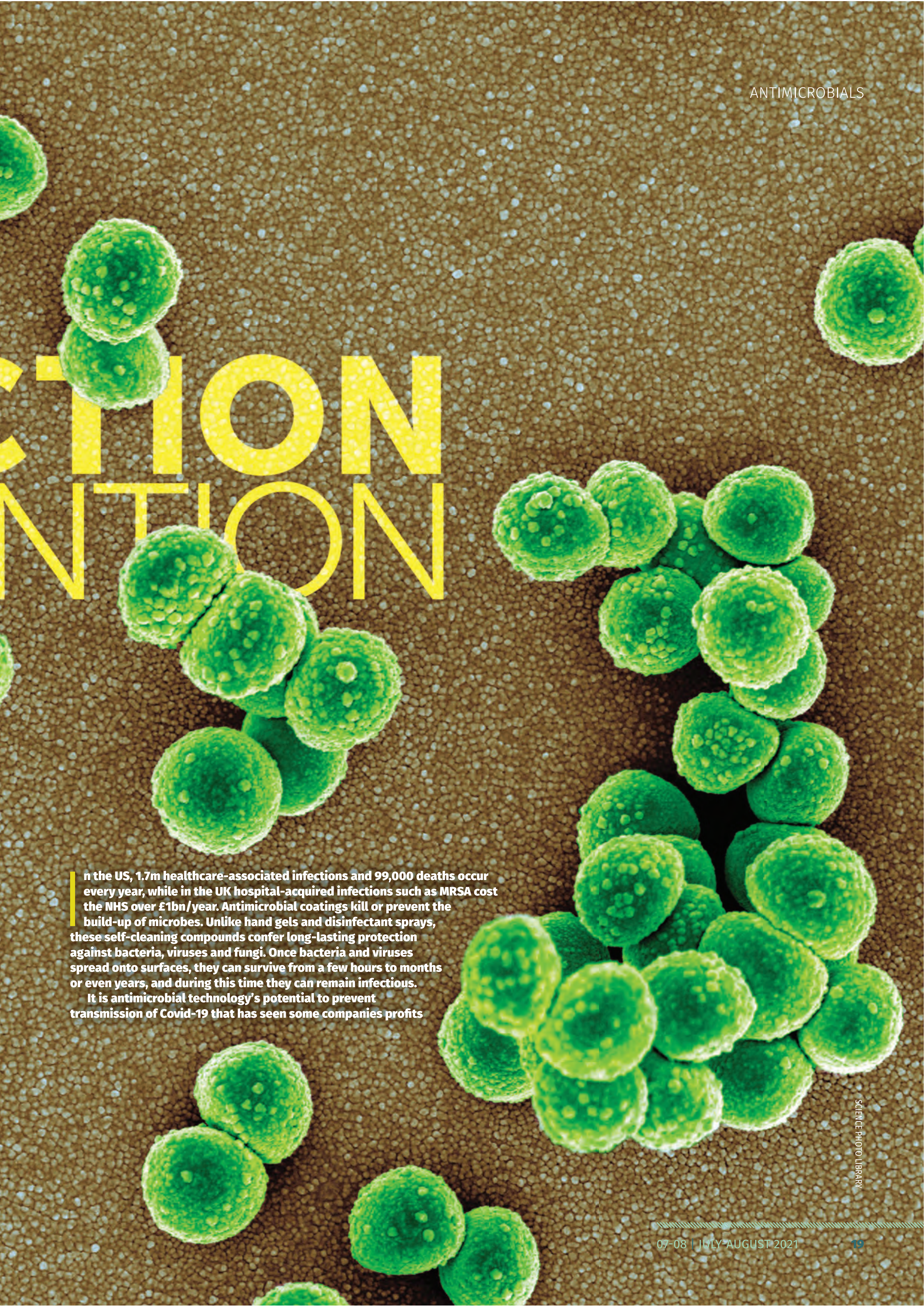
A range of new bacteria-killing coatings are on the market, but how effective are they, and could they contribute to antibiotic resistance? ***Jasmin Fox-Skelly*** *reports*



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In the US, 1.7m healthcare-associated infections and 99,000 deaths occur every year, while in the UK hospital-acquired infections such as MRSA cost the NHS over £1bn/year. Antimicrobial coatings kill or prevent the build-up of microbes. Unlike hand gels and disinfectant sprays, these self-cleaning compounds confer long-lasting protection against bacteria, viruses and fungi. Once bacteria and viruses spread onto surfaces, they can survive from a few hours to months or even years, and during this time they can remain infectious.

It is antimicrobial technology's potential to prevent transmission of Covid-19 that has seen some companies profits

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triple and quadruple in the last year alone – sales of antimicrobial films and face masks have rocketed during the pandemic.

Nadia Tsao, Principal Analyst at UK-based business intelligence firm IDTechEx, recently wrote a report identifying over 100 companies that are actively developing antimicrobial technologies and products, including over 60 companies focused exclusively in this area.[1]

'IDTechEx expects another year of strong growth in 2021, as companies finish many of the projects initiated in 2020,' says Tsao. 'As the world is slowly receiving Covid vaccinations, there is still a strong antimicrobial focus for reopening. We anticipate that most of the interest and response due to Covid-19 to wane by 2022.'

Nevertheless, the business intelligence firm predicts strong growth in the sector in the near to long term future, particularly in Asia.

At the Hong Kong University of Science and Technology (HKUST), professor of chemical engineering Yeung King Lun and his team have developed a coating that can provide 90 days of 'significant' protection against viruses including Covid-19. The coating, called multilevel antimicrobial polymer (MAP-1), took 10 years to develop and can be sprayed on surfaces that are frequently touched by the public, such as lift buttons and handrails. MAP-1 contains millions of nanocapsules enclosing active disinfectants. The nanocapsules are made with heat-sensitive polymers that release the disinfectants upon human touch, and are able to kill bacteria, viruses and spores even after the coating has dried.[2]

MAP-1 works in three ways, according to Yeung King Lun: by killing microbes on contact; preventing their adhesion onto the surface; and by releasing natural thyme oil, which has antimicrobial properties.

'MAP-1 consists of many different antimicrobial polymers self-assembled to form 600nm capsules,' says Yeung King Lun. 'On the surface of the capsule shell, there are different functional groups designed to kill microorganisms on contact and prevent their adhesion onto the surface'.

These groups directly interfere with the microbial surface, causing cell death in the case of bacteria, preventing the germination of spores, and rendering viruses non-infective.

£1bn

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>100

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Metals such as silver and copper have been used for thousands of years to prevent microbial infections.

99.99%

A single use, disposable surgical mask incorporating a zeolite carrier deactivated 99.99% of bacteria after one hour of surface contact and 99.99% of influenza virus after five minutes.

Following clinical tests at a Hong Kong hospital and a home for the elderly, the coating has been made available for commercial purchase by Germagic, a unit of the university's industrial partner, Chiaphua Industries, and was approved for official and mass consumer use in February 2020. It is hoped the technology could significantly reduce hospital acquired infections.

'Hand washing compliance is not only a problem for the general public, but also for healthcare providers,' says Yeung King Lun. 'As most hand disinfectants are not comfortable to use, compliance tends to be poor, especially during busy periods, and this could lead to cross-contamination and infections. We worked with the nursing staff of a public hospital to field test MAP-1 formulated hand foam for over six months. The feedback was excellent, and the study shows that microbes remain nonviable on the hand after four hours.'

Antimicrobial metals

The antimicrobial properties of metals such as silver and copper have been used for thousands of years to prevent infections. While metallic silver (Ag) is inert, insoluble in water, and unable to kill bacteria, ionic silver (Ag^+) is water soluble and highly reactive. Ag^+ is thought to attack bacterial cell membranes making them more permeable, and interfere with cell metabolism, resulting in over-production of toxic reactive oxygen species (ROS). Ionic copper is also known to efficiently kill bacterial cells, possibly through binding to proteins both on the cell wall and within the cell, causing loss of function.

Chemicals giant BASF has several antimicrobial polymer products in its *HyGentic* line which use integrated silver ions. Dow Chemical also markets *Silvadur*, a patented silver-technology introduced in 2012 that delivers silver ions to fabric surfaces and activates them in the presence of undesirable bacteria.

Meanwhile, UK-based Bioarmor has developed a wet-wipe containing an invisible nano-thin surface coating infused with silver particles. It can be applied to hard non-porous surfaces such as mobile phones, laptops, children's toys, work surfaces etc. The coating is under 120nm thick – less than 1/500th the thickness of a human hair. The silver particles are under 50nm in diameter, and work by binding to proteins in the bacterial cell membrane and cell wall, interfering with DNA replication and promoting the formation of harmful reactive oxygen species, causing the bacteria to die.

According to the company, independent UK labs have tested the wet wipes and found that they are able to reduce levels of *Staphylococcus aureus*, MRSA and *E. coli* by 99.9% for up to three months. They have also tested the product on Φ6 bacteriophage – a common test surrogate for the corona and influenza enveloped virus types – and found they reduce virus levels by 95%.

'Most antimicrobial products on the market are based on disinfectants and are for immediate use, but last only a very short time before needing numerous further re-applications,' says BioArmor Europe founder John Shaw. 'Our antimicrobial ingredient is a biocide that works over time. At this moment we are not aware of any other coatings that offer such a long-lasting level of anti-microbial protection.'

Sciessent, a US based global provider of antimicrobial solutions, has incorporated its active compound Silver Copper Zeolite (SCZ) into a range of medical devices, including in-body devices such as hernia meshes and central venous catheters. In-dwelling devices are particularly susceptible to bacteria colonisation and it's thought that up to one in four hospital acquired infections are caught this way.

Zeolites, such as those used by Sciessent, are minerals made from interlinked molecules of aluminate (AlO_4) and silicate (SiO_4). They have a 3D crystal structure with large open pores in which water and metal ions can reside. This allows them to act as ion exchangers, swapping metal ions for other positively charged ions in the environment.

SCZ works in just this way. It contains silver and copper ions which, in the presence of an aqueous solution, can travel out of the zeolite compound and interact with bacteria and viruses. Sciessent's zeolite powders can be added to materials such as plastics, paints, and synthetic fabrics, and may be bonded to surfaces such as stainless steel. The company recently incorporated its zeolite carrier into the outer layers of a surgical mask. Tests showed that a single use, disposable surgical mask incorporating a zeolite carrier deactivated 99.99% of bacteria after one hour of surface contact and 99.99% of influenza virus after five minutes. To date, Sciessent's technology has been integrated into over 3m respirator masks.

Preventing resistance

However, there are drawbacks to using metal ions such as copper, silver and zinc to kill bacteria, says Xaver Auer, CEO of Dyphox – a German spin-off company from the University Hospital Regensburg. 'Silver, for example, only works under wet conditions. Silver ions diffuse through water to reach bacteria on the surface, however, usually most surfaces are dry.'

This also means that coatings that use metal ions could cause a risk to the environment on their disposal, leading to toxic substances leaching out of the material into rivers, streams and soil. In addition, antimicrobial technologies that require the uptake of an ion or molecule such as silver, copper or zinc into the bacterial cell are a driving force of antimicrobial resistance.

'To resist such antimicrobial technologies, bacteria use their efflux pumps, which pump the toxic ions – and also antibiotic drugs – back out of the cell,' says Auer. 'Bacteria already have well-developed efflux pumps as they need to fight metal pollution to keep their concentration on surfaces constant. Therefore, antimicrobial technologies that increase the exposure of bacteria to metal ions are contributing to the bacteria's ability to pump antimicrobial agents and antibiotics back out.'

Instead, Dyphox has developed coatings that capitalise on the power of oxygen to destroy bacteria and viruses. Their colourless coating is applied as a thin film of liquid lacquer to a surface, which then dries rapidly to form a transparent coating. The coating contains a special photocatalyst dye capable of absorbing light in the visible region (400-700nm). The dye transfers excess energy from light to oxygen in the surrounding atmosphere, producing localised singlet oxygen, a type of ROS. This effectively destroys bacteria, viruses and fungi from the outside by oxidising their outer cell membrane and envelope. The thin gaseous layer of reactive oxygen – about 1μm in thickness – is short lived and completely harmless to humans.

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John Shaw *owner and founder, BioArmor Europe*

The benefits of singlet oxygen are that unlike more reactive oxygen radicals, it does not induce premature material ageing and is effective on dry and wet surfaces. And because it does not enter bacterial cells, it is unlikely to lead to antibiotic resistance. The coating was tested in a large-scale field study in two hospitals in Regensburg, Germany, where it was applied to high-touch surfaces such as bed rails, desks and computers.[3] Surfaces were treated either with an active antimicrobial coating or a control coating. After nine months, the number of bacteria on the active and control surfaces was determined and compared, revealing that the Dyphox coating was able to reduce the risk of high germ contamination on surfaces by up to 67%.

Another coating unlikely to lead to bacterial resistance is being developed by a team at the University of Birmingham. According to the researchers, *NitroPep*, can be applied to almost any surface and lasts for up to ten years. It uses chlorhexidine – found in mouthwash – as a microbial agent and works by 'popping' bacteria when they land on a surface, just as a row of pins would pop a balloon. As it provides a physical method of destroying pathogens, rather than interfering with metabolism or protein function like silver and copper-based coatings, *NitroPep* could be a valuable tool in combatting antimicrobial resistance.

The coating is ideal for regularly handled and touched areas such as doorknobs, medical equipment, and handrails, and can be applied to surfaces in any environment, from hospitals to GP surgeries, trains, buses, homes and offices, say the researchers. It can also be applied to air conditioning units to filter pathogens, making it a useful solution for busy commuter trains.

In a clinical trial conducted with the Royal Centre for Defence Medicine and the Royal Navy, researchers coated *NitroPep* onto surfaces – including door handles, an operating theatre and part of a communal toilet – on board a Royal Fleet Auxiliary ship.[4]

Over an eleven-month period while the ship was at sea, 'control' surfaces and those coated in *NitroPep* were swabbed on a weekly basis and the results analysed in the laboratory at the University of Birmingham. The results showed that the coating was effective against five different bacteria responsible for hospital-acquired infections – *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus*, *Pseudomonas aeruginosa* and *Escherichia coli*. Even better, the *NitroPep* coating killed bacteria within five minutes – far more rapidly than currently commercially available technologies, which do not have a significant effect on bacteria until up to 24 hours. Subsequently, studies have shown that *NitroPep* also shows efficacy against the SARS-CoV-2 virus in under five minutes. Researchers have now formed a spinout company, also called *NitroPep*, to commercialise the technology.

Overall, although the outlook for antimicrobial coatings over the next ten years is positive, some believe that the potential impact of coatings on the environment and on driving antibiotic resistance may cause issues with regulatory bodies. Previously approved antimicrobial additives have later been banned by regulatory bodies around the world due to their impacts on human health and the environment. 'There is potential that widespread use of antimicrobial technologies can accelerate the development of antimicrobial resistance in bacteria,' says Tsao.

'Combined with the slowdown over the past 10-20 years in antibiotic development, the world may be looking at future infectious disease outbreaks far, far worse than Covid-19. There is thus a likelihood that regulation/management may become more stringent, and demand additional clinical studies on efficacy and environmental effects.'

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