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Smart surfaces to tackle infection and antimicrobial resistance

Jonathan Otter, Kieran Brophy, Jonathan Palmer, Nicholas Harrison, Jason Riley, Daryl Williams, Gerald Larrouy-Maumus

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Headlines

Issues

- Contaminated surfaces and medical devices contribute to the transmission of healthcare-associated infection (HCAI) and the spread of antimicrobial resistance (AMR).
- Surface-attached biofilms (communities of microbial and non-microbial matter on surfaces) support microbial survival, persistence, and can protect microbes from attack by biocides and antibiotics.
- Biofilms also play a role in several important infection pathways including infections related to medical devices (e.g. catheter-associated urinary tract infections), prosthesis-related infections (e.g. infected hip joints), and water-borne infections (e.g. *Pseudomonas* and *Legionalla* contamination of hospital water systems). These pathways are increasingly recognised in the transmission of pathogens that can cause HCAI and increase AMR.
- A 2016 Public Health England survey of over 48,000 patient records found that 6.6% of patients acquired HCAI in hospitals.

Solution

- Antimicrobial surfaces could disrupt the microbial habit by reducing microbial attachment and/or killing attached microbes.
- The design, manufacture and testing of antimicrobial surface technologies must involve multidisciplinary teams from molecular science, engineering, medicine and business.
- Potential application areas for antimicrobial surfaces include:
  - Improving the design of medical devices in order to reduce the risk of infection;
  - Reducing the risk of infection related to surgically implanted prosthesis (such as hip and knee joints);
  - Transforming the clinical environment to have touch surfaces with antimicrobial properties (e.g. coated bed rails) particularly for the prevention of infection in vulnerable patient groups such as adults and neonates in intensive care;
  - To make hospital water system less prone to contamination with bacteria such as *Pseudomonas* and *Legionella*.
- In addition to applications in the hospital environment of developed countries, antimicrobial surfaces should be developed with low and middle-income (LMIC) settings in mind, where these surfaces could mitigate the impact of additional challenges related to LMIC settings (such as lack of power and clean water).
- The spread of infection and antimicrobial resistance in the clinical environment cannot be tackled by antimicrobial surfaces alone, but be employed as part of a combined approach involving clinical and cleaning staff following protocols developed to prevent the spread of microbes, and the responsible distribution and use of antibiotics.

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Objectives of this Briefing Paper

The Institute for Molecular Science and Engineering (IMSE) has brought together world-leading experts at Imperial College London in the fields of bio-mechanical engineering, surface engineering, medicine, infection control, infectious disease management and microbiology to develop new solutions for a range of clinical and medical device needs.

In this Briefing Paper, we will assess the current state of the art in the development of antimicrobial surfaces for the clinical environment and medical devices. We will also discuss the mitigation of surface contamination in human medicine in which antimicrobial resistance (AMR) presents a significant threat to public health, and financial burden to public health systems and summarise possible solutions.

Box 1: Ideal properties of an antimicrobial surface

When considering possible antimicrobial surface technologies, we developed a list of criteria to assess their viability. These criteria should be considered by manufacturers in the design stage:

Safe. The surface must remain safe for regular contact with patients, staff and visitors, with particular consideration of likely contact with sensitive areas and broken skin.

Healthcare Economics. The introduction of antimicrobial surfaces will engender associated additional costs, which must represent good value healthcare (taking into account resultant cost savings).

Simple application technology. Ideally, the antimicrobial properties of the surface would be put in place during manufacture or applied as liquid agent to the surface in question.

Long term. The surface should remain antimicrobial for months or years, without the need for re-application.

Rapid antimicrobial activity. For effective healthcare applications, surfaces with an antimicrobial activity that occurs in seconds or minutes (rather than hours) are needed.

Prevention of biofilm formation. The ability to prevent the formation of biofilms, or disrupt biofilms that have been formed, is a property of some oxidizing disinfectants.[1,2] This property may be shared by a surface that exerts antimicrobial activity through oxidation. Modification of the physical structure of a surface may also inhibit biofilm formation.

Compatibility with current cleaning and disinfection products. Any chemicals used for regular cleaning and disinfection should not interfere with the antimicrobial activity of the surface, either in the short or long-term.

Retention of activity with low-level soiling. Surfaces in hospitals often retain and accumulate organic matter. However, it's not yet understood how much the presence of organic matter or dirt would interfere with the activity of an antimicrobial surface, and it is likely to depend on the type of surface.

Does not promote clinically-significant resistance or reduced-susceptibility. There is a theoretical risk that continuous sub-lethal exposure of microbes could occur on the surface, and that this may lead to the development of resistance or reduced susceptibility to an antimicrobial surface. However, there is currently no specific evidence for resistance as a result of the implementation of antimicrobial surfaces in hospitals.

Sporicidal activity. *C. difficile* spores present a particular challenge to antimicrobial surfaces. There is concern that introducing a surface that is not effective against *C. difficile* spores could provide a selective advantage to *C. difficile*, potentially leading to increased levels of infection by this microbe.

Introduction

Microbes that cause infection can be spread by many and varied routes, some of which involve direct or indirect contact with surfaces. Such surfaces include:[3]

1. Hospital surfaces (e.g. countertops, doors, and beds)
2. Surgical tools and medical devices (e.g. venous and urinary catheters)
3. Hospital water systems

A 2016 Public Health England survey of over 48,000 patient records found that 6.6% of patients acquired a healthcare-associated infection (HCAI) in hospital.[4] The most common types of HCAI are respiratory infections (including pneumonia and infections of the lower respiratory tract) (29.2% of all HCAI), urinary tract infections (17.4%) and surgical site infections (15.0%). Each one of these infections means additional use of National Health Service (NHS) resources, greater patient discomfort and a decrease in patient safety.

Molecular science and engineering approaches can be employed to develop "smart" surfaces that could reduce microbial attachment, actively destroy microbes, and disrupt the microbial habitat. Such antimicrobial surfaces have the potential to provide effective, low cost solutions to combat microbial contamination, transmission and antimicrobial resistance.

Microbial contamination of surfaces in healthcare

There are a number of areas in human medicine where contaminated surfaces play a role in the development and transmission of infection. For example, contaminated surfaces impact healthcare in the use of indwelling medical devices and surgical prosthesis, such as catheters and artificial hips. The surface of the implant can become contaminated with a bacterial biofilm, leading to serious and difficult-to-treat infections. According to The Royal College of Surgeons, in the UK alone there were 122,154 hip replacements during 2014–2015; this is a huge increase from 89,919 replacements in 2005, and it is predicted that the number of such procedures will increase at a similar pace in the future. This represents a major growing challenge to health service providers like the UK's NHS.[5]

Touch-points in the rooms of patients with healthcare-associated infections (HCAI) can become contaminated with pathogens, which can then form a reservoir for onward transmission. Indeed, a patient admitted to a room where the previous occupant was infected or colonised with key antibiotic-resistant bacteria is twice as likely to acquire the same pathogen.[6]

These issues are especially important in healthcare facilities with particularly vulnerable patients, such as adult and paediatric intensive care, transplant, burns, haematology and oncology units. There are also significant opportunities to apply this technology in clinical environments in low and middle income country (LMIC) settings.

Contaminated surfaces also play a role in infection transmission in hospital water systems. Pipework, taps, drains, and other parts of the water system can become contaminated with infection-causing bacteria, which are particularly dangerous for susceptible patient groups. For this reason, national guidelines in the UK specify regular sampling of key parts of hospital water systems for *Pseudomonas* and *Legionella* bacteria.

Antimicrobial resistance

Since their initial discovery over 90 years ago, antibiotics are still the most effective strategy to treat bacterial infections. However, the misuse and overuse of antibiotics in human healthcare, and in industrial and farming applications, has resulted in the development and spread of antibiotic-resistant bacteria.

Tackling antimicrobial resistance (AMR) is high on the agenda for scientists and governments. According to The Review on Antimicrobial Resistance, published by the Wellcome Trust and UK government,[7] infections related to antimicrobial resistance are already costing 50,000 lives each year in Europe and the US alone. At least 700,000 deaths occur globally each year as a result of drug resistance in illnesses such as bacterial infections, malaria, HIV/AIDS and tuberculosis. This is predicted to increase in future, as "routine surgeries and minor infections become life-threatening once again and the hard-won victories against infectious diseases of the last fifty years will be jeopardised".[8] Unless new solutions are developed to address AMR, global costs are estimated to reach US $3Tn annually by 2050 and an additional ten million people could die each year; cumulated costs could reach over US $100Tn.[7, 9]

Box 2: How can surfaces contribute to the development and spread of antimicrobial resistance?

AMR develops when administered antibiotics do not result in eradication of the cause of the infection. On a surface, bacteria can changes their physiology allowing them to be protected from the action of antibiotics and biocides, making it more likely that bacteria with a higher level of natural resistance will survive, which drives the development of antibiotic resistance.[1] This happens in a four-step process as shown in Figure 1:

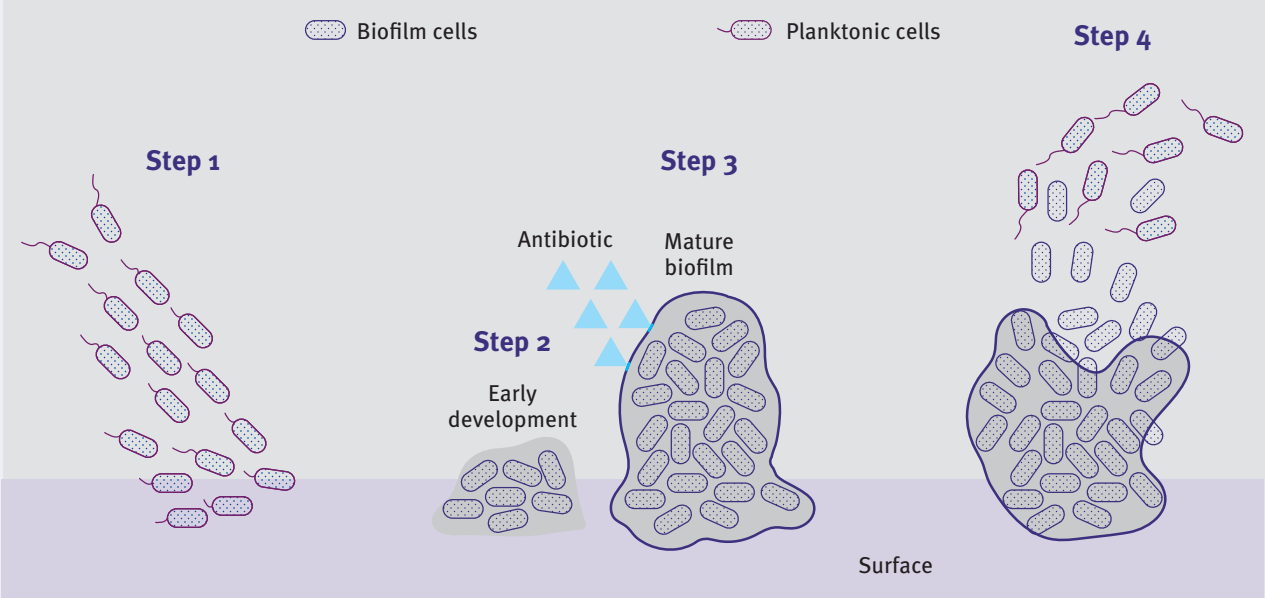

Figure 1. The four-step process by which bacteria provide a breeding ground for the transfer of AMR-related genetic material between microbes.

Step 1: Individual planktonic bacteria cells – cells that are able to swim or float in a liquid – adhere to the solid surface.[10–12]

Step 2: Once on the surface, planktonic cells secrete a sugary glue (termed exopolymeric substances, or EPS), and multiply, forming a biofilm layer several cells thick. The bacteria can communicate using multiple signalling pathways.[13–15]

Step 3: When there are enough bacteria in the biofilm, the glue forms a protective layer around the bacteria which antibiotics cannot easily penetrate.[10, 11, 16]

Step 4: Planktonic cells formed in the mature biofilm are then dispersed and the process can repeat.

How could surfaces help prevent infection and fight antimicrobial resistance?

An antimicrobial surface would have the potential to reduce bacterial attachment and biofilm formation on a surface, thereby reducing the opportunity for transmission and infection.

Box 3: Why is it of importance to Government, the National Health Service, and medical device companies to consider new developments in antimicrobial surfaces?

- **Conventional approaches are not sufficient to tackle biofilms and surface attached cells.** The issues linked with microbial biofilms on medical devices, hospital surfaces, and hospital water systems illustrate that conventional approaches are not fully effective, and creates space for supporting technologies such as antimicrobial surfaces.
- **Developing effective, low-cost strategies to fight HCAI and AMR is a key target for government and health service providers.** Biofilms can pose direct pathogenic risks to personnel *via* surface contact. The spread of biological species from biofilms or biofilm precursors remains one of the primary challenges across all application spaces, including product contamination and human infection.
- **Minimising health and safety risks.** Effective antimicrobial surfaces in the healthcare environment and on indwelling devices and prosthetic material would reduce the risk of infection and help to tackle the development of AMR. Also, improved control of environmental microbes may reduce the need for disinfectant use, which would reduce chemical exposure for staff and reduce costs.
- **Regulatory Changes.** Concerns about environmental pollution and toxicity are leading to regulatory changes, limiting the use of previously widely employed biocidal agents and biofilm control approaches.
- **Greener product formulations for biofilm control.** The use of more sustainable and naturally-derived ingredients in manufactured products is an industry-wide movement in response to consumer pressure.

Candidate antimicrobial surfaces to tackle healthcare-acquired infections and antimicrobial resistance

There are several approaches to making a surface antimicrobial:

1. **Surface topography**
   Physically alter the properties of a surface to make it less able to support microbial contamination and/or easier to clean.

2. **In-built and slow release antimicrobial agents**
   Permanently "manufacture in" an agent with antimicrobial activity, e.g. this is an intrinsic property of some metal surfaces, or a surface can be engineered with antimicrobial agents that are gradually released.

3. **Self-cleaning and self-polishing surfaces**
   These methods typically rely on liquid to periodically remove the outer layer of coating on a surface to be replaced with an underlying uncontaminated layer.

1. Surface topography

A surface's properties can be tailored for two separate applications: antimicrobial (decrease the viability of surface-associated microbes) or anti-adhesive (decrease the ability of microbes to attach to the surface). These solutions typically avoid the use of anti-bacterial chemicals (thus the bacteria cannot adapt and become drug resistant) and are safe for humans.

Antimicrobial surface patterns

Example: Cicada wings

Cicada are a large group of insects whose wings exhibit antimicrobial properties. As shown in Figure 2, the surface of a cicada's wing consists of nanoscale spikes that can puncture the cell walls of bacteria. These nanoscale spikes have been shown to be particularly effective against some types of bacteria, including *Escherichia coli, and Pseudomonas aeruginosa* (which are Gram-negative), but not *Bacillus subtilis* and *Staphylococcus aureus* (which are Gram-positive).[17] This selectivity is thought to be due to differences between the cell walls of different types of bacteria, for example, *Bacillus subtilis* and *Staphylococcus aureus* have stiffer cell walls and are therefore at a lower risk of having their cell walls punctured by the surface spikes.[18]

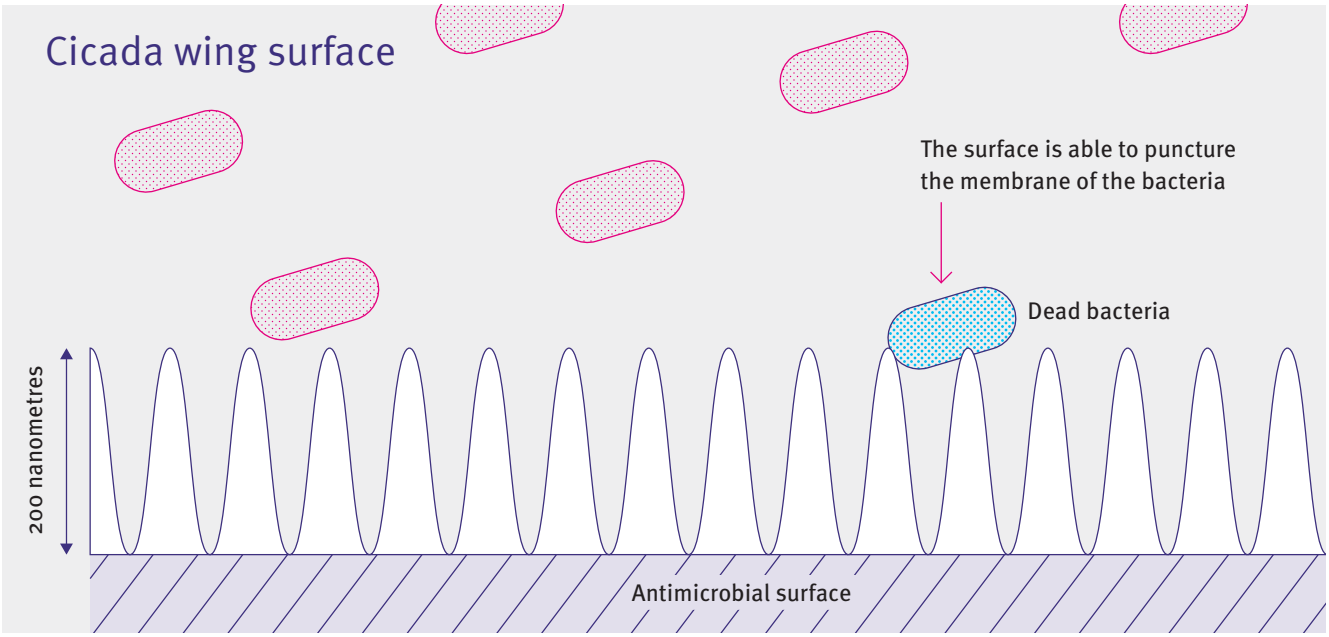

Figure 2. Bacteria impaled on cicada wing surface (not to scale).[18]

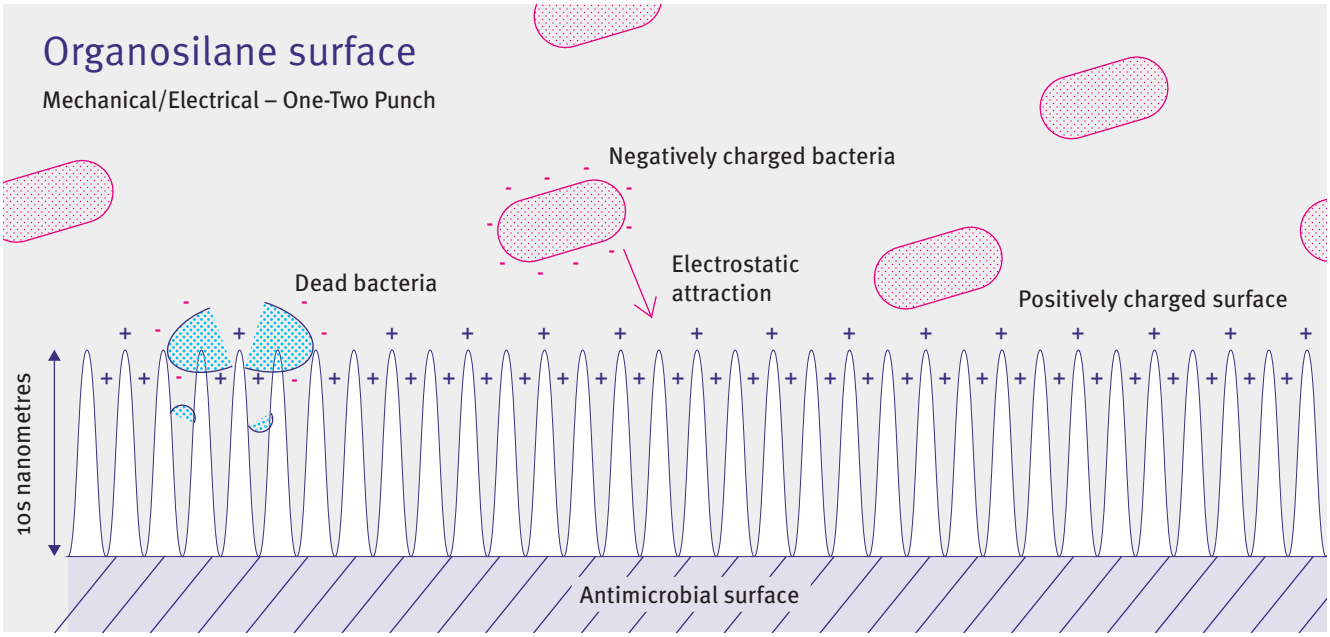

Figure 3. Positively charged spikes attract the negatively charged bacteria (not to scale). The cell walls of the bacteria are then pierced by the surface spikes, killing the bacteria.

Building on these cicada wing observations, surfaces with nanoscale spikes have recently been developed that use a metal organic framework (MOF). These surfaces are positively charged which attract the generally negatively charged bacteria onto the surface where they are punctured. They have proven to be particularly effective in removing both *Escherichia coli* and *Staphylococcus aureus* from surfaces.[19]

Example: Organosilane

Organosilane molecules with a positive charge can be bonded to surfaces. The positive charge attracts negatively charged bacteria onto spikes, formed out of a chain of molecules, which puncture the cell wall of the bacteria[20] (Figure 3).

A small number of initial studies indicate that this method is worthy of further investigation.[21–23] Some indicate that organosilane causes a significant reduction in the number of surface bacteria,[24, 25] whilst others suggest no reduction.[20, 26] These studies illustrate both the difficulties of achieving a suitable bond between the surface and the spike, and, like cicada wing studies, the differences in the cell walls of different types of bacteria (certain bacteria cell walls are punctured by the surface spikes, whilst others are not).

Application: Touch surfaces in the clinical environment

- The advantage of organosilane products is they can be attached to both soft and hard surfaces. This means they can form an antimicrobial coating effective on many different types of surfaces, from bedrails to clothing, carpets, and walls.
- They could be used to create "retrofitted" antimicrobial touch surfaces in the clinical environment. This means that rather than manufacturing-in antimicrobial surfaces, it may be possible to convert an existing clinical environment using organosilane. This could reduce the burden of contamination in the near-patient environment and reduce the risk of transmission.

Anti-adhesive surfaces

Reductions in microbial attachment have been observed in response to the engineering of corrugated surface topographies on nanoscales. As with other surface manipulation methodologies, the results are application dependent.

Surface roughness

Many anti-adhesive surfaces utilise very fine scale surface roughness. It has been shown that surfaces that have features between 1–100mm recruit and retain microbes, whereas introducing micro scale roughness (1 to ≤1000µm) decreases microbial attachment. Therefore, materials with multiple length-scale topographies are recommended for development as they could limit biofouling agents at macro, micro and possibly nano length-scales.[27–29]

Manufacturing surfaces that have features at micro and nanometre scales may represent an approach that can be used in a broad number of antifouling applications, and – when combined with other technologies – could form the basis of the next generation of smart antifouling solutions.

Example: Sharklet™

A good example of an anti-adhesive surface that inhibits growth and biofilm formation solely through surface design is Sharklet™. As the name suggests, the surface mimics the approximate topography and geometry of shark skin.

The surface consists of microscopic features arranged in a diamond pattern as shown in Figure 4. This topography creates mechanical stress on settling bacteria, disrupting normal function within the bacteria and forcing them to search for a different surface on which to attach.[41] This acts to create a natural self-cleaning anti-adhesive surface.[30]

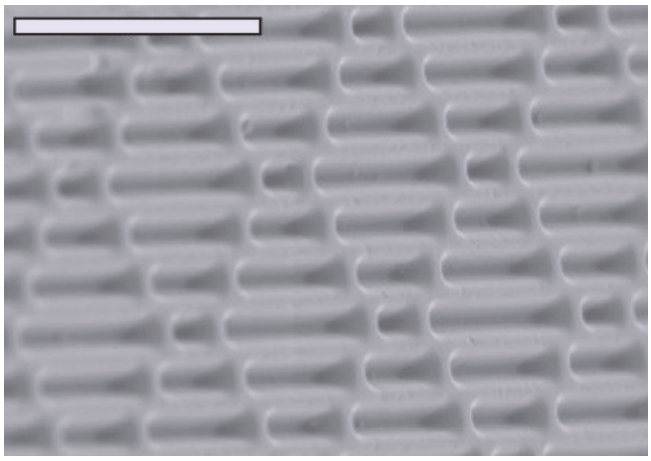

Figure 4. An example of the Sharklet™ diamond pattern on an acrylic material.[42] The scale bar in the micrograph represents 20 µm.

Application: Hospital contact surfaces

- When applied to high touch surfaces, Sharklet™ reduced surface contamination of *Staphylococcus aureus* (MSSA) and antimicrobial-resistant *Staphylococcus aureus* (MRSA) by as much as 97 percent and 94 percent, respectively.[42]

Application: Medical devices

- Sharklet™ has been used to limit the spread of microbes upstream within a catheter tube.[31, 32] It has been shown to be extremely successful in the reduction of *Escherichia coli*, *Staphylococcus aureus*, and general biofilm coverage on surfaces.[30, 32]

2. In-built and slow-release antimicrobial agents

Copper alloys

Antimicrobial copper surfaces are made from copper or alloys of copper, such as brass or bronze. Copper and copper alloys have a natural ability to kill bacteria quickly, and are used in the vast majority of commercial antimicrobial coatings. Copper alloys are the most commonly evaluated option for antimicrobial surfaces, and have demonstrated *in vitro* activity against a range of pathogens, and have been effective at reducing healthcare associated infections.[33–35] As shown in Figure 5, its use relies on the production of copper ions (Cu^{2+}) that are considered to be the predominant antimicrobial species.[36]

The Environmental Protection Agency (EPA), which regulates antimicrobial agents and materials in the United States, found that copper alloys kill more than 99.9% of disease-causing bacteria within two hours, however this required regular cleaning as a prerequisite to their effectiveness.[37–39] The long-term safety, durability, acceptability and cost-effectiveness of the use of copper alloys as antimicrobial surfaces has not been formally evaluated.

Application: Antimicrobial touch surfaces

- Creating antimicrobial touch surfaces from copper alloys within the clinical setting (such as bedrails and door handles) can reduce the burden of contamination in the near-patient environment and reduce the risk of transmission. However the price of copper is likely to be prohibitive for wide-spread use.

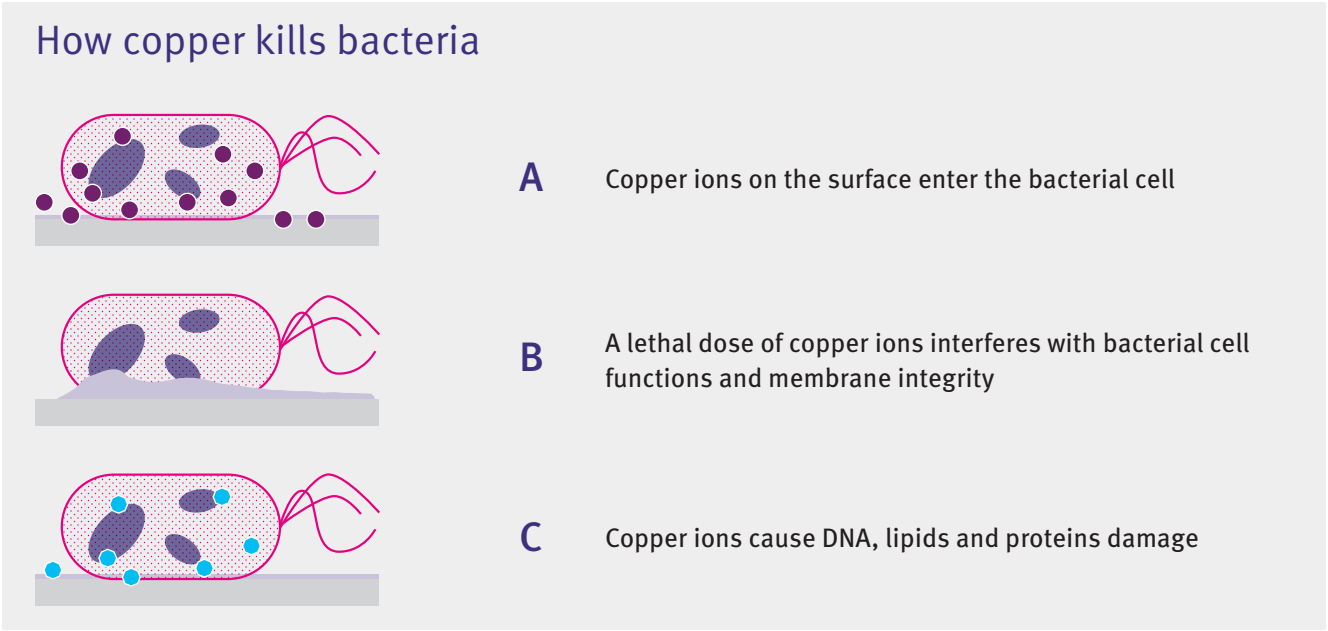

Figure 5. Illustration of how copper kills bacteria.

Application: Hospital environment

- Copper alloys have also proved effective against fungal bacteria, a 2010 study concluded that "copper could be used in air-conditioning systems in buildings, particularly in hospital environments where patients are more susceptible to fungal infections".[40]

Application: Hospital water systems

- Copper has been used for pipes and taps in hospitals to reduce the levels of waterborne bacteria that can cause infections in patients (such as *P. aeruginosa*) and in patients, staff, and visitors (such as *L. pneumonpila*).

Silver

Similarly to copper, at the silver-air interface silver ions are released which prevent DNA from replicating and hence spreading resistance.[41,42] Silver has been shown to be toxic to a wide range of pathogens, however concerns due to cost have restricted its use to applications that require only small concentrations.

Application: Medical devices

- Using silver alloy catheters, for example, in hospitalised patients requiring short-term urinary catheterization reduces the incidence of infections, and is likely to produce cost savings compared with standard catheters.[43]

Application: Water treatment

- Emerging evidence suggests that contaminated drains can be an important reservoir for AMR bacteria in healthcare settings. Drains are often contaminated with high levels of bacteria and biofilms. Antimicrobial surfaces could reduce the level of contamination and biofilms and reduce the risk of transmission. Nanoparticles of silver have been shown to reduce the risk of microbial contamination of water.[44]

3. Self-Cleaning and self-polishing surfaces

Photocatalytic coatings

A photocatalytic surface can absorb light and pass on the energy to other molecules. One of the most widely used photocatalytic surfaces is titanium dioxide (TiO2), which is non-toxic, cheap and abundant. If titanium oxide absorbs light at a specific wavelength in water and oxygen, an hydroxyl free radical – a molecule with an unpaired electron – is produced. Hydroxyl free radicals are very reactive and kill bacteria by attacking the cell membrane.

Photocatatlytic surfaces are especially effective in the hospital environment due to their self-regenerating biocidal effect that makes such surfaces active for long periods of time.

Application: Hospital surfaces

- Titanium dioxide has been successfully used as an antimicrobial coating for several types of surface, including on ceramic tiles[45] and self-cleaning windows.[46]

Application: Medical devices

- Titanium dioxide coated silicone catheters can be sterilized and cleaned simply by irradiation with low-intensity ultra violet light.[47]

Application: Water treatment

- Titanium dioxide coatings on sand grains have been used for water decontamination applications.[48]

Self-polishing coatings

Self-polishing technologies have particularly useful anti-biofouling properties when applied on the exterior of hulls of ships. This has become especially popular in recent years as new regulations are introduced banning, or severely restricting, the use of toxic paint on the exterior of ships.

Most of these "tin free" paint systems rely on the use of sea water soluble pigments such as copper oxides (Cu_2O, CuO). As shown in Figure 6, the surface layer is broken up by water, resulting in the release of a biocide. This constant erosion of the surface results in the exposure of fresh biocides.

Provided sufficient care is taken to ensure the realised biocide does not have unintended consequences downstream after its release, this concept could be applied to healthcare settings. A key consideration is the biocide released; many plant extracts are well known for their antimicrobial properties and much research is devoted to their application to protect food from pathogens.[49] Rosin, for example, is an abietic acid which is naturally produced by pine trees, which could be used as a natural biocide in self-polishing coatings. However, only limited research has been done on investigating their efficacy on surfaces of healthcare units or on medical devices, such as tympanostomy tubes.[50] It has also been suggested tea-tree oil could also be effective against MRSA.[51]

Application: Water treatment

- Self-polishing coatings could be of relevance for healthcare applications as they rely on liquid to remove the outer layer of coating to be replaced with an underlying fresh layer. Direct applications could include water pipes and drains in hospitals.

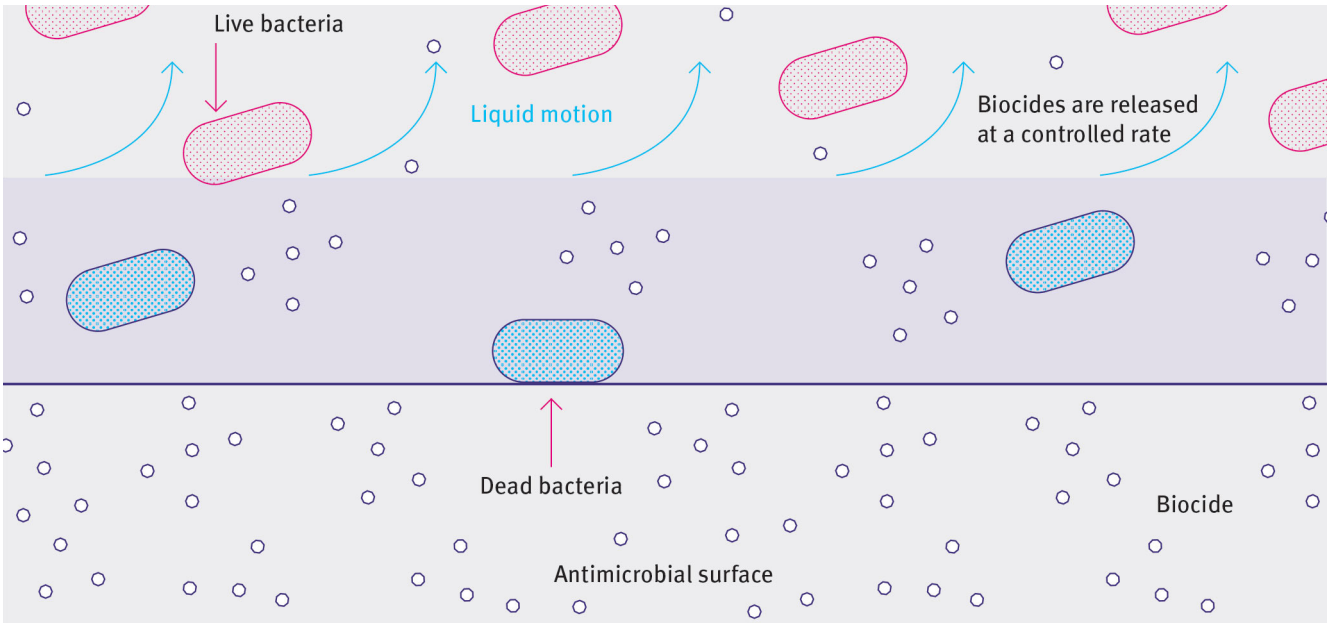

Figure 6. Schematic of the removal of the outer layer of coating to be replaced with an underlying fresh layer.

Conclusion

The potential for antimicrobial surfaces

Antimicrobial surfaces have the potential to reduce microbial attachment, kill bacteria, and disrupt the microbial habitat by making the surface easier to clean. This would reduce the risk of infection from bacteria on the device surface, and transform the clinical environment by helping to prevent the spread of infection in vulnerable patient groups such as adults and neonates in intensive care. Antimicrobial surfaces also could make hospital water systems less prone to contamination with bacteria such as *Pseudomonas* and *Legionella*.

Each candidate antimicrobial surface outlined in this Briefing Paper has its own strengths and weaknesses depending on the given application or infection. Therefore one of the key conclusions of this Briefing Paper is that the spread of infection and antimicrobial resistance in the clinical environment cannot be completely tackled by antimicrobial surface technologies on their own. Such technologies must be employed as part of a joint approach involving clinical and cleaning staff as well as the responsible use of antibiotics.

In order to realise the potential benefits of innovative vid surfaces in the clinical environment, more studies to measure the impact of antimicrobial surfaces on infection, antimicrobial resistance and environmental impact are needed.

Further investigations on antimicrobial surfaces should also be developed with low and middle income settings in mind, where “smart” surfaces could mitigate the impact of some challenges related to LMIC settings, such as a lack of clean water and reliable power sources.

The need for a multidisciplinary approach

Research conducted by expert specialists has been a vital driver for advances in specific disciplines such as physics, chemistry, engineering and medicine. It can also be a barrier that slows down the innovation that we now need in the face of numerous global challenges. The optimal solution for engineering an antimicrobial surface for any particular context is likely to involve harnessing a combination of the different solutions discussed in this Briefing Paper. For rapid innovation of solutions to address antimicrobial resistance we need to integrate molecular science with engineering, medicine and business.

Exploiting the latest molecular science and engineering solutions for antimicrobial surfaces whilst considering the manufacture, distribution and overall costs of a solution is challenging. Imperial College London has world leading subject matter experts in infectious disease, its transmission and epidemiology; medical devices; the understanding of biofilms; the physics, chemistry and engineering of nanomaterials; theory modelling and simulation; and the generation of innovative sustainable business systems. Rapid innovation requires a convergent approach to science and engineering which goes beyond simply facilitating the communication between these physical scientists, clinicians, engineers and entrepreneurs.

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About the authors

At present, Imperial researchers across various departments are investigating antimicrobial surfaces. These researchers include:

Jonathan Otter is an epidemiologist focused on Infection Prevention and Control at Imperial College Healthcare NHS Trust in London, and an Honorary Senior Lecturer in the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at Imperial College London.

Kieran Brophy is the Communications Manager at the Institute for Molecular Science and Engineering. He is responsible for organising and coordinating Briefing Papers, communications and public engagement activities for the Institute.

Jonathan Palmer was a postdoctoral researcher looking at microbial adhesion and biofilm formation at the Surfaces and Particle Engineering Laboratory in Imperial College London.

Nicholas Harrison is a Professor of Computational Materials science, a Fellow of the Institute of Physics and of the Royal Society of Chemistry, and a Co-Director of the Institute for Molecular Science and Engineering. He has a long standing interest in the development of multi-scale multi-physics models of advanced materials including the design and optimisation of materials with novel electronic, magnetic and chemical properties. He is the discoverer of the hardest known oxide material and the highest temperature molecular magnet.

Jason Riley is a Professor of Materials Electrochemistry in the Department of Materials at Imperial College London. His team investigates in the application of electrochemistry in nanoscience and nanotechnology with applications in intelligent wound dressings, solar cells, force transducers, rheology and display devices.

Daryl Williams is a Professor of Particle Science in the Department of Chemical Engineering research interests focus on the particulate materials and material surfaces and their role in product manufacture including both biological and non-biological materials.

Gerald Larrouy-Maumus is a senior lecturer in molecular microbiology at the MRC-Centre for Molecular Bacteriology and Infection, Department of Life Sciences at Imperial College London. Gerald is focused on antimicrobial resistance and infectious diseases, especially human Tuberculosis caused by Mycobacterium tuberculosis (Mtb), which is one of mankind's most successful intracellular pathogens.

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