Pearson BTEC Level 3 Nationals Extended Diploma

Applied Science

Unit 7: Contemporary Issues in Science

Part A

8 May 2018 – 22 May 2018
Supervised period: 6 hours

Paper Reference
31629H

You do not need any other materials.

Instructions

- **Part A** contains material for the completion of the preparatory work for the set task.
- **Part A** is given to learners 2 weeks before **Part B** is scheduled. Learners are advised to spend no more than 6 hours on **Part A**.
- **Part A** must be given to learners on the specified date so that learners can prepare in the way specified.
- **Part A** is specific to each series and this material must only be issued to learners who have been entered to undertake the task in the relevant series.
- **Part B** materials must be issued to learners on the date specified by Pearson.

Turn over ▶

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Instructions to Teachers/Tutors

This paper must be read in conjunction with the unit information in the specification and the BTEC Nationals Instructions for Conducting External Assessments (ICEA) document. See the Pearson website for details.

This set task has a preparatory period. **Part A** sets out how learners should prepare for the completion of the **Part B** task under supervised conditions.

Part A is given to learners two weeks before **Part B** is scheduled. Learners are advised to spend no more than 6 hours on **Part A**.

Learners should undertake independent research on the case study given in this **Part A** booklet.

Centres must issue this booklet at the appropriate time and advise learners of the timetabled sessions during which they can prepare. It is expected that scheduled lessons or other timetabled slots will be used for the preparation.

Learners should familiarise themselves with the specific concepts and terminology used in the articles.

Learners may prepare summary notes on the articles. Learners may take up to four sides of notes of this type into the supervised assessment (**Part B** booklet).

These notes should only include information about scientific terminology, quantities and concepts used in the articles and a summary of the scientific issue discussed. This will enable learners to interpret, analyse and evaluate the articles in **Part B**. Other content is not permitted.

Part B must be completed under supervision in a single 2 hour and 30 minute session timetabled by Pearson. A supervised rest break is permitted.

The supervised assessment should be completed in the **Part B** Task and Answer booklet.

Teachers/tutors should note that:

- learners should not be given any direct guidance or prepared materials.
- learners should not be given any support in writing or editing notes.
- all work must be completed independently by the learner.
- learner notes will be retained securely by the centre after **Part B** and may be requested by Pearson if there is suspected malpractice.

Refer carefully to the instructions in this taskbook and the BTEC Nationals Instructions for Conducting External Assessments (ICEA) document to ensure that the preparatory period is conducted correctly and that learners have the opportunity to carry out the required activities independently.

Instructions for Learners

Read the set task information carefully.

This is **Part A** of the set task and gives information you need to use to prepare for **Part B** of the set task.

In **Part B** you will be asked to carry out specific activities using the information in this **Part A** booklet and your preparatory notes.

In your preparation for **Part B** using this **Part A** booklet, you may prepare short notes to refer to when completing the set task. Your notes may be up to four sides and may be hand written or word processed. Your notes should only include information about scientific terminology, quantities and concepts used in the articles and a summary of the scientific issue discussed. This will enable you to interpret, analyse and evaluate the articles in **Part B**. Other content is not permitted.

You will complete **Part B** under supervised conditions.

You must work independently and must not share your work with other learners.

Your teacher/tutor may give guidance on when you can complete the preparation.

Your teacher/tutor can not give you feedback during the preparation period.

You must not take your preparatory notes out of the classroom at anytime and you must hand the notes in to your teacher on completion.

Your notes will be made available to you at the beginning of the supervised assessment.

Set Task Brief

You are provided with the following articles:

Article 1: Doling out too many antibiotics 'will make even scratches deadly': WHO warns that crisis could be worse than AIDS
http://www.dailymail.co.uk/health/article-2616794/Antibiotic-resistance-needs-taken-seriously-AIDS-Implications-bacteria-evading-drugs-devastating-says-landmark-report.html

Article 2: Antimicrobial resistance – a global epidemic. Prepared by secretariat of WHO, WIPO and WTO
http://www.who.int/phi/news/Trilateral_AMR_background_finalpdf.pdf?ua=1

Article 3: Honey: A realistic antimicrobial for disorders of the skin
http://www.sciencedirect.com/science/article/pii/S168411821500033X

Your notes should only include information about scientific terminology, quantities and concepts used in the articles and a summary of the scientific issue discussed.

You should spend up to a maximum of six hours to complete your preparatory notes. You may take up to four sides of A4 notes into the supervised assessment.

Part A Set Task Information

Article 1

Extract from 'Doling out too many antibiotics 'will make even scratches deadly': WHO warns that crisis could be worse than AIDS'

This is an edited version of an article that appeared in the 'Daily Mail' newspaper in April 2014.

- Spread of deadly superbugs that evade antibiotics is happening globally
- It's now a major threat to public health, the World Health Organisation (WHO) says
- It could mean minor injuries and common infections become fatal

Deaths from cuts and grazes, diarrhoea and flu will soon be common as antibiotics lose their power to fight minor infections, experts have warned.

The World Health Organisation says the problem has been caused by antibiotics being so widely prescribed that bacteria have begun to evolve and develop resistance.

It claims the crisis is worse than the AIDS epidemic – which has caused 25 million deaths worldwide – and threatens to turn the clock back on modern medicine.

The WHO warns that the public should 'anticipate many more deaths' as it may become routine for children to develop lethal infections from minor grazes, while hospital operations become deadly as patients are at risk of developing infections that were previously treatable.

Doctors are increasingly finding that antibiotics no longer work against urinary and skin infections, tuberculosis and gonorrhoea.

The WHO is urging the public to take simple precautions, such as washing hands to prevent bacteria from spreading in the first place.

Doctors are also being told to prescribe antibiotics sparingly and ensure patients finish the full course, as if they stop mid-way the bacteria may become resistant. In England last year some 41.7 million prescriptions were written out, up from 37.2 million in 2006.

Dr Keiji Fukuda, the WHO's assistant director for health security, said: 'Without urgent, co-ordinated action, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill.

SUPERBUGS: THE GUIDE TO BUGS RENDERING ANTIBIOTICS OBSOLETE

MRSA – patients infected with MRSA (methicillin-resistant Staphylococcus aureus) are 64 per cent more likely to die than those with a non-resistant form of S. aureus.

People infected by resistant superbugs are also likely to stay longer in hospital and may need intensive care, pushing up costs.

C. difficile – this bacteria produces spores that are resistant to high temperatures and is very difficult to eliminate. It is spread through contaminated food and objects and can cause blood poisoning and tears in the large intestine.

E. coli – this now accounts for one in three cases of bacterial infections in the blood in the UK and a new strain is resistant to most antibiotics. It is highly contagious and could cause more than 3,000 deaths a year.

Acinetobacter Baumannii – a common bacteria which is resistant to most antibiotics and which can easily infect patients in a hospital. It can cause meningitis and is fatal in about 80 per cent of patients.

CRKP – this is a bacterium that is associated with extremely difficult to treat blood infections and meningitis. It is resistant to nearly all antibiotics and is fatal in 50 per cent of cases.

Multi-drug resistant tuberculosis is estimated to kill 150,000 people globally each year.

NDM-1 – a bacteria detected in India of which some strains are resistant to all antibiotics.

'Effective antibiotics have been one of the pillars allowing us to live longer, live healthier, and benefit from modern medicine.

'Unless we take significant actions to improve efforts to prevent infections, and also change how we produce, prescribe and use antibiotics, the world will lose more and more of these global public health goods and the implications will be devastating.

'We should anticipate to see many more deaths.

'We are going to see people who have untreatable infections.'

Only last month, Britain's Chief Medical Officer Dame Sally Davies criticised GPs for needlessly 'dishing out' antibiotics to patients.

In the largest study of its kind, the WHO looked at data from 114 countries on seven major types of bacteria. Experts are particularly concerned about bacteria responsible for pneumonia, urinary tract infections, skin infections, diarrhoea and gonorrhoea.

They are also worried that antiviral medicines are becoming increasingly less effective against flu.

Dr Danilo Lo Fo Wong, a senior adviser at the WHO, said: 'A child falling off their bike and developing a fatal infection would be a freak occurrence in the UK, but that is where we are heading.'

THE COUPLE WHO LOST BABY TO INFECTION AFTER SUPERBUG OUTBREAK

The human cost of the rising number of superbugs is becoming all too familiar.

Distraught young couple Jenna and Andrew Hannon lost their second son to an infection at a hospital neo-natal unit in Bristol.

Little Oliver was born early at 24 weeks and although he had seemed well enough to go home with his parents, he soon fell dangerously ill.

He was taken to Southmead Hospital but the infection had taken hold and the youngster passed away.

Tragically the couple had lost another prematurely born son, Travis, to infection in 2010, just five-and-a-half hours after his birth at 26 weeks.

An inquest into Oliver's death later found he had been killed by the pseudomonas bacteria.

He was one of three babies in the hospital to be hit by the killer bacteria, which was later linked to baby deaths around the country.

An investigation took place at the hospital into Oliver's death, but it could not find what caused his infection.

The inquest was told that Oliver was being given two types of antibiotics before he died as a precaution, but neither specifically fought pseudomonas.

As a result of the investigation, the hospital also now uses antibiotics which more specifically target the bacteria.

British experts likened the problem to the AIDS epidemic of the 1980s. Professor Laura Piddock, who specialises in microbiology at the University of Birmingham, said: 'The world needs to respond as it did to the AIDS crisis.

'We still need a better understanding of all aspects of resistance as well as new discovery, research and development of new antibiotics.'

The first antibiotic, penicillin, was developed by Sir Alexander Fleming in 1929. But their use has soared since the 1960s, and in 1998 the Government issued guidelines to doctors urging them to curb prescriptions. Nonetheless, surveys suggest they are still prescribed for 80 per cent of coughs, colds and sore throats.

Link to video: WHO warns antibiotic-resistant bacteria is spreading.
www.dailymail.co.uk/embed/video/1093014.html

Jennifer Cohn of the international medical charity Médecins Sans Frontières agreed with the WHO's assessment and confirmed the problem had spread to many corners of the world.

'We see horrendous rates of antibiotic resistance wherever we look in our field operations, including children admitted to nutritional centres in Niger, and people in our surgical and trauma units in Syria,' she said.

Earlier this month, Government body NICE said that one in 16 patients are developing infections on NHS wards because of poor hygiene among staff.

NICE said 800 patients a day, the equivalent of 300,000 a year, are infected by a member of staff or by dirty equipment. It is estimated the infections cause 5,000 deaths annually and contribute to another 15,000.

WHAT CAUSES ANTIBIOTIC RESISTANCE?

Antibiotics are substances that kill or interfere with the growth of microorganisms, especially bacteria. But not all microorganisms are susceptible to all antibiotics, according to Public Health England.

Microorganisms which are not killed or inhibited by an antibiotic are called 'antibiotic resistant'.

They continue to grow and multiply in the presence of that antibiotics.

There are several ways in which bacteria can be resistant. Some destroy the antibiotic, for example by producing enzymes against it; some prevent the antibiotic getting into their cells; others get the antibiotic out of their cells before it can harm them.

HOW DOES RESISTANCE DEVELOP?

Some bacteria are naturally resistant; new resistances also arise spontaneously by chance mutations and these resistant strains then multiply.

Some resistances can be passed from one bacterium to another, spreading resistance between species. Loops of DNA (called plasmids) carry the resistance genes from one bacterium to another.

When an antibiotic is given, it kills the sensitive bacteria, but any resistant ones can survive and multiply.

The more antibiotics are used (in animals and agriculture as well as in man) the greater will be the "selective pressure", favouring resistant strains – i.e. survival of the fittest.

Antibiotics don't 'cause' resistance; rather, they create an environment which favours the growth of resistant variants which already exist in nature or arise by chance.

Article 2

Extract from 'Antimicrobial resistance – a global epidemic'

This is an edited version of an article prepared by the secretariats of WHO, WIPO and WTO.

Not an expert in AMR? Watch this 5-minutes video explaining the most important facts: https://www.youtube.com/watch?v=xZbcwi7SfZE

Antimicrobial resistance (AMR) occurs when bacteria, parasites, viruses and fungi become resistant to antimicrobial drugs that are used for treating the infections they cause. Every time an antimicrobial medicine is used, it diminishes the effectiveness for all users, because its usage increases the possibility for the bacteria to become resistant. Antimicrobial resistance threatens the effective prevention and treatment of an increasing range of infections, including blood poisoning, pneumonia, diarrhoea, gonorrhoea, tuberculosis, HIV/AIDS and malaria.

Resistance against antibiotics (medicines used to prevent and treat bacterial infections) is an urgent problem because antibiotics are a cornerstone of modern medicine and most medicinal procedures in human and animal health rely on functioning antibiotics.

What causes antimicrobial resistance?

Antimicrobial resistance is mainly driven by inappropriate use. Global antibiotic consumption in humans has increased by 36% between 2000 and 2010. Half of this increased use is regarded as unnecessary, e.g. when antibiotics are used to treat illnesses like common colds that are caused by viruses, where antibiotics have no effect. In many countries, antibiotics can be bought without prescription or do not have underlying standard treatment guidelines. These factors increase antibiotic resistance because of a lack of knowledge of proper antibiotic use.

The problem of resistance is not only evident in human medicine consumption. Antibiotics are also used in veterinary medicine, for growth promotion in animals and disease prevention in agriculture, aquaculture and horticulture. In the US, for example, more than 70% of antibiotics are used in agricultural production, primarily for growth promotion and prophylaxis. Worldwide consumption in animals is estimated to rise by 67% from 63,151 tons in 2010 to 105,596 tons in 2030.

How does resistance develop?

Resistant bacteria can be transmitted to humans through various channels such as the food chain, animal-to-human contact, and the environment.

Globalization fuels the spread of antimicrobial resistance where transmission is facilitated by increased trade, travel and both human and animal migration. Travellers often carry home resistant bacteria from holidays or business trips. An example of globalization fuelling the spread of antimicrobial resistance is seen in the strain of bacteria resistant to the antibiotic colistin. Colistin is widely used in Chinese livestock which has likely led the bacteria to evolve, gain resistance and transmit from livestock to humans through food. This strain was reported earlier this year in the US and Europe. This example shows that antimicrobial resistance cannot be tackled in isolation by individual countries but needs global cooperation.

Why is antimicrobial resistance a problem?

Antimicrobial resistance affects high-, low- and middle-income countries. There are particular diseases that have higher rates of antimicrobial resistance such as tuberculosis and gonorrhoea. Recent global estimates in 2013 reveal 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB) with extensively drug-resistant tuberculosis (XDR-TB) present in 100 countries. Further, there are treatment failures as a result of resistance to treatments of last resort for diseases such as gonorrhoea. Consequently, there is a risk that gonorrhoea may become untreatable if no vaccines or new treatments are being developed.

A reliable estimate of the global burden of antimicrobial resistance is difficult to obtain as data is not systematically and consistently collected. However, estimates from Europe indicate that the excess mortality due to resistant bacteria in hospital infections exceeds 25,000 annually, with annual costs of at least €1.5 billion. Outpatient data from the US indicates more than 63,000 deaths annually due to resistant bacterial infections.

A combination of having less developed health systems, higher rates of infectious diseases and low quality and improper use of antibiotics, among other factors, increases the burden of antimicrobial resistance in low- and middle-income countries. For example, the crude infectious disease mortality rate in India is 416.75 per 100,000 persons with bacterial resistance increasing over time. Between 2008 and 2013, E. coli resistance to a type of antibiotics – a third-generation cephalosporins – increased from 70% to 83%. This highlights the increasing burden of antimicrobial resistance in developing countries.

Additionally, antimicrobial resistance causes extra health care costs and leads to loss of productivity. Patients with resistant infections are more expensive and difficult to treat and are more likely to require longer hospitalisation than patients infected with drug susceptible strains. As a consequence, antimicrobial resistance has major economic costs, estimated at $55 billion annually in the US alone. The World Economic Forum annual risk report has been listing the spread of infectious diseases – including the rise of resistant pathogens – among the high-impact risks to the global economy.

Although resistant strains of bacteria are not a new phenomenon, increased speed of resistance to antimicrobial medicines and especially to last resort antibiotics for some bacterial infections, has turned antimicrobial resistance into one of the greatest threats for human health. In a post-antibiotic era, common infections and minor injuries can be fatal. This is far from being an apocalyptic fantasy, but a very real possibility for the 21st century.

What are measures against antimicrobial resistance?

There are a number of possible measures against antimicrobial resistance including improvement of hygiene, infection control to prevent spread of resistant bacteria, development of new antimicrobials against which bacteria are not resistant, improved conservation efforts to maintain the effectiveness of new antimicrobials and of existing drugs.

Stewardship, innovation and access are three key objectives in addressing antimicrobial resistance.

Stewardship

Stewardship describes the careful and responsible management of resources entrusted to one's care. With respect to antimicrobials, stewardship refers to appropriate antimicrobial treatment to improve patient outcomes while minimizing the development and spread of resistance.

While access to effective antimicrobials is a prerequisite for productive and sustainable agriculture, in particular in relation to animal husbandry, antibiotics have to be used with more responsibility. Therefore, effective stewardship in tackling antimicrobial resistance requires a global multidisciplinary collaborative effort across industries.

Innovation

There is a severe lack of investment in new medicines against microbes. The market-based innovation system has insufficient incentives because the return on investment in antibiotic research is too small to attract the required R&D investments. The low return on investment can be explained by a number of factors. Antibiotics have a short treatment course compared to medications for chronic diseases which leads to lower treatment costs. Additionally, while new antibiotics are needed, they will face competition with existing generic products. Fostering appropriate use can also mean that new antibiotics are only used very conservatively to delay resistance building as much as possible which will diminish the revenue that the inventor can generate. These and other factors have led to minimal antibiotics breakthroughs since the 1980s and increased on-going concern about the lack of new products in the pipeline.

New innovative and comprehensive incentive initiatives are needed to complement the existing innovation model to foster the development of new antibiotics. This could include a mixture of push mechanisms (e.g. grants for basic research and clinical trials, product development partnerships), pull incentives (e.g. milestone prizes or market entry rewards) and regulatory measures (e.g. specific regulatory pathways). All these market measures have to factor in the public health objectives of antibiotic conservation and access.

Access

The problem of infectious diseases and antibiotic use plays out very differently across the globe. Certain countries are less exposed to the problem than others because of successful infection control programmes in hospitals. Further, while some countries experience overuse, many people still lack access to antibiotics, and more people die because of this lack than of resistant infections. Despite an increase in worldwide antibiotic consumption, lack of access even to affordable generics remains a huge problem in many countries.

Pneumonia accounts for 15% of all deaths of children under 5 years old, killing an estimated 922,000 children in 2015. Only one-third of children with bacterial pneumonia receive the antibiotics they need.

Antibiotics protected by patents will often have a higher price, which constrains access. One option to overcome this barrier is using delinkage in the development of new antibiotics as described above. Voluntary licensing agreements have emerged as a tool that has helped improve affordable access to patented medicines for HIV/AIDS and hepatitis.

In the long run, building strong health systems is the most sustainable approach to ensuring affordable access to good-quality essential medicines, including antimicrobial medicines and vaccines, as well as diagnostics and other vital interventions.

Increased international attention

WHO adopted the Global Action Plan on Antimicrobial Resistance (GAP-AMR) in 2015. The plan focuses on a comprehensive approach meaning that actions in all relevant sectors should be implemented synergistically. To tackle antimicrobial resistance, the global action plan sets out five strategic objectives:

- to improve awareness and understanding of antimicrobial resistance;
- to strengthen knowledge through surveillance and research;
- to reduce the incidence of infection;
- to optimize the use of antimicrobial agents; and
- to develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The GAP-AMR has been endorsed through resolutions by both the Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OiE).

In addition to the GAP-AMR, the World Health Assembly in 2016 discussed options for a global development and stewardship framework on antimicrobial resistance. The purpose of such a possible framework would be to add value and achieve strategic objectives identified in the GAP-AMR focusing on:

- preservation of antimicrobial medicines through a stewardship framework covering control, distribution and appropriate use;
- development of new health technologies for preventing and controlling antimicrobial resistance; and
- promotion of affordable access to existing and new antimicrobial medicines and diagnostic tools.

Antimicrobial resistance will be discussed at the United Nations General Assembly's 71st session in September 2016 in New York.

While antimicrobial resistance affects every country, each country should take actions that address the needs and capabilities of their health system to preserve global antibiotic resources.

Antimicrobial resistance is a multi-faceted global issue requiring a shared responsibility by all countries to protect citizen health and combat the global threat posed by AMR.

Article 3

Extract from 'Honey: A realistic antimicrobial for disorders of the skin'

This is an edited version of an article that appeared in volume 49, issue 2 of the Journal of Microbiology, Immunology and Infection in April 2016. The article was written by Pauline McLoone, Mary Warnock and Lorna Fyfe.

Resistance of pathogenic microorganisms to antibiotics is a serious global health concern. In this review, research investigating the antimicrobial properties of honeys from around the world against skin relevant microbes is evaluated. A plethora of *in vitro* studies have revealed that honeys from all over the world have potent microbicidal activity against dermatologically important microbes. Moreover, *in vitro* studies have shown that honey can reduce microbial pathogenicity as well as reverse antimicrobial resistance. Studies investigating the antimicrobial properties of honey *in vivo* have been more controversial. It is evident that innovative research is required to exploit the antimicrobial properties of honey for clinical use and to determine the efficacy of honey in the treatment of a range of skin disorders with a microbiological etiology.

Introduction

In traditional medicine, honey has been recognized around the world for its skin-healing properties. The ancient Greeks and Egyptians, for example, used topical application of honey to treat skin wounds and burns, and Persian traditional medicine documented honey to be effective in the treatment of wounds, eczema, and inflammation.[1,2]

Microorganisms have been associated with the pathophysiology of a range of dermatological disorders. Wound infections, for example, are commonly caused by the microorganisms *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, and infection with *S. aureus* is common in atopic dermatitis.[3,4] Another example is *Malassezia* yeasts, which have been associated with the skin conditions pityriasis versicolor, seborrheic dermatitis, atopic dermatitis, and psoriasis.[5] Conventional treatments for some of these conditions are unsatisfactory, e.g. corticosteroids cause skin thinning and UV radiation therapy has been associated with the development of skin cancer.[6]

Scientists first reported the ability of honey to kill disease-causing microbes in the late 1800s, but with the advent of antibiotics in the early 1900s, scientific interest in honey waned.[7] Today, with the emergence of antibiotic-resistant microbial strains, such as methicillin-resistant *S. aureus* (MRSA) – a cause of difficult-to-treat wound infections and a global health concern – honey has again caught the attention of medical researchers.[7,8]

In clinical practice today, Manuka honey produced by honey bees (*Apis mellifera*) collecting nectar from the Manuka tree (*Leptospermum scoparium*) is used topically in the management of wound infections.[9] Products include gamma-irradiated honey in gels, ointments, and impregnated dressings. Revamil honey is another medical-grade honey commonly used in clinical practice for wound care.[10] It is produced in greenhouses by manufacturers in The Netherlands, but further details about the origin of this honey have not been disclosed.

In this review, research findings on the antimicrobial activities of honeys from around the world, against skin relevant microbes, are evaluated. Furthermore, mechanisms of the antimicrobial properties of honey are explored. The principal aim was to understand more about the therapeutic potential of honey as a treatment option for skin diseases with a microbiological etiology.

Antimicrobial properties of Manuka honey against skin relevant microbes: *in vitro* studies

The most widely researched honey, to date, is Manuka honey from New Zealand. Studies have shown that Manuka honey has antimicrobial activity *in vitro* against the most common wound-infecting microorganisms, including MRSA, *S. aureus*, *P. aeruginosa*, and *E. coli*.[11,12] Manuka honey can also inhibit the growth of *Streptococcus pyogenes*, a cause of cellulitis, impetigo, and necrotizing fasciitis, and the dermatophyte *Trichophyton mentagrophyte*, a cause of ringworm.[11,13] Indeed, Manuka honey has been shown to inhibit the growth of a range of dermatophytes, including *Epidermophyton floccosum*, *Microsporum canis*, *Microsporum gypseum*, *Trichophyton rubrum*, and *Trichophyton tonsurans*, indicating that honey may be a therapeutic in the treatment of dermatophytosis (tinea infections).[13] Studies have reported that *Candida albicans* is more resistant to Manuka honey than many other microbial species.[14,15] Manuka honey has also been shown to have antiviral activity *in vitro* against varicella zoster virus, suggesting that honey may be a therapeutic for viral skin rashes.[16] The antiviral properties of honey against other skin relevant viruses such as human papilloma virus may be worth investigating.

As the antimicrobial activity of honey varies not only between different types of honey but also between batches of the same type of honey, Manuka honey is often ascribed a unique Manuka factor (UMF). The UMF is a measure of the strength of the antibacterial activity of the honey against *S. aureus* and is calculated based on the concentration of a phenol solution that gives a similar zone of growth inhibition, in a radial diffusion assay, to the honey being tested. A criticism of the UMF classification is that it is a measure of activity against *S. aureus* only and not against other relevant microbes.

Antimicrobial activity of honeys from around the world against skin relevant microbes: *in vitro* studies

A plethora of scientific papers have reported *in vitro* antimicrobial activity of honeys from all over the world; some examples are discussed in this section.

Honey produced in South Gondar, Ethiopia, by the bee *Apis mellipodae*, a stingless bee, is used in traditional medicine in Ethiopia to treat a variety of diseases including skin infections.[17] Using the method of agar well diffusion, Andualem[17] demonstrated that this honey inhibited the growth of the wound-infecting microbes *E. coli* and *S. aureus* with minimal inhibitory concentrations (MICs) of 12.5% and 6.25%, respectively.

In a study by Pimentel *et al*.,[18] honey samples collected from the stingless bee *Melipona compressipes manaosensis* in Manaus, Amazonas, Brazil, were active against *E. coli*, *S. aureus*, *Proteus vulgaris*, and *Klebsiella* species. Using agar well diffusion assays, it was demonstrated that honey collected during the rainy season inhibited the growth of *E. coli* only in the undiluted form, while honey collected during the dry season inhibited the growth of *E. coli*, *S. aureus*, and a range of other microbes at much more diluted concentrations. These results clearly show the influence of seasonality on the antibacterial activity of honey. Plant-derived factors or entomological factors such as the health of the bee colonies can be affected by seasons, with consequences for the antimicrobial activity of the honey produced. Researchers also compared the ability of honey to inhibit microbial growth evaluated by agar well diffusion with that assessed by a broth dilution assay, and found that the broth dilution assay was a more sensitive method, most likely due to better movement of the antimicrobial components of honey in liquid broth than in agar. Rutin, a flavonoid previously shown to have antibacterial activity, was identified in honey by high-performance liquid chromatography.

Kuncic et al.[19] reported that Slovenian honeys from diverse floral origins had antibacterial activity against *E. coli*, *P. aeruginosa*, and *S. aureus*. Slovenian chestnut and pasture honeys were found to be most active; for example, the MIC of the chestnut honey against *S. aureus* was found to be 2.5%. *C. albicans* was not inhibited by any of the Slovenian honeys tested, and *Candida parapsilosis* and *Candida tropicalis* were inhibited only by honey of concentrations higher than 50%.

In other studies, the growth of *C. albicans* was inhibited by Jujube honey, a honey obtained from bee keepers in Al-baha, Saudi Arabia, prepared by bees feeding on the plant *Ziziphus jujuba*, and by a mixture of honey, olive oil, and beeswax containing multifloral honey from the United Arab Emirates.[20,21] Such findings indicate the potential of some honeys for use in the treatment of skin disorders caused by *C. albicans* such as cutaneous candidiasis.

Tualang honey, obtained from bees (*Apis dorsata*) feeding on Tualang trees (*Koompassia excelsa*) in the jungles of Malaysia, was found to inhibit the growth of MRSA, *S. aureus*, *Streptococcus pyogenes*, *P. aeruginosa*, and *E. coli* in a broth dilution assay, with MICs comparable with those of Manuka honey.[11]

In 2013, researchers at Queen Margaret University, Edinburgh, Scotland, reported the antimicrobial activity of a Scottish honey, called Portobello honey.[22] Portobello honey was produced by honey bees in an apple orchard in Portobello, Edinburgh, Scotland. Five concentrations of the Portobello honey and medical-grade Manuka Honey (0%, 1%, 10%, 50%, and 70%) were tested against *S. aureus*, *P. aeruginosa*, and *E. coli* using agar disc diffusion and a broth dilution assay. The agar disc diffusion method did not demonstrate any antimicrobial activity of the honeys tested; however, it was reported that the honey remained on the surface of the disc and did not diffuse into the agar. The broth dilution assay, by contrast, demonstrated antimicrobial activity of Portobello and Manuka honeys at concentrations of 50% and 70%, which were found to inhibit the majority of all the bacterial species tested. The MIC of Portobello honey was not calculated, but the authors concluded that honey is a superior antibacterial agent.

In a study by Carnwath et al.,[23] the antimicrobial activities of a selection of 10 honeys against 10 microorganisms were tested at the Department of Veterinary Medicine, University of Glasgow, Scotland. The honeys tested included medical-grade and shop-bought Manuka honeys, Scottish heather honey (from a local bee-keeper), blossom honey, Vipers bugloss honey, Inverness floral honey, and Glasgow floral honey. The microorganisms tested included MRSA, *S. aureus*, *E. coli*, *P. aeruginosa*, and *Acinetobacter baumannii*. Serial dilutions of the honeys were prepared in distilled water and mixed with equal volumes of nutrient agar, to produce final honey concentrations ranging from 2% to 16%. Plates were inoculated with the appropriate microorganism and incubated aerobically overnight. All the honeys tested demonstrated antimicrobial activity, but the Scottish heather honey was found to be most active, which inhibited the growth of all the microorganisms tested, with MICs ranging from <2% to 6%. The Scottish heather honey was even more active than all the Manuka honeys used in the study.

Remarkably, *in vitro* research has also shown that honey can actually reverse antibiotic resistance, suggesting that honey used in combination with antibiotics may have additional therapeutic effects.[24] A suggested mechanism is via honey-induced downregulation of *mecR1* gene product, a transducer associated with antibiotic resistance in MRSA. Indeed, Muller et al.[25] reported that Manuka honey worked synergistically with the antibiotic rifampicin to inhibit the growth of MRSA and clinical isolates of *S. aureus*.

The evidence is clear that, in a laboratory setting, honeys from all over the world have potent antimicrobial activity against skin relevant microbes (Table 1). Indeed, the antimicrobial activity of honey from Iran has been shown to be comparable with that of the sulfonamide family of antibiotics.[26] The microorganism *S. aureus* is clearly inhibited by honeys of different floral origins. In addition to wound infections, *S. aureus* is an important cause of furuncles, styes, and impetigo. Honey has broad-spectrum antimicrobial properties; it may also have therapeutic value in the treatment of other skin disorders, in which microbes have been associated with the etiology of the disease, as well as those disorders that are commonly treated with topical antibiotics, e.g., acne. Analysis of the antimicrobial activity of different types of honey against other dermatologically relevant microbes should be encouraged.

Table 1. Activity of some honeys from around the world against common skin relevant microbes

Type of honey	MRSA	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Candida albicans*	Dermatophytes	*Malassezia* species	HPV
Manuka honey[a]	+[12]	+[11]	+[11,12]	+[11,12]	–[14,15]	+[13]	†	†
Scottish heather honey[b]	+[23]	+[23]	+[23]	+[23]	†	†	†	†
Portobello honey[b]	†	+[22]	+[22]	+[22]	†	†	†	†
Tualang honey[c]	+[11]	+[11,27]	+[11,27]	+[11,27]	†	†	†	†

Numbers in brackets are references.

HPV = human papilloma virus; MRSA = methicillin-resistant *S. aureus*; + = active; – not active or low activity; † = unknown.

[a] New Zealand.
[b] Scotland.
[c] Malaysia.

Antimicrobial properties of honey: *in vivo* human studies

The majority of studies to date have demonstrated the antimicrobial activity of honey against a range of microbial strains including clinical isolates, using *in vitro* antimicrobial assays. Fewer studies have demonstrated the antimicrobial activity of honey *in vivo*; studies carried out so far have mainly investigated the antimicrobial activity of honey in relation to wound infections. In the 1st decade of the 21st century, several case studies involving wound patients produced optimistic findings. A brief report by Cooper et al.[28] described how treatment of a *S. aureus*-infected, recalcitrant surgical wound in a 38-year-old female with Manuka honey-impregnated dressings and oral coamoxiclav resulted in significant healing of the wound and bacterial clearance 7 days after commencing the treatment. The wound was 3 years old, and had failed to respond to other conventional wound treatments and antibiotics during the 3-year period prior to commencing the honey/antibiotic combination therapy. Natarajan et al.[29] treated an MRSA-infected leg ulcer of an immunosuppressed patient with topical application of Manuka honey; consequently, MRSA was eradicated and the wound successfully healed. Chambers[30] reported bacterial clearance in three cases of MRSA-infected leg ulcers following treatment with topical Manuka honey, while Visavadia et al.[31] reported that Manuka honey, based on clinical experience, was now one of their first-line treatments for infected wounds at the Maxillofacial Unit at the Royal Surrey County Hospital, Guildford, Surrey.

Larger clinical studies have produced more controversial findings. Gethin and Cowman[32] recruited 108 patients with venous leg ulcers and treated them with either Manuka honey or hydrogel. In their study, Manuka honey successfully eliminated MRSA from 70% of MRSA-infected wounds; in comparison, hydrogel eradicated MRSA from only 16% of infected wounds. For *P. aeruginosa*-infected wounds, Manuka honey cleared infection in just 33% of wounds, whereas hydrogel cleared infection in 50% of wounds. Jull et al.,[33] in a randomized clinical trial of 368 participants, reported no significant difference in occurrence of infection in venous leg ulcers treated with either Manuka honey-impregnated dressings or usual care. Another clinical study showed no significant difference, in terms of development of peritoneal dialysis-related infections when patients undergoing peritoneal dialysis were treated with either Medihoney antibacterial wound gel (containing honey from *Leptospermum* species) or the topical antibiotic mupirocin applied to catheter exit sites.[34]

Antimicrobial properties of honey: *in vivo* animal studies

Antimicrobial effects of honey have been observed in animal studies *in vivo*. Al-Waili[35] reported that application of a natural honey from the United Arab Emirates to *S. aureus* or *Klebsiella* species-inoculated surgical wounds induced in mice reduced the time for bacterial elimination to occur. Khoo et al.[36] reported that Tualang honey was superior to hydrofiber and hydrofiber silver dressings in reducing the growth of bacteria in *P. aeruginosa*-inoculated burn wounds induced in Sprague Dawley rats. Conversely, hydrofiber and hydrofiber silver dressings were superior to Tualang honey in reducing bacterial growth in *A. baumannii*-inoculated wounds, while there was no significant difference between the three treatments in inhibiting the growth of bacteria in *Klebsiella pneumoniae*-inoculated wounds. Gunaldi et al.[37] investigated the antimicrobial activity of Manuka honey in clearing MRSA infection in MRSA-inoculated spinal implants inserted in rats. The results showed that while Manuka honey significantly reduced MRSA growth on the implants, it did not eradicate the MRSA entirely. In the vertebral column of the rats, MRSA growth was also reduced more in the Manuka honey-treated group compared to the control group, but this was not statistically significant.

It could be said that the research findings for the antimicrobial activity of honey *in vivo* have not been as "outstanding" as those observed *in vitro*, and the reasons for this require investigation. Human and animal cells are known to contain the enzyme catalase, an enzyme that breaks down hydrogen peroxide (an important antimicrobial component of some honeys) into hydrogen and oxygen. If the antimicrobial properties of honey are due to hydrogen peroxide, the antimicrobial activity may be reduced when honey comes into contact with live cells.[38] Innovative research that can overcome obstacles associated with *in vivo* use of honey is urgently required.

It is also important to consider that some honeys have been shown to be contaminated with bacteria and fungi, and therefore non-gamma-irradiated honeys may not be suitable for application on damaged skin.[23] The production of medical-grade honeys, suitable for use in clinical practice, from local honeys would be economically advantageous and beneficial to local communities.

Effects of honey on microbial pathogenicity of skin relevant microbes: *in vitro* studies

Incredibly, recent research has shown that the antimicrobial properties of honey *in vitro* are more than bactericidal because honey has also been shown to reduce bacterial pathogenicity. The ability of pathogenic microbes to cause diseases is partly due to the production of pathogenicity factors. *S. aureus*, for example, produces a range of disease-causing proteins, including catalase, hemolysins (α, β, γ, and δ), epidermolytic toxins, and enterotoxins. Alpha-toxin (α-hemolysin) causes tissue damage during wound infections by creating pores in host cell membranes, allowing the discharge of low-molecular-weight compounds, and by inducing cytokine production and apoptosis.

Recently, Jenkins et al.[39] reported that Manuka honey reduced the expression of α-toxin in MRSA. Expression of other virulence genes, quorum sensing genes, and genes associated with cell division was also reduced. Lee et al.[40] reported that three types of honeys (Korean acacia, Korean polyfloral, and American clover honeys) at a concentration as low as 0.5% significantly inhibited pathogenic *E. coli* O157:HA biofilm formation *in vitro*. Furthermore, low concentrations of the Korean acacia honey reduced the expression of curli genes (*csgBAC*), quorum sensing genes (AI-2 importer, indole biosynthesis), and virulence genes (*LEE* genes) in the bacterial strain. Kronda et al.[41] reported that sublethal concentrations of Manuka honey reduced siderophore production, a virulence factor that scavenges iron for bacterial growth, in clinical and nonclinical strains of *P. aeruginosa*. Manuka honey has also been shown to alter the structure of *P. aeruginosa*; scanning and transmission electron microscopy revealed changes in cell shape and cell lysis following incubation with honey.[42] A honey flavonoid extract was also found to alter membrane integrity and branching processes associated with virulence in *C. albicans*.[43]

In addition to the more commonly investigated wound pathogens, subinhibitory concentrations of Manuka honey and Slovakian honeys (Hawthorn, honeydew, and acacia) significantly inhibited *Proteus mirabilis* and *Enterobacter cloacae* biofilm formation *in vitro*.[44]

In vivo studies investigating the efficacy of sublethal concentrations of honey against biofilms would advance our knowledge of the ability of honey to modulate bacterial pathogenicity.

Antimicrobial mode of action of honey

The antimicrobial properties of honey have been attributed to its multiple components, including high sugar concentration, low pH, hydrogen peroxide (H_2O_2), methylglyoxal (MGO), antimicrobial peptide bee defensin-1, and other compounds such as polyphenols that have not been fully elucidated.

The high sugar concentration and low moisture content of honey cause osmotic stress to microbial cells, and low pH is unfavorable for the growth of many microorganisms. However, if a sugar solution with identical sugar components and pH to that of honey is prepared, the antimicrobial activity of the sugar solution is often considerably lower than that of honey, suggesting that other factors in the honey are responsible for its antimicrobial activity.[23]

Honey bees add an enzyme, called glucose oxidase, to the collected nectar during the honey-making process, which converts the glucose in the honey into hydrogen peroxide (H_2O_2) and gluconic acid. H_2O_2 is toxic to many microbes. During the ripening of honey, glucose oxidase is inactivated but regains its activity if the honey is diluted. In a study by Kwakman et al.,[10] it was found that Revamil honey produced 3.47 ± 0.25 mM H_2O_2 in 40% (v/v) honey after 24 hours, but no H_2O_2 was detectable in the Manuka honey they tested, suggesting that nonperoxide factors are responsible for the antimicrobial activity of Manuka honey.

Manuka honey has been shown to contain high levels of MGO, 44-fold higher than Revamil honey. MGO in Manuka honey is produced by the nonenzymatic conversion of dihydroxyacetone present at high concentrations in the nectar of *L. scoparium* flowers. The change occurs slowly during honey storage. Kwakman et al.[10] reported that neutralization of MGO in Manuka honey abolished the antimicrobial activity of the honey against *S. aureus*, but did not abolish the antimicrobial activity against *E. coli* and *P. aeruginosa*. The authors concluded that MGO is not fully responsible for Manuka honey's nonperoxide antimicrobial activity and that other components, possibly polyphenols, may be responsible.

Polyphenols derived from plant nectar are natural organic chemicals characterized by the presence of multiple phenol structural units. Many are antioxidants, e.g., flavonoids. The antibacterial properties of flavonoids have been attributed to the inhibition of bacterial energy metabolism, bacterial DNA gyrase, and cytoplasmic membrane function.[45] Researchers in New Zealand identified the polyphenol methyl syringate as the major component of the phenolic fraction of Manuka honey.[46] A novel glycoside of methyl syringate, named leptosin, was recently identified in Manuka honey, and its levels were found to correlate positively with the UMF.[47] Identification of phenolic compounds in honey may be important for the production of new antimicrobials, and therefore the analysis of the phenolic profile of active honeys should be encouraged. Combinations of polyphenols may be more effective, as they may act synergistically to inhibit microbial growth, or structural alteration of individual polyphenols can be employed to enhance antimicrobial activity.

Bee defensin-1 is an antimicrobial peptide that is part of the honey bee innate immune system. It is secreted by the hypopharyngeal gland of honey bees and can enter honey via bee saliva during the regurgitation process of honey making. Bee defensin-1 has a strong activity against Gram-positive bacteria including *S. aureus*. Kwakman et al.[48] identified bee defensin-1 in Revamil honey but not in Manuka honey.

Raw honey may also contain propolis, a substance composed of plant resins and used by bees to seal the hive. Scientific research has shown that propolis has antimicrobial properties.[49]

The research of Kwakman et al.[48] demonstrates the diversity and complexity of the antimicrobial components of different types of honeys. Analysis of the antimicrobial components of other active honeys will be important for a fuller understanding of their applicability in medicine.

It can be concluded from *in vitro* studies that honey has powerful antimicrobial activity against dermatologically relevant microbes. These findings are particularly promising in current times when the problem of antimicrobial drug resistance is considered a global crisis and the World Health Organization (2014)[50] has acknowledged the possibility of a postantibiotic era in which common infections can kill. Even more exciting are the *in vitro* findings that honey can reverse antimicrobial resistance and reduce microbial pathogenicity. Despite these optimistic findings *in vitro*, the use of honey in clinical practice today as an antimicrobial agent does not appear to have yet reached its full potential. Innovative research that can maximally exploit the antimicrobial properties of this natural substance and overcome obstacles associated with *in vivo* use may, in the future, lead to the production of an antimicrobial agent that is highly valued in clinical practice. Interestingly, no honey-resistant microbial strains have emerged to date, and this may be unlikely because of the multifactorial nature of the antimicrobial properties of honey. As honeys from diverse floral origins have been shown to have antimicrobial activity against a range of skin relevant microbes, research should continue to investigate the efficacy of honey in the treatment of other types of skin disorders where microbes have been implicated in the pathophysiology of the disease. There are countless varieties of honeys being produced worldwide, and some may have superior antimicrobial activities that are yet to be discovered.

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Pearson BTEC Level 3 Extended Diploma

Centre Number

Learner Registration Number

Applied Science

Unit 7: Contemporary Issues in Science

Part B

Tuesday 22 May 2018
Time: 2 hours 30 minutes

Paper Reference
31629H

You do not need any other materials.

Total Marks

Instructions

- Use **black** ink or ball-point pen.
- **Fill in the boxes** at the top of this page with your name, centre number and learner registration number.
- Answer **all** questions.
- Answer the questions in the spaces provided
  – *there may be more space than you need.*
- **Part A** will need to have been used in preparation for completion of **Part B**.
- **Part B** must be undertaken in a single sitting of 2 hours and 30 minutes in the assessment session timetabled by Pearson.
- **Part B** materials must be issued to learners for the specified session.
- **Part B** is specific to each series and this material must only be issued to learners who have been entered to undertake the task in the relevant series.
- **Part B** should be kept securely until the start of the 2 hour and 30 minute supervised assessment session.

Information

- The total mark for this paper is 50.
- The marks for **each** question are shown in brackets
  – *use this as a guide as to how much time to spend on each question.*
- The three articles are at the back of **Part B**.

Advice

- Read each question carefully before you start to answer it.
- Try to answer every question.
- Check your answers if you have time at the end.

Turn over ▶

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P 5 2 3 1 2 A 0 1 4 0

Pearson

Instructions to Teachers/Tutors and/or Invigilators

This paper must be read in conjunction with the unit information in the specification and the BTEC Nationals Instructions for Conducting External Assessments (ICEA) document. See the Pearson website for details.

Part B set task is undertaken under supervision in a single session of 2 hours and 30 minutes in the timetabled session. Centres may schedule a supervised rest break during the session.

Part B set task requires learners to apply understanding gained through familiarisation with the articles. Learners should bring in notes as defined in **Part A**.

Learners must complete the set task using this task and answer booklet.

Maintaining security

- Only permitted materials for the set task can be brought into the supervised environment.
- During any permitted break and at the end of the session materials must be kept securely and no items removed from the supervised environment.
- Learner notes related to **Part A** must be checked to ensure length and contents meet limitations.
- Learner notes from **Part A** will be retained securely by the centre after **Part B** and may be requested by Pearson if there is suspected malpractice.

After the session, the teacher/tutor and/or invigilator will confirm that all learner work was completed independently as part of the authentication submitted to Pearson.

Outcomes for submission

This task and answer booklet should be submitted to Pearson.

Each learner must complete an authentication sheet.

Instructions for Learners

Read the set task information carefully.

Complete all your work in this taskbook in the spaces provided**.**

This session is of 2 hours 30 minutes (during the day). Your tutor/invigilator will tell you if there is a supervised break. Plan your time carefully.

You have prepared for the set task given in this **Part B** booklet. Use your notes prepared during **Part A** if relevant. Attempt all of the questions in **Part B**.

Your notes must be your own work and will be retained by your centre until results are issued.

You will complete this set task under supervision and your work will be kept securely during any breaks taken.

You must work independently throughout the supervised assessment period and should not share your work with other learners.

Outcomes for submission

You will need to submit the following on completion of the supervised assessment period:

- a completed **Part B** taskbook.

You must complete a declaration that the work you submit is your own.

Set Task

Answer ALL questions. Write your answers in the spaces provided.

1 Discuss the implications of the scientific issue identified in the articles.

(12)

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(Total for Question 1 = 12 marks)

2 Identify the different organisations/individuals mentioned in the articles and suggest how they may have an influence on the scientific issue.

(6)

(Total for Question 2 = 6 marks)

3 Discuss whether article 3 has made valid judgements.

In your answer you should consider:

- how the article has interpreted and analysed the scientific information to support the conclusions/judgments being made
- the validity and reliability of data
- references to other sources of information.

(12)

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(Total for Question 3 = 12 marks)

4 Suggest potential areas for further development and/or research of the scientific issue from the three articles.

(5)

(Total for Question 4 = 5 marks)

5 You are an infection control nurse.

You have been asked to raise awareness among district nurses of the problem with antibiotic-resistant microbes that cause skin (topical) infections such as leg ulcers.

One of the roles of a district nurse is to visit the homes of elderly patients to change their medical dressings for skin infections such as leg ulcers.

Your task is to write an article for district nurses about the possible benefits and limitations of using medical grade honey dressings to treat skin infections.

Use information from the three articles provided for this task.

When writing your article you should consider:

- who is likely to read the article
- what you would like the reader to learn from the article.

(15)

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Part A Set Task Information

Article 1

Extract from 'Doling out too many antibiotics "will make even scratches deadly": WHO warns that crisis could be worse than AIDS'

This is an edited version of an article that appeared in the 'Daily Mail' newspaper in April 2014.

- Spread of deadly superbugs that evade antibiotics is happening globally
- It's now a major threat to public health, the World Health Organisation (WHO) says
- It could mean minor injuries and common infections become fatal

Deaths from cuts and grazes, diarrhoea and flu will soon be common as antibiotics lose their power to fight minor infections, experts have warned.

The World Health Organisation says the problem has been caused by antibiotics being so widely prescribed that bacteria have begun to evolve and develop resistance.

It claims the crisis is worse than the AIDS epidemic – which has caused 25 million deaths worldwide – and threatens to turn the clock back on modern medicine.

The WHO warns that the public should 'anticipate many more deaths' as it may become routine for children to develop lethal infections from minor grazes, while hospital operations become deadly as patients are at risk of developing infections that were previously treatable.

Doctors are increasingly finding that antibiotics no longer work against urinary and skin infections, tuberculosis and gonorrhoea.

The WHO is urging the public to take simple precautions, such as washing hands to prevent bacteria from spreading in the first place.

Doctors are also being told to prescribe antibiotics sparingly and ensure patients finish the full course, as if they stop mid-way the bacteria may become resistant. In England last year some 41.7million prescriptions were written out, up from 37.2million in 2006.

Dr Keiji Fukuda, the WHO's assistant director for health security, said: 'Without urgent, co-ordinated action, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill.

SUPERBUGS: THE GUIDE TO BUGS RENDERING ANTIBIOTICS OBSOLETE

MRSA - patients infected with MRSA (methicillin-resistant Staphylococcus aureus) are 64 per cent more likely to die than those with a non-resistant form of S. aureus.

People infected by resistant superbugs are also likely to stay longer in hospital and may need intensive care, pushing up costs.

C. difficile - this bacteria produces spores that are resistant to high temperatures and are very difficult to eliminate. It is spread through contaminated food and objects and can cause blood poisoning and tears in the large intestine.

E. coli - this now accounts for one in three cases of bacterial infections in the blood in the UK and a new strain is resistant to most antibiotics. It is highly contagious and could cause more than 3,000 deaths a year.

Acinetobacter Baumannii - a common bacteria which is resistant to most antibiotics and which can easily infect patients in a hospital. It can cause meningitis and is fatal in about 80 per cent of patients.

CRKP - this is a bacterium that is associated with extremely difficult to treat blood infections and meningitis. It is resistant to nearly all antibiotics and is fatal in 50 per cent of cases.

Multi-drug resistant tuberculosis is estimated to kill 150,000 people globally each year.

NDM-1 - a bacteria detected in India of which some strains are resistant to all antibiotics.

'Effective antibiotics have been one of the pillars allowing us to live longer, live healthier, and benefit from modern medicine.'

Unless we take significant actions to improve efforts to prevent infections, and also change how we produce, prescribe and use antibiotics, the world will lose more and more of these global public health goods and the implications will be devastating.

'We should anticipate to see many more deaths.

'We are going to see people who have untreatable infections.'

Only last month, Britain's chief medical officer Dame Sally Davies criticised GPs for needlessly 'dishing out' antibiotics to patients.

In the largest study of its kind, the WHO looked at data from 114 countries on seven major types of bacteria. Experts are particularly concerned about bacteria responsible for pneumonia, urinary tract infections, skin infections, diarrhoea and gonorrhoea.

They are also worried that antiviral medicines are becoming increasingly less effective against flu.

Dr Danilo Lo Fo Wong, a senior adviser at the WHO, said: 'A child falling off their bike and developing a fatal infection would be a freak occurrence in the UK, but that is where we are heading.'

THE COUPLE WHO LOST BABY TO INFECTION AFTER SUPERBUG OUTBREAK

The human cost of the rising number of superbugs is becoming all too familiar.

Distraught young couple Jenna and Andrew Hannon lost their second son to an infection at a hospital neo-natal unit in Bristol.

Little Oliver was born early at 24 weeks and although he had seemed well enough to go home with his parents, he soon fell dangerously ill.

He was taken to Southmead Hospital but the infection had taken hold and the youngster passed away.

Tragically the couple had lost another prematurely born son, Travis, to infection in 2010, just five-and-a-half hours after his birth at 26 weeks. An inquest into Oliver's death later found he had been killed by the pseudomonas bacteria. He was one of three babies in the hospital to be hit by the killer bacteria, which was later linked to baby deaths around the country.

An investigation took place at the hospital into Oliver's death, but it could not find what caused his infection.

The inquest was told that Oliver was being given two types of antibiotics before he died as a precaution, but neither specifically fought pseudomonas.

As a result of the investigation the hospital also now uses antibiotics which more specifically target the bacteria.

British experts likened the problem to the AIDS epidemic of the 1980s. Professor Laura Piddock, who specialises in microbiology at the University of Birmingham, said: 'The world needs to respond as it did to the AIDS crisis.

'We still need a better understanding of all aspects of resistance as well as new discovery, research and development of new antibiotics.'

The first antibiotic, penicillin, was developed by Sir Alexander Fleming in 1929. But their use has soared since the 1960s, and in 1998 the Government issued guidelines to doctors urging them to curb prescriptions. Nonetheless, surveys suggest they are still prescribed for 80 per cent of coughs, colds and sore throats.

Link to video: WHO warns antibiotic-resistant bacteria is spreading.
www.dailymail.co.uk/embed/video/1093014.html

Jennifer Cohn of the international medical charity Médecins Sans Frontières agreed with the WHO's assessment and confirmed the problem had spread to many corners of the world.

'We see horrendous rates of antibiotic resistance wherever we look in our field operations, including children admitted to nutritional centres in Niger, and people in our surgical and trauma units in Syria,' she said.

Earlier this month, Government body NICE said that one in 16 patients are developing infections on NHS wards because of poor hygiene among staff.

NICE said 800 patients a day, the equivalent of 300,000 a year, are infected by a member of staff or by dirty equipment. It is estimated the infections cause 5,000 deaths annually and contribute to another 15,000.

WHAT CAUSES ANTIBIOTIC RESISTANCE?

Antibiotics are substances that kill or interfere with the growth of microorganisms, especially bacteria. But not all microorganisms are susceptible to all antibiotics, according to Public Health England.

Microorganisms which are not killed or inhibited by an antibiotic are called 'antibiotic resistant'.

They continue to grow and multiply in the presence of that antibiotics.

There are several ways in which bacteria can be resistant. Some destroy the antibiotic, for example by producing enzymes against it; some prevent the antibiotic getting into their cells; others get the antibiotic out of their cells before it can harm them.

HOW DOES RESISTANCE DEVELOP?

Some bacteria are naturally resistant; new resistances also arise spontaneously by chance mutations and these resistant strains then multiply.

Some resistances can be passed from one bacterium to another, spreading resistance between species. Loops of DNA (called plasmids) carry the resistance genes from one bacterium to another.

When an antibiotic is given, it kills the sensitive bacteria, but any resistant ones can survive and multiply.

The more antibiotics are used (in animals and agriculture as well as in man) the greater will be the "selective pressure", favouring resistant strains - i.e. survival of the fittest.

Antibiotics don't 'cause' resistance; rather, they create an environment which favours the growth of resistant variants which already exist in nature or arise by chance.

Article 2

Extract from 'Antimicrobial resistance - a global epidemic'

This is an edited version of an article prepared by the secretariats of WHO, WIPO and WTO.

Not an expert in AMR? Watch this 5-minutes video explaining the most important facts: https://www.youtube.com/watch?v=xZbcwi7SfZE

Antimicrobial resistance (AMR) occurs when bacteria, parasites, viruses and fungi become resistant to antimicrobial drugs that are used for treating the infections they cause. Every time an antimicrobial medicine is used, it diminishes the effectiveness for all users, because its usage increases the possibility for the bacteria to become resistant. Antimicrobial resistance threatens the effective prevention and treatment of an increasing range of infections, including blood poisoning, pneumonia, diarrhoea, gonorrhoea, tuberculosis, HIV/AIDS and malaria.

Resistance against antibiotics (medicines used to prevent and treat bacterial infections) is an urgent problem because antibiotics are a cornerstone of modern medicine and most medicinal procedures in human and animal health rely on functioning antibiotics.

What causes antimicrobial resistance?

Antimicrobial resistance is mainly driven by inappropriate use. Global antibiotic consumption in humans has increased by 36% between 2000 and 2010. Half of this increased use is regarded as unnecessary, e.g. when antibiotics are used to treat illnesses like common colds that are caused by viruses, where antibiotics have no effect. In many countries, antibiotics can be bought without prescription or do not have underlying standard treatment guidelines. These factors increase antibiotic resistance because of a lack of knowledge of proper antibiotic use.

The problem of resistance is not only evident in human medicine consumption. Antibiotics are also used in veterinary medicine, for growth promotion in animals and disease prevention in agriculture, aquaculture and horticulture. In the US, for example, more than 70% of antibiotics are used in agricultural production, primarily for growth promotion and prophylaxis. Worldwide consumption in animals is estimated to rise by 67% from 63,151 tons in 2010 to 105,596 tons in 2030.

How does resistance develop?

Resistant bacteria can be transmitted to humans through various channels such as the food chain, animal-to-human contact, and the environment.

Globalization fuels the spread of antimicrobial resistance where transmission is facilitated by increased trade, travel and both human and animal migration. Travellers often carry home resistant bacteria from holidays or business trips. An example of globalization fuelling the spread of antimicrobial resistance is seen in the strain of bacteria resistant to the antibiotic colistin. Colistin is widely used in Chinese livestock which has likely led the bacteria to evolve, gain resistance and transmit from livestock to humans through food. This strain was reported earlier this year in the US and Europe. This example shows that antimicrobial resistance cannot be tackled in isolation by individual countries but needs global cooperation.

Why is antimicrobial resistance a problem?

Antimicrobial resistance affects high-, low- and middle-income countries. There are particular diseases that have higher rates of antimicrobial resistance such as tuberculosis and gonorrhoea. Recent global estimates in 2013 reveal 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB) with extensively drug-resistant tuberculosis (XDR-TB) present in 100 countries. Further, there are treatment failures as a result of resistance to treatments of last resort for diseases such as gonorrhoea. Consequently, there is a risk that gonorrhoea may become untreatable if no vaccines or new treatments are being developed.

A reliable estimate of the global burden of antimicrobial resistance is difficult to obtain as data is not systematically and consistently collected. However, estimates from Europe indicate that the excess mortality due to resistant bacteria in hospital infections exceeds 25,000 annually, with annual costs of at least €1.5 billion. Outpatient data from the US indicates more than 63,000 deaths annually due to resistant bacterial infections.

A combination of having less developed health systems, higher rates of infectious diseases and low quality and improper use of antibiotics, among other factors, increases the burden of antimicrobial resistance in low- and middle-income countries. For example, the crude infectious disease mortality rate in India is 416.75 per 100,000 persons with bacterial resistance increasing over time. Between 2008 and 2013, E. coli resistance to a type of antibiotics – a third-generation cephalosporins – increased from 70% to 83%. This highlights the increasing burden of antimicrobial resistance in developing countries.

Additionally, antimicrobial resistance causes extra health care cost and leads to loss of productivity. Patients with resistant infections are more expensive and difficult to treat and are more likely to require longer hospitalisation than patients infected with drug susceptible strains. As a consequence, antimicrobial resistance has major economic costs, estimated at $55 billion annually in the US alone. The World Economic Forum annual risk report has been listing the spread of infectious diseases – including the rise of resistant pathogens – among the high-impact risks to the global economy.

Although resistant strains of bacteria are not a new phenomenon, increased speed of resistance to antimicrobial medicines and especially to last resort antibiotics for some bacterial infections has turned antimicrobial resistance into one of the greatest threats for human health. In a post-antibiotic era, common infections and minor injuries can be fatal. This is far from being an apocalyptic fantasy, but a very real possibility for the 21st Century.

What are measures against antimicrobial resistance?

There are a number of possible measures against antimicrobial resistance including improvement of hygiene, infection control to prevent spread of resistant bacteria, development of new antimicrobials against which bacteria are not resistant, improved conservation efforts to maintain the effectiveness of new antimicrobials and of existing drugs.

Stewardship, innovation and access are three key objectives in addressing antimicrobial resistance.

Stewardship

Stewardship describes the careful and responsible management of resources entrusted to one's care. With respect to antimicrobials, stewardship refers to appropriate antimicrobial treatment to improve patient outcomes while minimizing the development and spread of resistance.

While access to effective antimicrobials is a prerequisite for productive and sustainable agriculture, in particular in relation to animal husbandry, antibiotics have to be used with more responsibility. Therefore, effective stewardship in tackling antimicrobial resistance requires a global multidisciplinary collaborative effort across industries.

Innovation

There is a severe lack of investment in new medicines against microbes. The market-based innovation system has insufficient incentives because the return on investment in antibiotic research is too small to attract the required R&D investments. The low return on investment can be explained by a number of factors. Antibiotics have a short treatment course compared to medications for chronic diseases which leads to lower treatment costs. Additionally, while new antibiotics are needed, they will face competition with existing generic products. Fostering appropriate use can also mean that new antibiotics are only used very conservatively to delay resistance building as much as possible which will diminish the revenue that the inventor can generate. These and other factors have led to minimal antibiotics breakthroughs since the 1980s and increased on-going concern about the lack of new products in the pipeline.

New innovative and comprehensive incentive initiatives are needed to complement the existing innovation model to foster the development of new antibiotics. This could include a mixture of push mechanisms (e.g. grants for basic research and clinical trials, product development partnerships), pull incentives (e.g. milestone prizes or market entry rewards) and regulatory measures (e.g. specific regulatory pathways). All these market measures have to factor in the public health objectives of antibiotic conservation and access.

Access

The problem of infectious diseases and antibiotic use plays out very differently across the globe. Certain countries are less exposed to the problem than others because of successful infection control programmes in hospitals. Further, while some countries experience overuse, many people still lack access to antibiotics, and more people die because of this lack than of resistant infections. Despite an increase in worldwide antibiotic consumption, lack of access even to affordable generics remains a huge problem in many countries.

Pneumonia accounts for 15% of all deaths of children under 5 years old, killing an estimated 922,000 children in 2015. Only one-third of children with bacterial pneumonia receive the antibiotics they need.

Antibiotics protected by patents will often have a higher price, which constrains access. One option to overcome this barrier is using delinkage in the development of new antibiotics as described above. Voluntary licensing agreements have emerged as a tool that has helped improve affordable access to patented medicines for HIV/AIDS and hepatitis.

In the long run, building strong health systems is the most sustainable approach to ensuring affordable access to good-quality essential medicines, including antimicrobial medicines and vaccines, as well as diagnostics and other vital interventions.

Increased international attention

WHO adopted the Global Action Plan on Antimicrobial Resistance (GAP-AMR) in 2015. The plan focuses on a comprehensive approach meaning that actions in all relevant sectors should be implemented synergistically. To tackle antimicrobial resistance, the global action plan sets out five strategic objectives:

- to improve awareness and understanding of antimicrobial resistance;
- to strengthen knowledge through surveillance and research;
- to reduce the incidence of infection;
- to optimize the use of antimicrobial agents; and
- to develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The GAP-AMR has been endorsed through resolutions by both the Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OiE).

In addition to the GAP-AMR, the World Health Assembly in 2016 discussed options for a global development and stewardship framework on antimicrobial resistance. The purpose of such a possible framework would be to add value and achieve strategic objectives identified in the GAP-AMR focusing on:

- preservation of antimicrobial medicines through a stewardship framework covering control, distribution and appropriate use;
- development of new health technologies for preventing and controlling antimicrobial resistance; and
- promotion of affordable access to existing and new antimicrobial medicines and diagnostic tools.

Antimicrobial resistance will be discussed at the United Nations General Assembly's 71st session in September 2016 in New York.

While antimicrobial resistance affects every country, each country should take actions that address the needs and capabilities of their health system to preserve global antibiotic resources.

Antimicrobial resistance is a multi-faceted global issue requiring a shared responsibility by all countries to protect citizen health and combat the global threat posed by AMR.

Article 3

Extract from 'Honey: A realistic antimicrobial for disorders of the skin'

This is an edited version of an article that appeared in volume 49, issue 2 of the Journal of Microbiology, Immunology and Infection in April 2016. The article was written by Pauline McLoone, Mary Warnock and Lorna Fyfe.

Resistance of pathogenic microorganisms to antibiotics is a serious global health concern. In this review, research investigating the antimicrobial properties of honeys from around the world against skin relevant microbes is evaluated. A plethora of *in vitro* studies have revealed that honeys from all over the world have potent microbicidal activity against dermatologically important microbes. Moreover, *in vitro* studies have shown that honey can reduce microbial pathogenicity as well as reverse antimicrobial resistance. Studies investigating the antimicrobial properties of honey *in vivo* have been more controversial. It is evident that innovative research is required to exploit the antimicrobial properties of honey for clinical use and to determine the efficacy of honey in the treatment of a range of skin disorders with a microbiological etiology.

Introduction

In traditional medicine, honey has been recognized around the world for its skin-healing properties. The ancient Greeks and Egyptians, for example, used topical application of honey to treat skin wounds and burns, and Persian traditional medicine documented honey to be effective in the treatment of wounds, eczema, and inflammation.[1, 2]

Microorganisms have been associated with the pathophysiology of a range of dermatological disorders. Wound infections, for example, are commonly caused by the microorganisms *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli*, and infection with *S. aureus* is common in atopic dermatitis.[3,4] Another example is *Malassezia* yeasts, which have been associated with the skin conditions pityriasis versicolor, seborrheic dermatitis, atopic dermatitis, and psoriasis.[5] Conventional treatments for some of these conditions are unsatisfactory, e.g., corticosteroids cause skin thinning and UV radiation therapy has been associated with the development of skin cancer.[6]

Scientists first reported the ability of honey to kill disease-causing microbes in the late 1800s, but with the advent of antibiotics in the early 1900s, scientific interest in honey waned.[7] Today, with the emergence of antibiotic-resistant microbial strains, such as methicillin-resistant *S. aureus* (MRSA)—a cause of difficult-to-treat wound infections and a global health concern, honey has again caught the attention of medical researchers.[7,8]

In clinical practice today, Manuka honey produced by honey bees (*Apis mellifera*) collecting nectar from the Manuka tree (*Leptospermum scoparium*) is used topically in the management of wound infections.[9] Products include gamma-irradiated honey in gels, ointments, and impregnated dressings. Revamil honey is another medical-grade honey commonly used in clinical practice for wound care.[10] It is produced in greenhouses by manufacturers in The Netherlands, but further details about the origin of this honey have not been disclosed.

In this review, research findings on the antimicrobial activities of honeys from around the world, against skin relevant microbes, are evaluated. Furthermore, mechanisms of the antimicrobial properties of honey are explored. The principal aim was to understand more about the therapeutic potential of honey as a treatment option for skin diseases with a microbiological etiology.

Antimicrobial properties of Manuka honey against skin relevant microbes: *in vitro* studies

The most widely researched honey, to date, is Manuka honey from New Zealand. Studies have shown that Manuka honey has antimicrobial activity *in vitro* against the most common wound-infecting microorganisms, including MRSA, *S. aureus, P. aeruginosa*, and *E. coli*.[11,12] Manuka honey can also inhibit the growth of *Streptococcus pyogenes*, a cause of cellulitis, impetigo, and necrotizing fasciitis, and the dermatophyte *Trichophyton mentagrophyte*, a cause of ringworm.[11,13] Indeed, Manuka honey has been shown to inhibit the growth of a range of dermatophytes, including *Epidermophyton floccosum, Microsporum canis, Microsporum gypseum, Trichophyton rubrum*, and *Trichophyton tonsurans*, indicating that honey may be a therapeutic in the treatment of dermatophytosis (tinea infections).[13] Studies have reported that *Candida albicans* is more resistant to Manuka honey than many other microbial species.[14,15] Manuka honey has also been shown to have antiviral activity *in vitro* against varicella zoster virus, suggesting that honey may be a therapeutic for viral skin rashes.[16] The antiviral properties of honey against other skin relevant viruses such as human papilloma virus may be worth investigating.

As the antimicrobial activity of honey varies not only between different types of honey but also between batches of the same type of honey, Manuka honey is often ascribed a unique Manuka factor (UMF). The UMF is a measure of the strength of the antibacterial activity of the honey against *S. aureus* and is calculated based on the concentration of a phenol solution that gives a similar zone of growth inhibition, in a radial diffusion assay, to the honey being tested. A criticism of the UMF classification is that it is a measure of activity against *S. aureus* only and not against other relevant microbes.

Antimicrobial activity of honeys from around the world against skin relevant microbes: *in vitro* studies

A plethora of scientific papers have reported *in vitro* antimicrobial activity of honeys from all over the world; some examples are discussed in this section.

Honey produced in South Gondar, Ethiopia, by the bee *Apis mellipodae*, a stingless bee, is used in traditional medicine in Ethiopia to treat a variety of diseases including skin infections.[17] Using the method of agar well diffusion, Andualem[17] demonstrated that this honey inhibited the growth of the wound-infecting microbes *E. coli* and *S. aureus* with minimal inhibitory concentrations (MICs) of 12.5% and 6.25%, respectively.

In a study by Pimentel et al,18 honey samples collected from the stingless bee *Melipona compressipes manaosensis* in Manaus, Amazonas, Brazil, were active against *E. coli, S. aureus, Proteus vulgaris*, and *Klebsiella* species. Using agar well diffusion assays, it was demonstrated that honey collected during the rainy season inhibited the growth of *E. coli* only in the undiluted form, while honey collected during the dry season inhibited the growth of *E. coli, S. aureus*, and a range of other microbes at much more diluted concentrations. These results clearly show the influence of seasonality on the antibacterial activity of honey. Plant-derived factors or entomological factors such as the health of the bee colonies can be affected by seasons, with consequences for the antimicrobial activity of the honey produced. Researchers also compared the ability of honey to inhibit microbial growth evaluated by agar well diffusion with that assessed by a broth dilution assay, and found that the broth dilution assay was a more sensitive method, most likely due to better movement of the antimicrobial components of honey in liquid broth than in agar. Rutin, a flavonoid previously shown to have antibacterial activity, was identified in honey by high-performance liquid chromatography.

Kuncic et al[19] reported that Slovenian honeys from diverse floral origins had antibacterial activity against *E. coli, P. aeruginosa*, and *S. aureus*. Slovenian chestnut and pasture honeys were found to be most active; for example, the MIC of the chestnut honey against *S. aureus* was found to be 2.5%. *C. albicans* was not inhibited by any of the Slovenian honeys tested, and *Candida parapsilosis* and *Candida tropicalis* were inhibited only by honey of concentrations higher than 50%.

In other studies, the growth of *C. albicans* was inhibited by Jujube honey, a honey obtained from bee keepers in Al-baha, Saudi Arabia, prepared by bees feeding on the plant *Ziziphus jujuba*, and by a mixture of honey, olive oil, and beeswax containing multifloral honey from the United Arab Emirates.[20,21] Such findings indicate the potential of some honeys for use in the treatment of skin disorders caused by *C. albicans* such as cutaneous candidiasis.

Tualang honey, obtained from bees (*Apis dorsata*) feeding on Tualang trees (*Koompassia excelsa*) in the jungles of Malaysia, was found to inhibit the growth of MRSA, *S. aureus, Streptococcus pyogenes, P. aeruginosa*, and *E. coli* in a broth dilution assay, with MICs comparable with those of Manuka honey.[11]

In 2013, researchers at Queen Margaret University, Edinburgh, Scotland, reported the antimicrobial activity of a Scottish honey, called Portobello honey.[22] Portobello honey was produced by honey bees in an apple orchard in Portobello, Edinburgh, Scotland. Five concentrations of the Portobello honey and medical-grade Manuka Honey (0%, 1%, 10%, 50%, and 70%) were tested against *S. aureus, P. aeruginosa*, and *E. Coli* using agar disc diffusion and a broth dilution assay. The agar disc diffusion method did not demonstrate any antimicrobial activity of the honeys tested; however, it was reported that the honey remained on the surface of the disc and did not diffuse into the agar. The broth dilution assay, by contrast, demonstrated antimicrobial activity of Portobello and Manuka honeys at concentrations of 50% and 70%, which were found to inhibit the majority of all the bacterial species tested. The MIC of Portobello honey was not calculated, but the authors concluded that honey is a superior antibacterial agent.

In a study by Carnwath et al.,[23] the antimicrobial activities of a selection of 10 honeys against 10 microorganisms were tested at the Department of Veterinary Medicine, University of Glasgow, Scotland. The honeys tested included medical-grade and shop-bought Manuka honeys, Scottish heather honey (from a local bee keeper), blossom honey, Vipers bugloss honey, Inverness floral honey, and Glasgow floral honey. The microorganisms tested included MRSA, *S. aureus, E. coli, P. aeruginosa*, and *Acinetobacter baumannii*. Serial dilutions of the honeys were prepared in distilled water and mixed with equal volumes of nutrient agar, to produce final honey concentrations ranging from 2% to 16%. Plates were inoculated with the appropriate microorganism and incubated aerobically overnight. All the honeys tested demonstrated antimicrobial activity, but the Scottish heather honey was found to be most active, which inhibited the growth of all the microorganisms tested, with MICs ranging from <2% to 6%. The Scottish heather honey was even more active than all the Manuka honeys used in the study.

Remarkably, *in vitro* research has also shown that honey can actually reverse antibiotic resistance, suggesting that honey used in combination with antibiotics may have additional therapeutic effects.[24] A suggested mechanism is via honey-induced downregulation of *mecR1* gene product, a transducer associated with antibiotic resistance in MRSA. Indeed, Muller et al[25] reported that Manuka honey worked synergistically with the antibiotic rifampicin to inhibit the growth of MRSA and clinical isolates of *S. aureus*.

The evidence is clear that, in a laboratory setting, honeys from all over the world have potent antimicrobial activity against skin relevant microbes (Table 1). Indeed, the antimicrobial activity of honey from Iran has been shown to be comparable with that of the sulfonamide family of antibiotics.[26] The microorganism *S. aureus* is clearly inhibited by honeys of different floral origins. In addition to wound infections, *S. aureus* is an important cause of furuncles, styes, and impetigo. Honey has broad-spectrum antimicrobial properties; it may also have therapeutic value in the treatment of other skin disorders, in which microbes have been associated with the etiology of the disease, as well as those disorders that are commonly treated with topical antibiotics, e.g., acne. Analysis of the antimicrobial activity of different types of honeys against other dermatologically relevant microbes should be encouraged.

Table 1.
Activity of some honeys from around the world against common skin relevant microbes

Type of honey	MRSA	Staphylococcus aureus	Pseudomonas aeruginosa	Escherichia coli	Candida albicans	Dermatophytes	Malassezia species	HPV
Manuka honey[a]	+[12]	+[11]	+[11,12]	+[11,12]	–[14,15]	+[13]	†	†
Scottish heather honey[b]	+[23]	+[23]	+[23]	+[23]	†	†	†	†
Portobello honey[b]	†	+[22]	+[22]	+[22]	†	†	†	†
Tualang honey[c]	+[11]	+[11,27]	+[11,27]	+[11,27]	†	†	†	†

Numbers in brackets are references.

HPV = human papilloma virus; MRSA = methicillin-resistant *S. aureus*; + = active; –not active or low activity; † = unknown.

a New Zealand.
b Scotland.
c Malaysia.

Antimicrobial properties of honey: *in vivo* human studies

The majority of studies to date have demonstrated the antimicrobial activity of honey against a range of microbial strains including clinical isolates, using *in vitro* antimicrobial assays. Fewer studies have demonstrated the antimicrobial activity of honey *in vivo*; studies carried out so far have mainly investigated the antimicrobial activity of honey in relation to wound infections. In the 1st decade of the 21st century, several case studies involving wound patients produced optimistic findings. A brief report by Cooper et al[28] described how treatment of a *S. aureus*-infected, recalcitrant surgical wound in a 38-year-old female with Manuka honey-impregnated dressings and oral coamoxiclav resulted in significant healing of the wound and bacterial clearance 7 days after commencing the treatment. The wound was 3 years old, and had failed to respond to other conventional wound treatments and antibiotics during the 3-year period prior to commencing the honey/antibiotic combination therapy. Natarajan et al[29] treated an MRSA-infected leg ulcer of an immunosuppressed patient with topical application of Manuka honey; consequently, MRSA was eradicated and the wound successfully healed. Chambers[30] reported bacterial clearance in three cases of MRSA-infected leg ulcers following treatment with topical Manuka honey, while Visavadia et al[31] reported that Manuka honey, based on clinical experience, was now one of their first-line treatments for infected wounds at the Maxillofacial Unit at the Royal Surrey County Hospital, Guildford, Surrey.

Larger clinical studies have produced more controversial findings. Gethin and Cowman[32] recruited 108 patients with venous leg ulcers and treated them with either Manuka honey or hydrogel. In their study, Manuka honey successfully eliminated MRSA from 70% of MRSA-infected wounds; in comparison, hydrogel eradicated MRSA from only 16% of infected wounds. For *P. aeruginosa*-infected wounds, Manuka honey cleared infection in just 33% of wounds, whereas hydrogel cleared infection in 50% of wounds. Jull et al,[33] in a randomized clinical trial of 368 participants, reported no significant difference in occurrence of infection in venous leg ulcers treated with either Manuka honey-impregnated dressings or usual care. Another clinical study showed no significant difference, in terms of development of peritoneal dialysis-related infections when patients undergoing peritoneal dialysis were treated with either Medihoney antibacterial wound gel (containing honey from *Leptospermum* species) or the topical antibiotic mupirocin applied to catheter exit sites.[34]

Antimicrobial properties of honey: *in vivo* animal studies

Antimicrobial effects of honey have been observed in animal studies *in vivo*. Al-Waili[35] reported that application of a natural honey from the United Arab Emirates to *S. aureus* or *Klebsiella* species-inoculated surgical wounds induced in mice reduced the time for bacterial elimination to occur. Khoo et al[36] reported that Tualang honey was superior to hydrofiber and hydrofiber silver dressings in reducing the growth of bacteria in *P. aeruginosa*-inoculated burn wounds induced in Sprague Dawley rats. Conversely, hydrofiber and hydrofiber silver dressings were superior to Tualang honey in reducing bacterial growth in *A. baumannii*-inoculated wounds, while there was no significant difference between the three treatments in inhibiting the growth of bacteria in *Klebsiella pneumoniae*-inoculated wounds. Gunaldi et al[37] investigated the antimicrobial activity of Manuka honey in clearing MRSA infection in MRSA-inoculated spinal implants inserted in rats. The results showed that while Manuka honey significantly reduced MRSA growth on the implants, it did not eradicate the MRSA entirely. In the vertebral column of the rats, MRSA growth was also reduced more in the Manuka honey-treated group compared to the control group, but this was not statistically significant.

It could be said that the research findings for the antimicrobial activity of honey *in vivo* have not been as "outstanding" as those observed *in vitro*, and the reasons for this require investigation. Human and animal cells are known to contain the enzyme catalase, an enzyme that breaks down hydrogen peroxide (an important antimicrobial component of some honeys) into hydrogen and oxygen. If the antimicrobial properties of honey are due to hydrogen peroxide, the antimicrobial activity may be reduced when honey comes into contact with live cells.[38] Innovative research that can overcome obstacles associated with *in vivo* use of honey is urgently required.

It is also important to consider that some honeys have been shown to be contaminated with bacteria and fungi, and therefore non-gamma-irradiated honeys may not be suitable for application on damaged skin.[23] The production of medical-grade honeys, suitable for use in clinical practice, from local honeys would be economically advantageous and beneficial to local communities.

Effects of honey on microbial pathogenicity of skin relevant microbes: *in vitro* studies

Incredibly, recent research has shown that the antimicrobial properties of honey *in vitro* are more than bactericidal because honey has also been shown to reduce bacterial pathogenicity. The ability of pathogenic microbes to cause diseases is partly due to the production of pathogenicity factors. *S. aureus*, for example, produces a range of disease-causing proteins, including catalase, hemolysins (α, β, γ, and δ), epidermolytic toxins, and enterotoxins. Alpha-toxin (α-hemolysin) causes tissue damage during wound infections by creating pores in host cell membranes, allowing the discharge of low-molecular-weight compounds, and by inducing cytokine production and apoptosis.

Recently, Jenkins et al[39] reported that Manuka honey reduced the expression of α-toxin in MRSA. Expression of other virulence genes, quorum sensing genes, and genes associated with cell division was also reduced. Lee et al[40] reported that three types of honeys (Korean acacia, Korean polyfloral, and American clover honeys) at a concentration as low as 0.5% significantly inhibited pathogenic *E. coli* O157:HA biofilm formation *in vitro*. Furthermore, low concentrations of the Korean acacia honey reduced the expression of curli genes (*csgBAC*), quorum sensing genes (AI-2 importer, indole biosynthesis), and virulence genes (*LEE* genes) in the bacterial strain. Kronda et al[41] reported that sublethal concentrations of Manuka honey reduced siderophore production, a virulence factor that scavenges iron for bacterial growth, in clinical and nonclinical strains of *P. aeruginosa*. Manuka honey has also been shown to alter the structure of *P. aeruginosa*; scanning and transmission electron microscopy revealed changes in cell shape and cell lysis following incubation with honey.[42] A honey flavonoid extract was also found to alter membrane integrity and branching processes associated with virulence in *C. albicans*.[43]

In addition to the more commonly investigated wound pathogens, subinhibitory concentrations of Manuka honey and Slovakian honeys (Hawthorn, honeydew, and acacia) significantly inhibited *Proteus mirabilis* and *Enterobacter cloacae* biofilm formation *in vitro*.[44]

In vivo studies investigating the efficacy of sublethal concentrations of honey against biofilms would advance our knowledge of the ability of honey to modulate bacterial pathogenicity.

Antimicrobial mode of action of honey

The antimicrobial properties of honey have been attributed to its multiple components, including high sugar concentration, low pH, hydrogen peroxide (H_2O_2), methylglyoxal (MGO), antimicrobial peptide bee defensin-1, and other compounds such as polyphenols that have not been fully elucidated.

The high sugar concentration and low moisture content of honey cause osmotic stress to microbial cells, and low pH is unfavorable for the growth of many microorganisms. However, if a sugar solution with identical sugar components and pH to that of honey is prepared, the antimicrobial activity of the sugar solution is often considerably lower than that of honey, suggesting that other factors in the honey are responsible for its antimicrobial activity.[23]

Honey bees add an enzyme, called glucose oxidase, to the collected nectar during the honey-making process, which converts the glucose in the honey into hydrogen peroxide (H_2O_2) and gluconic acid. H_2O_2 is toxic to many microbes. During the ripening of honey, glucose oxidase is inactivated but regains its activity if the honey is diluted. In a study by Kwakman et al,[10] it was found that Revamil honey produced 3.47 ± 0.25 mM H_2O_2 in 40% (v/v) honey after 24 hours, but no H_2O_2 was detectable in the Manuka honey they tested, suggesting that nonperoxide factors are responsible for the antimicrobial activity of Manuka honey.

Manuka honey has been shown to contain high levels of MGO, 44-fold higher than Revamil honey. MGO in Manuka honey is produced by the nonenzymatic conversion of dihydroxyacetone present at high concentrations in the nectar of *L. scoparium* flowers. The change occurs slowly during honey storage. Kwakman et al[10] reported that neutralization of MGO in Manuka honey abolished the antimicrobial activity of the honey against *S. aureus*, but did not abolish the antimicrobial activity against *E. coli* and *P. aeruginosa*. The authors concluded that MGO is not fully responsible for Manuka honey's nonperoxide antimicrobial activity and that other components, possibly polyphenols, may be responsible.

Polyphenols derived from plant nectar are natural organic chemicals characterized by the presence of multiple phenol structural units. Many are antioxidants, e.g., flavonoids. The antibacterial properties of flavonoids have been attributed to the inhibition of bacterial energy metabolism, bacterial DNA gyrase, and cytoplasmic membrane function.[45] Researchers in New Zealand identified the polyphenol methyl syringate as the major component of the phenolic fraction of Manuka honey.[46] A novel glycoside of methyl syringate, named leptosin, was recently identified in Manuka honey, and its levels were found to correlate positively with the UMF.[47] Identification of phenolic compounds in honey may be important for the production of new antimicrobials, and therefore the analysis of the phenolic profile of active honeys should be encouraged. Combinations of polyphenols may be more effective, as they may act synergistically to inhibit microbial growth, or structural alteration of individual polyphenols can be employed to enhance antimicrobial activity.

Bee defensin-1 is an antimicrobial peptide that is part of the honey bee innate immune system. It is secreted by the hypopharyngeal gland of honey bees and can enter honey via bee saliva during the regurgitation process of honey making. Bee defensin-1 has a strong activity against Gram-positive bacteria including *S. aureus*. Kwakman et al[48] identified bee defensin-1 in Revamil honey but not in Manuka honey.

Raw honey may also contain propolis, a substance composed of plant resins and used by bees to seal the hive. Scientific research has shown that propolis has antimicrobial properties.[49]

The research of Kwakman et al[48] demonstrates the diversity and complexity of the antimicrobial components of different types of honeys. Analysis of the antimicrobial components of other active honeys will be important for a fuller understanding of their applicability in medicine.

It can be concluded from *in vitro* studies that honey has powerful antimicrobial activity against dermatologically relevant microbes. These findings are particularly promising in current times when the problem of antimicrobial drug resistance is considered a global crisis and the World Health Organization (2014)[50] has acknowledged the possibility of a postantibiotic era in which common infections can kill. Even more exciting are the *in vitro* findings that honey can reverse antimicrobial resistance and reduce microbial pathogenicity. Despite these optimistic findings *in vitro*, the use of honey in clinical practice today as an antimicrobial agent does not appear to have yet reached its full potential. Innovative research that can maximally exploit the antimicrobial properties of this natural substance and overcome obstacles associated with *in vivo* use may, in the future, lead to the production of an antimicrobial agent that is highly valued in clinical practice. Interestingly, no honey-resistant microbial strains have emerged to date, and this may be unlikely because of the multifactorial nature of the antimicrobial properties of honey. As honeys from diverse floral origins have been shown to have antimicrobial activity against a range of skin relevant microbes, research should continue to investigate the efficacy of honey in the treatment of other types of skin disorders where microbes have been implicated in the pathophysiology of the disease. There are countless varieties of honeys being produced worldwide, and some may have superior antimicrobial activities that are yet to be discovered.

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