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microbiologist

The role of community pharmacists

Two years on since the launch of Lord O'Neill's Review on Antimicrobial Resistance

Experts reflect on O'Neill's 'ten commandments'

Genetic resources in the high seas

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The fight of our lifetime

Antimicrobial resistance is the omnipresent threat that transcends the borders of individual scientific disciplines. Lord Jim O'Neill, who led the Review on Antimicrobial Resistance, stated in 2016 that "it needs to be seen as the economic and security threat that it is, and be at the forefront of the minds of heads of state, finance ministers, agriculture ministers, and of course health ministers, for years to come".

What has happened since the review was published? How are the scientific and political communities coming together to solve this insidious global health problem? What next? Are we doing enough? Lord O'Neill reflected on these questions in an article, published in the **Journal of Applied Microbiology,** where he gave his view on the progress within areas he popularized as the "ten commandments".

This special AMR issue of *Microbiologist* gives those working on the ground their say. And it is epic! When I started to receive the responses back from the approached authors, each one was like gold dust. Clinicians, big pharma, public health officials, farmers, lawyers, charities, manufacturers and academics update us with the very latest data and details on this clear and present danger.

Other than trying to spot movie titles in my editorial, I suggest you also make note of the **Early Career Scientist Research Symposium.** This year the ECS Committee have decided to tackle sexually transmitted infections, with keynote talks on treatment, infection modelling, charity sector campaigning, general trends and AMR. The event will take place in Manchester and will also host short presentations from those just starting out on their microbiological careers. Further details of the symposium and abstract submission deadlines can be found on page 9.

Jennie French, ECS Committee's Vice Chair, discusses sci-comms in our new early career scientist's column, *shaping the future*, and Lucy Harper postulates what's in store for the Society for Applied Microbiology in 2019 with some key moments from 2018.

I should also mention the **FEMS 2019** Conference in Glasgow. SfAM have teamed up with the Federation of European Microbiology Societies and will be having the mother of all annual conferences. Members of SfAM get not only a subsidized registration rate through the FEMS website but come back to us once you've registered and apply for the special SfAM/FEMS 2019 Congress Accommodation Grant worth up to £300.

I can't wait for 2019! Happy New Year all.

Paul Sainsbury
Editor

To reach that happy point, we need to have the many interested players stop talking, and start delivering. Action not words.

Collier, P. and O'Neill, Lord J. (2018). Two years on: an update on achievement towards the recommendations of the antimicrobial resistance report. *Journal of Applied Microbiology*, **125**(2), pp.308-312.

News

Features

A policy corner

Commercial

Thoughts on rapid diagnostics and antibiotic use

Of all the advances made in medicine and science, the development and use of antibiotics must be one of the most important. The effects of these drugs had helped us control previously deadly infections, improved patient outcomes following surgery and cancer treatments, and supported animal health.

The implementation of these drugs has saved millions of lives globally and many people now expect most maladies can be easily treated with a simple course of antibiotics. However, this has not been achieved without significant cost as this valuable and powerful medicine is under threat due to the rise of antimicrobial resistance (AMR). Professor Dame Sally Davies, the Chief Medical Officer for England, has clearly stated the need for action and issued a call to arms for the medical, veterinary and scientific community.

Interestingly, Dame Sally's call does not just include the medical fraternity but also the veterinary community. This is a critically important point as AMR is truly a '**One Health**' issue, with the effects of resistance being clearly observed in both sectors. There are those that present recriminations and accusations to one sector or the other in relation to who is responsible for the rise in resistance. I feel this is not helpful and serves no purpose. We as a collective are all affected and we need to act together to understand, control and ultimately limit the effects of AMR.

There is a big push to improve diagnostics, so that organism identity and sensitivity profiles can be determined, informing whether or not antibiotics should be administered and if so which ones. Targeted treatment is vital to protecting our antibiotics in the future. This is once again a One Health issue as the same thinking applies to the use of antimicrobials in the farmyard as it does in the GP office. This has been picked up by initiatives such as the UK AMR Diagnostic Collaborative, who are undertaking a large piece of work to help answer these and other pressing questions. Indeed, the work includes significant input from the One Health expert reference group. This group has members from the veterinary, medical, social science, environmental science, academic and industrial sectors, showing just how wide the reach of the One Health message actually can be.

I genuinely feel that this copy of *Microbiologist* really reflects the breadth and diversity of work that is coming together to help tackle the spectre of AMR and to try and keep it in check. I say keep it in check rather than solve the issue of AMR because ultimately resistance will always occur; it is a natural response to selective pressure. We need to also constantly adapt to be able to challenge the adaptation of the organisms we live with. As a community, microbiologists and colleagues from other sectors will come together to work on this One Health issue so we can truly say to the organisms #resistanceisfutile.

Mark Fielder
President of the Society for Applied Microbiology

Reflections on another successful year for SfAM

December provides a good opportunity to reflect on successes and achievements of the current year.

In March, the Executive Committee of SfAM completed the strategy for 2018–2021. Our core strategic aims focus on three themes: **Impact**, **Voice** and **Sustainability**. From these core aims we will structure our activity around priority areas which include: the microbiome, food safety and security, diversity and inclusion, antimicrobial resistance (AMR), preserving and protecting our oceans, and future applications of microbiology and biotechnology. We look forward to launching campaigns and projects within these areas and will be calling on your expertise, so look out for communications from me and the team.

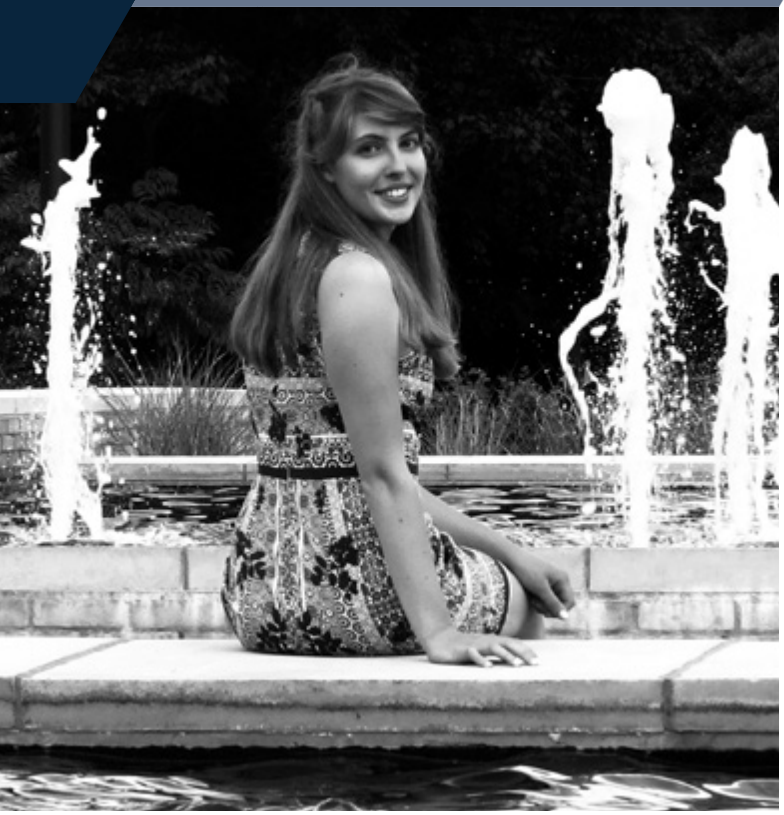
We introduced a new membership category in 2018. Fellow of the Society for Applied Microbiology recognizes individuals whose work has had a significant impact in raising the profile of an area of applied microbiology. This year we were honoured to personally award this prestigious membership to two individuals who have had a significant impact through their work. Lord Jim O'Neill, for his impact in raising the profile of AMR and Sir David Attenborough, who was awarded a Fellowship in recognition of the role he has played in championing the importance of microorganisms in the environment.

Our influence is increasingly felt in parliament, and more widely, with the development of two new briefing documents during 2018 on Food Safety After Brexit, and the Marine Microbiome. We are increasingly consulted by science policy groups and organizations for contributions, ensuring the voice of our members continues to be heard. These documents are publicly available and can be accessed via the new SfAM website, a clean and slick platform from which to showcase the work of SfAM and its members.

At the time of writing we are also coming to the end of a thorough review of the governance of the organization. The outcome of this review will ensure the Society's decision-making and governance processes are compliant, efficient, robust and follow best practice. This will provide a resilient foundation for all the work that we do.

None of these achievements could have taken place without the hard work of the excellent and motivated SfAM trustees, volunteers and the team here at Charles Darwin House. We look forward to taking the Society's strategy forward in 2019 from a new location and I'll be able to share more information about this in the March issue of *Microbiologist*.

Lucy Harper
Chief Executive of the Society for Applied Microbiology



Making an impact

Throughout my transfer from science to science communication I've often been asked to discuss whether scientists should be made to communicate their work. This is something that I've changed my view on, the deeper I've delved into communicating science. I have concluded that no, scientists should not be made to communicate their work.

Despite this view, engaging with the public can be highly rewarding and helps to break down barriers that still exist between the research community and members of the public. Research England encourages public engagement and released the *Concordat for Engaging the Public in Research* to highlight the importance of coordinating outreach activities in research organizations and higher education institutions alike.

Reaching out to the public with your research can often be a daunting task and is definitely not for everyone. At the last ECS symposium we had Sense About Science leading a workshop in which they challenged delegates to 'zoom out' of their research and discover the wider impacts and themes of their research. I saw that a lot of people struggled to do this, but that's not a bad thing. It makes sense that the more specialized you get and the deeper you get into a subject, the harder it is to remember what it was like to know nothing about it!

Before I started my Science Communication MSc I didn't have a clue about how to communicate science – even though it seemed like all you have to do is dumb it down.

What you actually have to consider, which was also highlighted by Sense About Science, is who you are communicating to, what their needs are and how you reach them. You then need to tailor your work to make it interesting to your audience; what aspects are they interested in? Are you going to write, make a bit of SciArt, coordinate a workshop activity, create a mobile app or something completely different?

Making time to take all this into consideration whilst also continuing with research, applying for grants and potentially publishing papers can be very hard. It is why I argue that it can be useful for some people to make use of science communicators. I've noticed there are more and more jobs for research communicators being advertised, which means that researchers are taking the pressure off themselves and handing the outreach baton over to people who want to communicate science for a living (like me).

Research exists to solve problems but if the end goal is shrouded in mystery, you can't make that research relevant to anyone.

Jennie French
SfAM Early Career Scientist Committee Vice Chair

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EarlyCareerScientists

ECS 2019
RESEARCH SYMPOSIUM

Wednesday 13 March 2019 | 10:00 – 17:00 | Manchester | UK

The Early Career Scientists 8th Research Symposium will be held in Manchester, with a focus on sexually transmitted infections (STIs). The symposium aims to bring together microbiologists, epidemiologists, public health researchers, academics, practitioners and, most importantly, early career scientists and undergraduate students. The symposium is a forum for those who wish to exchange and share their experiences, ideas and research.

It will also provide the chance to hear from keynote speakers who will discuss the treatment of STIs and consequences for control, multidrug resistant strains, vaccination and infection modelling, and the charity sector and campaigning.

Deadline for abstract submissions is 23 January 2019.
Visit www.sfam.org.uk for further details.

The symposium will offer a light lunch and refreshments for all delegates. Please help ensure the symposium's success by registering as soon as possible.

£12.50	ECS Undergraduate Members
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£95.00	Non-Members

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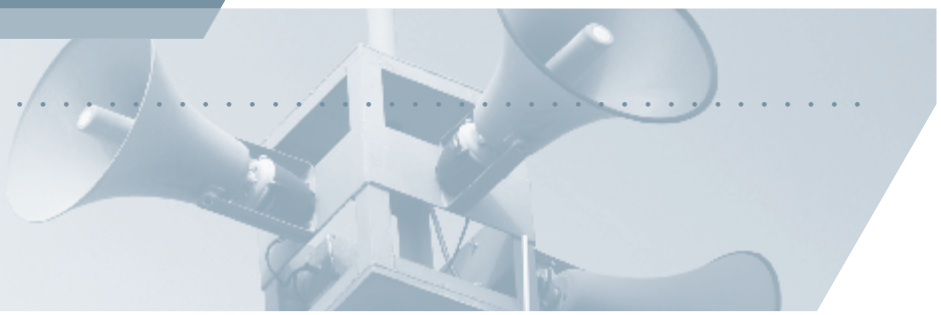

The first commandment | A massive global awareness campaign

The Review on Antimicrobial Resistance, commissioned by the UK Government in 2014 and chaired by the economist Lord O'Neill, gave rise to ten global recommendations aiming to decrease the spread of drug-resistant infections (O'Neill 2016). The first recommendation was to implement an internationally coordinated public awareness campaign to share knowledge about antimicrobial resistance (AMR) with the public and support positive behaviour change related to antibiotic use. The O'Neill review estimated that a global campaign would cost US$40–100 million per year.

The current landscape

There has also been an unprecedented level of attention to AMR on the global political stage, with AMR being discussed in G20 and United Nations (UN) meetings for the first time (Gurría 2017; UN News 2016). It has also garnered public attention with podcasts, print media, almost 50 TEDx talks (https://www.ted.com/search?q=antibiotic), regular TV documentaries (e.g., https://topdocumentaryfilms.com/antibiotic-resistance), and even a musical at the Edinburgh Fringe Theatre Festival (http://mouldthatchangedtheworld.com). For example, in England, with the launch of the national AMR campaign in 2017, more than 700 articles were published in the mainstream print media in the first month (personal correspondence, Public Health England [PHE] marketing team).

In 2016, the WHO commissioned an international survey to determine the knowledge gaps related to AMR awareness campaigns already being performed. There was a 60% response rate; 45 countries responded, of whom 80% had run at least one regional or national campaign between 2010 and 2016 (http://www.who.int/selection_medicines/committees/expert/21/applications/s6_antibiotic_awareness_campaigns.pdf; accessed 10 August 2018).

The following key points emerged from the survey: firstly, the most commonly used key messages revolved around the misuse or overuse of antibiotics causing resistance and making them ineffective; other messages highlighted the role of hand hygiene and the fact that antibiotics do not work against common respiratory illnesses. In addition, most campaigns (80%) targeted the general public and health professionals simultaneously and the lack of human and financial resources and political support were cited as the most commonly encountered challenges to achieving clinical or public health impact. The evaluation of the impact of these campaigns was suboptimal, with no formal evaluation in 60%, and the effectiveness of different messages was not assessed.

It is difficult to compare campaigns across countries as they are often complex and associated with increased knowledge. They may aim to reduce antibiotic use by supporting prescribers in using antibiotics less frequently, reducing the demand for antibiotics from the public and preventing self-medication or sharing antibiotics within households or amongst friends (Filippini *et al*. 2013).

The O'Neill review recommended a global campaign. However, evidence from this survey and literature review suggested that the same message may not have the same impact when translated into other languages, may be misunderstood or equally may not target the key misinformation or lack of knowledge in different countries.

The international efforts in the current landscape frequently focus on improving the knowledge of the public and health professionals about AMR. While the intended effect of these campaigns has not necessarily been to change prescribing behaviour among health professionals, many have aimed to create a supportive

climate such that clinicians are capable of prescribing antibiotics only when needed.

There are two international campaigns in progress at the moment. The longest running is the European Centre for Disease Prevention and Control (ECDC)-led European Antibiotic Awareness Day (EAAD) which has been run annually since 18 November 2008 and, by 2013, 43 countries across Europe were participating (Earnshaw *et al*. 2014). While it is difficult to measure the impact of EAAD, antibiotic use has been reported to have reduced from 42% to 34% across Europe from 2009 to 2015 (European Commission 2010; European Commission 2016). The first truly global campaign was developed by the WHO in 2015 with World Antibiotic Awareness Week.

Both campaigns develop resources for national use, particularly posters and social media messages, and often release annual AMR-related reports to coincide with the relevant dates to enable media and press reports. Both campaigns also require countries to engage in translating, further developing, printing and sharing the resources across their public health and healthcare services. However, they do not particularly focus on or target the general

population unless each individual country dedicates resources to deliver this within their own country.

A fundamental change will require public health efforts to move from static posters and information-based campaigns to dynamic social change movements. This should start at a young age to involve families and communities; for example, e-bug (http://www.e-bug.eu), a PHE-led collaboration in 28 countries, aims to raise awareness of AMR by providing free online games and teaching resources about microbes and antibiotics for children and young people. In October 2017, PHE also launched a national multimedia awareness campaign, *Keep Antibiotics Working*. Campaign messaging was well received across the media outputs: TV, radio, billboards, press, social media (over 10 million views of the main video, http://antibioticguardian.com/keep-antibiotics-working). Pre- and post-survey tracking demonstrated a positive impact on intended behaviour, with 78% of the public stating that they would be unlikely to ask their doctor for antibiotics (up by 5% from pre-campaign) (personal communication, PHE marketing team). General practitioners reported feeling supported by the campaign in their clinical decision-making related to antibiotic prescriptions.

Initiatives for the future: changing behaviour

As for most health-related behaviours, the gap between raising knowledge and awareness of AMR and changing the public and prescriber behaviour around the use of antimicrobial agents remains a challenge. In the hope of transitioning from awareness to engagement, using an online pledge-based approach among human and animal health professionals, scientists and educators, and the public, PHE launched the *Antibiotic Guardian* campaign in 2014 (Ashiru-Oredope and Hopkins 2015). Since the start of the campaign (2014) up to 31 December 2017, the website had been visited 470,968 times. This translated into 57,627 pledges from 129 countries. Antibiotic Guardians had pledged from 50% of countries worldwide. An impact evaluation carried out after the first year of the campaign highlighted that those who chose pledges on the website and became Antibiotic Guardians had increased knowledge and behaviour change (self-reported), as well as increased commitment to tackle AMR (Chaintarli *et al*. 2016).

Cultural aspects associated with antibiotic use are important factors in explaining cross-national differences in antibiotic prescribing (Deschepper *et al*. 2008). This information could be used to tailor key campaign messages to the local and regional culture for greatest impact. Indeed, a truly global and effective antimicrobial awareness campaign would spread information that would resonate well culturally in each country. This is highlighted by a recent UK study; Roope *et al*. (2018) explored the impact of AMR knowledge on doctor consultations for antibiotics and requests for antibiotics when ill with an influenza-like illness, using a risk preference survey. This highlighted that when confronted with this scenario those with poor AMR awareness were more likely to have health-seeking behaviour and ask for antibiotics more rather than less often. Psychologists and medical sociologists seldom participate in the design or implementation of awareness campaigns, but their expertise is suggested both by the Roope study and others as necessary in order to achieve a sustainable change in behaviour (McNulty *et al*. 2010).

Recommendations

There has been considerable progress in raising the global awareness of AMR as a public health threat since the publication of the O'Neill review in 2016. However, for a global campaign to be effective, more focus is needed on interacting with the public through multimodal media, adapting focused messages for each country and using culture-specific behavioural change approaches. Key components moving forward include using a One Health approach, where synergies exist, to disseminate information based on rigorous scientific evidence and coordinating multifaceted professional and public initiatives in future campaigns.

Very frequently it is difficult to disentangle the components of a public-facing AMR campaign from education of human and animal health workers and the role of incentivization to reduce antibiotic prescribing by human and animal health clinicians. Future campaigns should look at the impact of all measures and try to determine estimates of the effect of each component on both increasing knowledge and awareness and changing behaviour of both the prescriber and patient.

The O'Neill review recommended a global AMR awareness campaign. This has been partially realized through the WHO World Antibiotic Awareness Week and global public policy initiatives from the UN General Assembly and G20. This momentum will need each country to engage wholeheartedly, defining their local knowledge, attitude and behaviour campaign requirements. Social and cultural determinants for each country will also need to be considered alongside healthcare delivery in order to ensure that we keep antibiotics working for future generations.

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(Pictured left to right)

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The second commandment

Improve hygiene and prevent the spread of infection

The O'Neill review on antimicrobial resistance (AMR) has successfully shone a light on the global impact of AMR and its complexity in our daily lives outside health and care. The review's reports provoked both applause and criticism, nationally, internationally, politically and from those in the fields of microbiology, infection prevention and control (IPC), and health protection. There is of course no right and wrong; its purpose is to ignite debate and ultimately action to enable us to rise to the challenge we face from AMR. The prevention of infection, the cornerstone of reducing demand for antibiotics, will be central to what happens next.

O'Neill lists three broad steps to strengthen IPC, which are intended for enactment by the UK and globally, and whilst these remain relevant two years after the initial publication, they still require additional review and refinement. Some change is visible, but progress feels slow. O'Neill's report was not intended to deliver a strategy on AMR and its component elements but to direct action – it is therefore our responsibility to define the strategy collectively. Nurses and midwives constitute the largest single regulated health and care profession worldwide. From this perspective there are many opportunities nursing and midwifery can bring to AMR reduction globally that are not yet fully explored or indeed exploited. What O'Neill offers us is a way to influence our profession's contribution and needs, not from the perspective of vocation, public service or professionalism but the harsh business reality of the relationship between healthcare, patient safety and economic growth and prosperity to individual nations. The frustration O'Neill feels with the slow wheels of change is palpable and is felt by many working to reduce AMR. Acknowledging that change takes time appears out of step with the speed of the evolving threat of AMR – might our approaches to this new problem reflect the same approaches we have always taken which is why progress is slow? The global nursing and midwifery profession presents a significant untapped resource and can contribute to match the science of diagnostics and antibiotic development. Obstacles to change and its speed remain at the political and economic level, the influence of national and international agencies and individuals themselves whose priorities lie elsewhere. So what more could be done to make the recommendations of O'Neill more tangible two years on?

Prioritization of infection *prevention* and control

The prioritization of infection *prevention* and control and antimicrobial stewardship by UK and international governments is a positive step but still feels like a poor relation of health provision. Proactive prevention is promoted but remains a challenge to embed consistently at the practical and political level. It is difficult to visualize what the potential benefits of prevention might be years hence. And who pays for this?

'Culture' and 'behaviour' are frequently quoted as two main obstacles – could it be that the way we approach this problem has unintentionally separated IPC from mainstream health and care policy, practice guidance and workforce planning? The UK does well compared to many countries but we do not have a strong common theme of preventing infections in our public and emerging joint health and social care policy. At a practical level, with the exception of specialist guidance, we have separate IPC policies for the management of invasive devices and other practice areas – why? We have a unique opportunity to do things differently from now onwards and should adopt a new mantra to 'simplify and integrate' at every opportunity.

Distinguished by the type of infection, transmission route, affected body site, causative organism or device, populations and healthcare organizations, the breadth of IPC practice in developed countries is enormous. Without a new approach we risk reducing the impact of our work through fragmentation and lack of collective action, creating perceptions that it functions as a silo discipline of medicine or nursing. AMR brings with it opportunities to collaborate on a scale of multi-professionalism not seen before and we should embrace this now.

The benefits of focusing on broader prevention programmes, not always associated with traditional IPC, have potential to combine to effect change more widely and rapidly by focusing on people and conditions, bringing benefits to all. As one example of many, attempts to reduce antibiotic prescribing could instead take a broader approach on, for example, the diabetic foot, offering opportunities to combine the experience of diabetologists and wound care and IPC nurses, as well as professions allied to medicine such as podiatrists, pharmacists,

dieticians, etc., to enhance the quality of life of individuals and integrate the reduction of infection and antibiotic demand associated with this. Other approaches might focus on fuel poverty or continence to promote health or address immunization and screening programmes. In developing countries could micro-insurance be a lever for change? Our national priorities to address AMR need to broaden and integrate the potential for infection prevention fully and look for leadership outside of IPC or health for greater impact. For international programmes, such as the WHO's *Health 2020*, which aims to improve health and reduce health inequalities in Europe, partly through reductions in the burden of communicable disease, or the WHO's *Health In All Policies* programme, which promotes integration of health and wellness across a 'place' and the associated systems, the opportunity may be missed to clearly articulate the potential this can bring to reductions in AMR.

Changing the language and rhetoric of infection *prevention*

To be effective and bring about change 'we', those who work in the specialist field of IPC, need to bring others with us. The management of AMR is a vital component of effective health protection services, therefore our language and behaviours must be meaningful to the public, health and care professionals, politicians and policymakers alike. As in many other specialisms, we talk our own language and often find ourselves talking to and with the converted – an often-described 'echo chamber'.

To integrate IPC will require a change in language and a holistic approach to health, wellbeing and care – many health and care professionals and the public may struggle with what they see as the complexities of IPC but understand the language of preventing infection – a subtle but important shift. 'Preventing infection' breaks down invisible walls between hospital and community or home settings, permits alignment with communicable diseases and public health practice (including vaccination programmes and sanitation) and brings us closer to the public and societal norms. Any changes in language should not be viewed as a threat to the professional identity of specialists (professional protectionism), but an opportunity to ensure health and care professionals, the public and wider society recognize this priority, develop a mutual understanding of what is needed and offer opportunities for the full range of practitioners to shape and lead interventions to bring about change. Additionally, it may reduce the risk of defensive professional practice, an increasingly common issue in more-developed or higher-income countries that risks driving increased usage of antibiotics.

The management of AMR is a vital component of effective health protection services

The elephant in the room

Whilst recognizing the need of promoting the importance of infection prevention, O'Neill has not spoken directly of the impact of workforce issues in health and care systems. As we progress speedily towards 2020, there is a need to recognize the health and care workforce as a risk to AMR reduction globally. Recognition of the role and benefit of nurses and midwives in controlling disease and infection is increasing (All-Party Parliamentary Group on Global Health 2016); however, workforce challenges are rarely clearly articulated in national AMR action plans or international strategies. In the NHS, in England alone, there are currently approximately 40 000 nursing vacancies and in 2016, across the UK for the first time in a decade, more nurses left the profession than joined (Royal College of Nursing 2017). Likewise, Age UK has warned of risks to older people as demands increase in old age (Age UK 2018). Nursing workforce shortages bring many risks to patient safety, including the risk of acquiring infections, as staff may cut corners to maximize time and increase efficiency, to the detriment of essential practices such as hand hygiene, continence care or maintaining cleanliness of the patient or resident environment. Recruitment and retention of nurses and other professionals is essential; however, increasing numbers alone will not be enough. Today's new generation of health and care workers is not the stable and vocational workforce of 20 years ago. Migration, international mobility and a move away from traditional lifelong careers of our baby-boomer generation bring with them the need to reconsider this change more broadly and think forward as well as 'in the moment' to plan effectively. If we are truly to tackle AMR within and outside of hospitals, through public health and access to services then the impact of workforce shortages and changes must be better understood through the lens of AMR and with the support of adequate research funding in this area.

In conclusion, O'Neill's report remains a significant lever for action and change by bringing a different perspective to what has always traditionally been a niche speciality. We should all embrace this and lobby to implement actions in meaningful ways at the national and international level. The emerging theme is one of change and opportunity where the low- to high-income countries work and learn together to identify solutions. The future lies in alignment and integration, and in those who work with people and communities. Our role is not to solve the problem but to enable them to lead.

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The third commandment

Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment

Three years will have passed since the *Antimicrobials in Agriculture and the Environment* chapter was published as part of O'Neill's antimicrobial resistance (AMR) review (O'Neill 2015). It was advance warning of what would appear six months later in the final *Tackling Drug-resistant Infections Globally report*, which culminated in the cross-cutting 'ten commandments' (O'Neill 2016).

Since 1997 the Responsible Use of Medicines in Agriculture (RUMA) Alliance has been guiding the UK livestock sectors on scientific best practice in the use of animal medicines.

RUMA developed a comprehensive range of guidelines on responsible use of vaccines, anthelmintics, anti-parasiticides and antibiotics which have become the blueprint for the industry.

This gave British farmers and veterinary surgeons a picture of what 'good' looked like – how to use as little as possible but as much as necessary to treat and prevent disease that could otherwise cause pain or distress. This approach was the likely reason that in the lead-up to 2015, the UK had comparatively low levels of antibiotic sales in farm animals compared with other major food-producing countries in the EU (ECDC *et al*. 2017).

However, by 2015, links between antibiotic use in farming and drug-resistant infections in humans were being widely suggested in some media, despite limited scientific evidence.

When O'Neill's agriculture chapter was published, it quite rightly talked globally. But this resulted in the UK being referred to in the same breath as the USA where 70% of antibiotics are used in farming – twice the UK levels. And whilst use of antibiotics for farm animal growth promotion is still permitted in many countries, it has been banned in Europe since 2006 (European Commission 2005). Then news broke of a new form of resistance to colistin, a drug of last resort, identified in China and present in both meat animals and people. The evidence of the link between use in farming and human health in the UK may have still been unclear, but the reputational crisis was now unmistakeable.

With sector-led restrictions on colistin use already in place or in progress across many species, RUMA started serious urgent discussions with its members on how best to react to the wider challenges. Decisive action was taken by the organization so it could bring the farming industry into a much stronger position. It was clear that significant reductions were possible: after launching a stewardship programme in 2011, the British poultry meat sector had already achieved a 44% reduction in antibiotic use (British Poultry Council 2016).

By the time the full O'Neill AMR review was issued in May 2016, RUMA was ready to announce that the UK farming

industry not only accepted targets were necessary, but it would convene an expert group of farmers and veterinary surgeons to support each other in identifying targets suitable for each of their sectors. This became RUMA's Targets Task Force.

The O'Neill AMR review suggested an initial national target for every country in the world of 50mg kg^{-1}, to be achieved within ten years. The latest recorded sales data in the UK at that time was 62mg kg^{-1} for 2014 (Veterinary Medicines Directorate 2015). When the Government subsequently ratified this target and asked for it to be met by 2018, the UK farming industry were facing reductions of almost a fifth in four years.

But as it transpired, the farming industry had already been taking action. Sales data for 2015, published at the end of 2016 (Veterinary Medicines Directorate 2016), came out at 56mg kg^{-1}; a year later, 2016 data (Veterinary Medicines Directorate 2017) showed 45mg kg^{-1} – a 27% reduction overall to reach a record 'low' and pass the 50mg kg^{-1} target two years early (Defra 2017). By that time, individual sector targets taking us through to 2020 had been identified by the industry (RUMA 2017), coordinated

The targets set not just numerical goals for antibiotic use but non-numerical objectives for interventions that improve animal health

and led by the Targets Task Force, and agreed and endorsed by the Veterinary Medicines Directorate (VMD).

The targets set not just numerical goals for antibiotic use but non-numerical objectives for interventions that improve animal health. For many sectors, better collection of data relating to farm-level antibiotic usage is also an aim; while overall sales figures are a definitive indicator of progress, they take a year to compile and with many products licensed for multi-species use, they don't always show what's happening in each sector.

The benefits of usage data were made clear once poultry meat producers started to separate out where antibiotics licensed for both pigs and poultry were being used. This meant that by the time the targets were announced, the pig sector had gained a better idea of its position and had launched a comprehensive stewardship plan and online 'medicine book'. These are now being employed to help achieve their target of reducing use by more than 60% by 2020.

Ruminants – cattle and sheep – have always been lower users of antibiotics, so the Targets Task Force is seeking a 10% reduction in use in beef cattle and sheep, and 20% in dairy cattle, with a halving in use of the highest priority antibiotics by all. Their focus is hotspots – for example, *Escherichia coli* infection in newborn lambs; respiratory infections in calves and young cattle; and treatment of dairy cows at the end of their lactations.

The aim for gamebirds is to halve use; a fragmented and dispersed sector, their challenge is reaching decision-makers and changing behaviour in a very traditional environment.

Fish and laying hens, mainly operating in tight supply chains to directly supply processors, packers and retailers, already have low use, as has the poultry meat sector through its stewardship programme. So depending on the sector, these are looking instead at refining use, capturing better data or, if not already having done so, steadily reducing or eliminating the highest priority antibiotics.

How is agriculture doing?

Within the UK, the pig sector halved use between 2015 and 2017 (AHDB 2018). Notably, colistin use in pigs has plummeted and was reported as 0.01 mg kg^{-1} in 2017 against an EU-recommended maximum of 1 mg kg^{-1}. The gamebird sector has achieved a 36% reduction in the first year of its plan (Game Farmers Association 2017). Data collection for >100 000 cattle and sheep farmers is harder, but selective datasets – especially in dairy – show downward movement, especially in the use of the highest priority antibiotics. The poultry sectors exceeded their targets in 2017 (British Poultry Council 2018) and the fish sector is meeting its commitments despite climate-induced disease challenges.

These results mean a potential 12% reduction in 2017 sales data, when released. This may move UK average sales across all livestock sectors below 40 mg kg^{-1}, but much more remains to be done.

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The fourth commandment

Improve global surveillance of drug resistance and antimicrobial consumption in humans and animals

In the antimicrobial resistance (AMR) review led by O'Neill (2016), surveillance is described as 'the foundation of infectious disease management'.

Since the review, the UK has continued its work on AMR nationally and prioritized surveillance as part of its international commitments, which include the development of the Fleming Fund (www.flemingfund.org). Over the last three years we have worked to build this fund under the leadership of Dame Sally Davies and alongside an international network of partners, to provide support to countries in Africa and Asia as they establish surveillance systems for AMR in humans and animals.

So, how far have we got and what have we learned along the way?

Harnessing the power of data

In the O'Neill review three strands of data are identified:

1. **Resistance rates and their impact on health**
2. **Consumption of antibiotics**
3. **Molecular biological data to explain the biological basis of resistance**

The Fleming Fund supports putting data in the hands of decision-makers. We originally focused on the first two data sets but were challenged by the need for these actors to have a fuller picture and so have expanded our remit to: the burden of disease associated with AMR and the quality of antimicrobial medicines.

Armed with these four data sets, countries can make the most appropriate choices for investment, identify antibiotics to which patients should have access, and put in place the appropriate regulations, quality controls and guidance to ensure that antibiotics are of appropriate quality, and are used properly in both human and animal health.

Microbiological resistance

To ensure relevant data are collected in a consistent and comparable form, tools and protocols have been developed, through Fleming Fund grants to the WHO, the Food and Agriculture Organisation (FAO), and the World Organisation for Animal Health (OIE) and others, that can be used by all countries. These include:

- A tool for assessment of veterinary laboratory capacity (ATLASS) developed by FAO, which has been used in several countries to help us understand baseline capability (http://www.fao.org/asiapacific/news/detail-events/en/c/1129839)
- A protocol for establishment of basic surveillance of AMR and drug-resistant infections in hospitals in low-resource settings, developed by the London School of Hygiene and Tropical Medicine (LSHTM; Searle *et al*. 2017). This protocol has been designed to assist countries establish and develop their AMR surveillance, and facilitate their participation in global surveillance reporting through the WHO Global Antimicrobial Resistance Surveillance System (GLASS)
- A One Health protocol for surveillance of drug-resistant *E. coli* in human health, animal health and the environment, developed by WHO and FAO and now being piloted in Ghana, Bangladesh, Indonesia, Sri Lanka, Malaysia and Pakistan (Global Tricycle Surveillance; Matheu and Kane 2017).

With these tools available, the Fleming Fund Country Grants Programme then develops partnerships with countries to strengthen clinical and veterinary laboratories as well as establishing surveillance networks.

We reached a major milestone in February this year with the inauguration of a National Antimicrobial Resistance Reference Laboratory at the National Hospital for Tropical Diseases in Vietnam (Van Kinh *et al*. 2018). This will facilitate the establishment of wider national surveillance with a reference laboratory that can support quality assurance, and the collation, analysis and reporting of national AMR data.

Antimicrobial use

The relationship between the use of antibiotics and the prevalence of resistance is well established, but it is vital that data on use are collected locally and over time.

The OIE recently released its second annual report of antimicrobial use in animals (http://www.oie.int/fileadmin/Home/fr/Our_scientific_expertise/docs/pdf/AMR/Annual_Report_AMR_2.pdf), supported by the Fleming Fund. What we've seen through this is the higher use of antimicrobials (per kg animal biomass) in Asia compared with Africa.

While the development of these data is at an early stage, they provide some guidance on priorities, since high use in Asia may be driven by easy access and weak regulation, whereas the lower use in Africa may reflect poor access to antibiotics in general. The Fleming Fund is funding similar work on surveillance of use through the WHO.

Burden of disease

As we began to form new partnerships, we collectively reflected on the evidence needed to guide investment priorities when resources are stretched. Data on the burden of disease can begin to define the economic and human cost of AMR on a regular basis. The Fleming Fund, alongside the Wellcome Trust and the Bill & Melinda Gates Foundation, has now committed to funding the collection of data on the burden of disease associated with AMR and to make sure this is represented in the Global Burden of Disease study alongside other infectious diseases and causes of morbidity and mortality.

Quality of antimicrobial medicines

Our goal for improved surveillance is to optimize the use of antimicrobial medicines and make sure patients have access to effective treatment. Therefore, we should also be concerned that prevalence of poor quality (referred to as 'substandard and falsified' [SF]) medicines will lead to increased treatment failure. At the level of clinical practice, infectious disease treatment failure should trigger investigation of both the medicine (quality) and the pathogen (resistance). Countries need the capacity to do both. The Fleming Fund, alongside the Department for International Development (DFID), has launched a grant to the WHO to support collection and reporting of these data through the Global Surveillance and Monitoring System (GSMS; http://www.who.int/medicines/regulation/ssffc/publications/gsms-report-sf/en/Reports and Executive summary).

Data sharing

The Wellcome Trust has played a substantial role in pushing forward the agenda on AMR data. This includes establishment of the Surveillance and Epidemiology of Drug-Resistant Infections Consortium (SEDRIC; https://wellcome.ac.uk/what-we-do/our-work/surveillance-and-epidemiology-drug-resistant-infections-consortium), a global consortium that will provide technical expertise, knowledge and coordination to strengthen and support existing surveillance networks and activities as well as identifying gaps and barriers to improved surveillance.

More recently, Wellcome has supported the Open Data Institute (ODI) to increase the amount of antimicrobial surveillance data openly available, critically drawing together private and public sector organizations. The endeavour highlighted the true scale of the contribution pharmaceutical companies can make to global AMR surveillance and will continue to seek ways for these data to be open and comparable.

Other initiatives drawing data into the open are Epi-Net (www.epi-net.eu), which is an open web portal for AMR surveillance data launched by a consortium funded by the Innovative Medicines Initiative (IMI), and the Fleming Fund Regional Grants Programme, which will focus on the retrieval and publication of existing retrospective data.

An integrated and country-led approach to global surveillance

Global surveillance will be entirely ineffective if it is not fed by strong national surveillance systems, alongside an understanding and willingness to use the data to impact policy and practice. This takes time, political will and ownership from the AMR Country Coordinating Committees (or equivalent groups) who ultimately own any action on national surveillance.

What we've learned from early work is that many countries first need technical assistance to develop their National Action Plans for AMR, to ensure that these address both human and animal health. Therefore, the Fleming Fund has supported WHO and FAO in working with over 30 national governments in Africa and Asia for the development of their AMR National Action Plans. We've learned that this work has to come before investments to build up data and laboratory capacity if surveillance is to be systematic and sustainable.

A good example of this process from national action planning to investment in surveillance is in Ghana. The WHO and FAO partnered with Ghana, supported by the Fleming Fund, to finalize and publish their Action Plan on AMR and this has been followed by the establishment of a Fleming Fund Country Grant, led by the University of Ghana. This grant will enable Ghana to build up human and animal surveillance across 11 sentinel surveillance sites and laboratories. In addition, the country will host a number of Fleming Fund Fellows. Together, grants and fellowships seek to develop AMR surveillance capacity across a range of professional disciplines and strengthen connections across the One Health sectors.

What are we doing in the UK?

While the focus for the Fleming Fund is on lower-resource settings, all countries need to do more to develop high-quality data that will drive better use of antibiotics.

Closer to home, the UK continues to implement its own AMR strategy including the further development of the ground-breaking Public Health England (PHE) system – Fingertips (https://fingertips.phe.org.uk). This innovative tool is an open access data portal, bringing together relevant data on infections, AMR, prescribing and antimicrobial stewardship. Scotland and Wales have similar arrangements. Fingertips allows users in the healthcare

> Global surveillance will be entirely ineffective if it is not fed by strong national surveillance systems

sector to benchmark their performance against the national picture and similar organizations.

In the One Health picture, the UK hosts WHO, FAO and OIE reference centres for AMR through PHE, the Veterinary Medicines Directorate (with Cefas and the Animal and Plant Health Agency [APHA]) and Cefas. These centres provide vital technical assistance, quality assurance and training to laboratories and surveillance sites in the UK and around the world.

Is it all enough?

What we've seen is significant progress towards an enabling environment for global surveillance and investments towards building national surveillance systems. But looking forward, we recognize that even with initiatives like the Fleming Fund making steps forward to supporting 24 countries, there is still a lot more to be done, more investment needed and continued collaboration globally.

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The fifth commandment

Promote new, rapid diagnostics to cut unnecessary use of antibiotics

The need for point-of-care tests

In his report on antimicrobial resistance (AMR), O'Neill (2016) championed the role of diagnostics as his fifth commandment to 'promote new, rapid diagnostics to cut unnecessary use of antibiotics'. Sadly, in his recent letter in the *Journal of Applied Microbiology*, two years on from the original report, he noted a lack of progress in moving this initiative forward and stated that it 'needs much more commitment from health companies' (O'Neill 2018). So, as a recent recruit from clinical and public health microbiology into the *in vitro* diagnostic (IVD) industry, I wanted to explore what progress has been made, which new developments have taken place, which drivers for change have been introduced and discuss the likelihood of progress. To quote O'Neill's 2016 report, 'diagnostics are the single biggest potential game changer in the fight against AMR' because antibiotics are currently rarely prescribed based on a definitive diagnosis. In fact, it is more expensive and time-consuming for a doctor or patient to use a diagnostic test at the point of care (POC) than to use an antibiotic 'just in case', even if such a test may help reduce inappropriate antibiotic usage and help preserve the usefulness of antibiotics for everyone in future years. Current lab-based diagnostic technologies are often based on principles and technologies which are decades old and are not fit, in their current format, to inform prescribing practices at the bedside or in the doctor's office; we therefore need POC tests which can inform decision-making.

Existing technologies

Clearly the diagnostics industry needs to innovate and develop new technologies or ways of applying existing technology truly suited to POC testing if diagnostics are going to be 'the biggest potential game changer'. For example, a simple test which could accurately differentiate between viral and bacterial infections, preferably requiring little user interaction and results within a few minutes, would be a game changer and allow doctors to rule out inappropriate use of antibiotics when they are not required. Traditional markers of systemic inflammation, such as C-reactive protein (CRP) and procalcitonin (PCT) have been used in numerous clinical trials to attempt to differentiate between bacterial and viral infections and to direct antibiotic stewardship. However, they are still a long way from universal adoption, with CRP being highly sensitive but lacking specificity, and PCT being highly specific but lacking sensitivity (Hoeboer and Groeneveld 2013). The advent of transcriptomics, metabolomics and proteomics with improved bioinformatics has led to a 'big data' approach to identifying new, novel biomarkers of infection. However, IVD POC tests, based on these new markers, have not yet made it to market. Immunochromatographic tests, which work on a similar principle to pregnancy test strips to detect a patient's serological response to infection, have been around for more than a decade. Many of these qualitative immunoassay tests are targeted to diagnose sexually transmitted diseases, such as syphilis, based on the host's antibody response. However, their lack of specificity reduces their positive predictive value (PPV), limiting their use to low- and medium-income countries (LMICs), where disease prevalence is high. In high-income countries (HICs), where disease prevalence is low, a reduced PPV would lead to most of the positive test results being false positives.

The role of nucleic acid amplification tests (NAATs)

The introduction of NAATs has revolutionized diagnostic testing for a wide range of pathogens in the laboratory. For pathogens such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, NAATs have become the laboratory standard in HICs. However, such tests are usually performed within the diagnostic laboratory on high-throughput analysers. Several smaller POC-type NAAT analysers, such as the Roche Liat, the Alere i and GenePOC, which do facilitate NAAT testing away from the laboratory, potentially at the POC, have recently come to market. However, many of these systems and their tests are prohibitively expensive and have very limited assay menus, therefore limiting their uptake in HICs and making them unsuitable for LMICs which need inexpensive tests.

POC diagnostics to direct patient management and treatment

To influence antibiotic prescribing, diagnostic tests must either: (i) be very sensitive for the pathogen(s) they target, so the clinician can rule out infection with a bacterial pathogen and not prescribe an antibiotic or (ii) as well as being able to detect a pathogen in a patient sample, also be able to determine if it is sensitive or resistant to the antibiotic(s) of choice for that pathogen. For example, AMR has become a major concern in the treatment of *N. gonorrhoeae* infections worldwide, with strains of *N. gonorrhoeae* having developed resistance to all antimicrobials previously recommended for treatment (Wi *et al*. 2017). Ceftriaxone (CRO) or dual antimicrobial therapy, usually CRO plus azithromycin (AZM), currently are the only options for empirical first-line therapy in most countries. However, strains of *N. gonorrhoeae* have recently emerged that are resistant to all the available antibiotics, including CRO and AZM, and are therefore essentially untreatable. Rapid NAATs for both the detection of *N. gonorrhoeae* and its antimicrobial susceptibility would have the potential to direct more-informed antibiotic prescribing. However, there are many mechanisms of AMR in *N. gonorrhoeae*, so detecting them all requires highly multiplexed tests encompassing all the known variants in multiple genes within the pathogen, which is a challenge. In addition, the presence alone of the AMR marker may not always correlate with the phenotype and further complicate the interpretation of the test result. Even if an IVD developer successfully develops such a gonorrhoea resistance assay, locks down the assay design and eventually gets it though regulatory approval and to market, *N. gonorrhoeae* will have evolved further resistance mechanisms so IVD developers are almost always going to be 'chasing their tails'.

An example of where POC testing could rule out infection with a bacterial pathogen, leading to a clinician not prescribing an inappropriate antibiotic, is acute pharyngitis (sore throat), which is one of the most common reasons for general practitioner (GP) visits. *Streptococcus pyogenes* or group A streptococcus (GAS) is the most common bacterial cause of acute pharyngitis and timely and accurate diagnosis is necessary to facilitate treatment of this pathogen to avoid serious secondary complications of infection, such as post-streptococcal glomerulonephritis, invasive disease, rheumatic fever and rheumatic heart disease. Only a relatively small percentage of patients with acute pharyngitis (20-30% of children and a smaller percentage of adults) have GAS pharyngitis, therefore accurate identification of those patients is necessary to avoid inappropriate antibiotic use. A rapid, molecular diagnostic test has the potential to facilitate specific and sensitive detection of GAS and to rule out GAS infection, leading to more-informed antibiotic prescribing. However, the test must have a very high level of sensitivity or high negative predictive value (NPV) to rule out infection.

Where is the innovation?

The lack of progress in developing POC tests to help direct antibiotic prescribing, particularly by the bigger players in the IVD industry, is disappointing. I have heard representatives from several of the larger IVD companies bemoan that the process of product development is very long and how difficult it is to get a test through regulatory approval and to market. Although the road to market may be long and arduous it shouldn't stop them thinking outside of the box and coming up with new innovative tests. From walking around the industry exhibitions at IVD conferences it appears that most of the innovation is coming from start-ups and small- and medium-sized enterprises (SMEs) who are trying to bring disruptive new technologies to market. Regulatory bodies also need to innovate and make the path through regulatory approval less burdensome, particularly for innovative new tests, so the road to market is accelerated; akin to a 'regulatory-light' version of the process.

What incentives are there for the IVD industry?

In O'Neill's 2016 report, a diagnostic market stimulus (DMS) was proposed to provide top-up payments when diagnostics are purchased, like the way that the Global Alliance for Vaccines Initiative (Gavi) has revolutionized global vaccine coverage. In 2017, the case for a Global Alliance for Medical Diagnostics Initiative (GAMDI) was published in *Diagnostics*, as a rallying call for the international community and existing organizations to establish GAMDI, a Gavi for diagnostics (Mugambi *et al*. 2017).

Allied to this, the WHO has published the first Essential Diagnostics List (http://www.who.int/medical_devices/diagnostics/WHO_EDL_2018.pdf) listing 113 diagnostic tests it considers essential to every healthcare system in the world. The establishment of GAMDI will hopefully reduce barriers and increase incentives for developing and implementing new diagnostics. There are other initiatives, including the Longitude Prize, which is a £10 million prize fund with an £8 million pay-out, that will reward an IVD developer who develops a diagnostic POC test that will

> The introduction of NAATs has revolutionized diagnostic testing for a wide range of pathogens

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help to conserve antibiotics for future generations and improve the delivery of global healthcare. There is also the Combating Antimicrobial Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), whose mission is to accelerate global antibacterial innovation by investing in the development of new antibiotics and other therapeutics, and to fund the development of novel IVD POC tests to reduce inappropriate antibiotic usage. Hopefully the combined support of these organizations, the further development of the WHO Essential Diagnostics List and the establishment of GAMDI will propel the development of novel and effective POC tests from the research lab to the patient.

O'Neill's statement that IVD diagnostic research 'needs much more commitment from health companies' is correct in some respects; however, we need to acknowledge that IVD research and innovation require funding. The UK Government's response to *The Review on Antimicrobial Resistance* downplayed the importance of diagnostics, choosing to concentrate on funding pharmaceutical research into developing new antimicrobials (Department of Health 2016). Therefore, we need to hold our own Government to account to ensure that it meets its commitments to funding IVD research, and ensure the funding is spent on the research most likely to deliver the biggest improvements to diagnostics. Finally, those tasked with determining where research funding is spent need to remember that much of the innovation in POC IVD research is coming from SMEs and start-ups, therefore we need to ensure innovative technologies are not overlooked in funding rounds. O'Neill is right in saying 'diagnostics are the single biggest potential game changer in the fight against AMR', and hopefully appropriate funding will lead to the development of POC tests which will impact on antimicrobial prescribing, improve healthcare outcomes for patients, and hopefully conserve antibiotics for future generations.

The thoughts expressed are my own and may not represent those of QuantuMDx Group Ltd.

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The sixth commandment

Promote the development and use of vaccines and alternatives

The O'Neill report recommends the development and use of vaccines and alternatives. What is special about vaccines is that they do not result in antimicrobial resistance (AMR). Resistance does not develop because vaccines are used as a preventive rather than a therapeutic measure (Kennedy and Read 2017). Some commentators have even posited that 'because AMR is intrinsic to antibiotic use, the only long-term solution to AMR is preventing the infections that necessitate their use' (Clift and Salisbury 2017).

The example of typhoid (caused by the bacterium *Salmonella* Typhi)

Development of vaccines as a solution to AMR does not typically top the list of actions to be taken, although the connection is increasingly being made. Seth Berkley, the CEO of Gavi, the Vaccine Alliance, has emphasized this point for new typhoid conjugate vaccines (TCV) saying, '*Not only could this vaccine save lives, it could also prove to be a valuable weapon in the fight against antimicrobial resistance*.' An antibiotic-resistant strain of *Salmonella* Typhi had already emerged in the 1970s (http://www.coalitionagainsttyphoid.org/why-typhoid/drug-resistant-typhoid, accessed 25 September 2018), reaching epidemic levels in Africa, but it was the multidrug-resistant strain H58 in Pakistan that caused serious alarm. The discovery of multidrug-resistant typhoid was used as a rationale to speed-up the availability of a new vaccine. As Klemm (2018) from the Wellcome Trust noted, the discovery of H58 in Pakistan was used as an argument by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization to recommend the use of the vaccine. A TCV, called Typbar-TCV, was prequalified by the WHO in early 2018 and Gavi has directed US$85 million for its introduction in poor countries (WHO 2018a).

A vaccine-centred approach

There are other ways in which vaccines can help to combat AMR. First, vaccines can be used for animals as well as humans, with livestock use of antimicrobials exceeding human use in some countries (Aidara-Kane *et al*. 2018). Second, there are different settings for vaccine use: routinely, in outbreak or emergency scenarios or in hospitals to vaccinate healthcare workers specifically in order to halt the spread of disease. Third, vaccines can have other functions, such as helping to reduce: antibiotic use (e.g., pertussis, meningococcal, and Hib vaccines), antibiotic misuse (e.g. the influenza vaccine); or associated infections, where antibiotics are often required (e.g., varicella vaccine). In considering vaccines as a strategy for tackling AMR, the problem needs to be framed more inclusively; as Atkins and Flasche (2018) put it, the time has come to 'formally integrate the effect of vaccines on antimicrobial resistance into decision-making in public health'.

A pathogen-centred approach is currently being pursued, in order to determine which pathogens are resistant to which antimicrobials, with stewardship and developing new antibiotics prioritized. However, vaccines are not often being designed to target resistant pathogens (Atkins and Flasche 2018). Even though reports such as the O'Neill report list a variety of strategies or 'commandments', a narrow lens is still taken to focus on AMR pathogens – highlighted when mycobacteria (including *Mycobacterium tuberculosis* causing TB in humans), were not initially included in AMR prioritization at the WHO. It was deemed that TB was 'already a globally established priority for which innovative new treatments are urgently needed' (WHO 2017) but pushback on this decision eventually led to inclusion of TB in the priority list (Hasan *et al*. 2018). This example shows a contradiction between wanting to

think about AMR in pathogen terms when much of global health policy and funding is organized on the grounds of competing disease groups.

A solution through vaccination could be forefronted by concentrating on diseases affected by AMR and their potential vaccines. As the Parliamentary Office of Science and Technology (POST) notes in a recent research briefing, 'The WHO has developed a list of pathogens where AMR is of most concern and new antibiotics are needed; there is no equivalent for vaccines' (POSTnote, July 19, 2018). A priority list of vaccines against AMR could be created. Other researchers argue that there is a scarcity of modelling studies quantifying the public health effect of vaccines on AMR and the AMR benefits of vaccines not being factored into cost-effectiveness analyses of vaccines by governments and pharmaceutical companies (Atkins and Flasche 2018). Without metrics to rank and quantify the effectiveness of vaccines for AMR, advocacy power to influence decisions in the public health policy realm is limited.

Tuberculosis is the disease estimated to cause the highest number of deaths (one in four) from AMR per year

Therefore, concentrating on the preventative potential of vaccines, let us take a look at two diseases – gonorrhoea and tuberculosis – which are highly affected by AMR. For these diseases, the level of AMR has led to calls for vaccines as the only sustainable solution. Both diseases have been affected by AMR for many decades (Kirchhelle 2018), but the advancement of multidrug-resistant strains hastens calls for antibiotic alternatives.

Gonorrhoea (caused by the bacterium *Neisseria gonorrhoeae*)

Gonorrhoea has become a drug-resistant pathogen. In March 2018, a UK patient with a sexual partner in Southeast Asia was identified with the first known case of gonorrhoea resistant to two of the most commonly used drugs, azithromycin and ceftriaxone (Press Association 2018). Around the same time two cases were also notified in Australia (ECDC 2018). None of the cases were epidemiologically linked. Other cases may have occurred in low- and middle-income countries but surveillance to diagnose and report untreatable gonorrhoea infections is inadequate. There are also no affordable, rapid, point-of-care diagnostic tests and new forms of treatment will continue to be needed. Even though three new candidate drugs are in different stages of clinical development (solithromycin in Phase III and zoliflodacin and gepotidacin in Phase II), the point that clinical application is reached, if the drug is viable, is many years away (WHO 2018b).

Neither will new drugs be a long-term solution to antibiotic-resistant gonorrhoea. Some hope is on the horizon for a vaccine. A remarkable discovery in 2017 was that the outer membrane vesicle (OMV) *Neisseria meningitidis* serogroup B vaccine (MeNZB) introduced in New Zealand proved effective (in the short term) in reducing gonorrhoea cases by 31% (Petousis-Harris *et al*. 2017). Prospective trials should be conducted to determine whether the OMV-based meningococcal vaccine Bexsero is also protective against gonorrhoea.

Tuberculosis (TB, caused by the bacterium *Mycobacterium tuberculosis*)

TB is the disease estimated to cause the highest number of deaths (one in four) from AMR per year, often through co-infection with other diseases such as HIV/AIDS. Multidrug-resistant TB (resistance to two of the most commonly used drugs, isoniazid and rifampicin) totals nearly half a million cases annually, and extensively drug-resistant TB (resistance to four commonly used drugs) accounts for about 6% of those cases. The WHO reported extensively drug-resistant TB in 123 Member States in 2016 and resistance is increasing.

A vaccine, the Bacille Calmette–Guérin (BCG), was developed around 1920 and gives some protection to young children against severe forms of TB (e.g., TB meningitis). It is less effective in preventing pulmonary TB in adults, which is the most common and infectious form. Thirteen experimental vaccines are currently in clinical trials at various phases. Even though there is a robust pipeline, remaining challenges according to scientists are to continue to generate the necessary funding and to develop clinical trial sites in order to establish correlates of protection (Graves and Hokey 2011).

Making connections

New vaccines for diseases affected by AMR are not the only issue. Wider use of existing vaccines and vaccines targeting hospital-acquired infections and animals also need consideration. In addition, a number of alternative approaches could have the potential to tackle AMR, including phage therapy, antibodies and probiotics. A key lesson to be taken from O'Neill's 'ten commandments' is that connections must be made across the board, to think of AMR in terms of diseases and their vaccines. AMR cannot be tackled vertically as an isolated problem of pathogen and antibiotic, but interlinkages must be explored with other aspects of scientific enquiry and social organizational change, including recognizing existing

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global health logics. Hutchinson *et al*. (2018) similarly urge for integrated solutions through greater connections across sectoral and disciplinary lines. Strengthening the argumentation for vaccines is one important part of building connections. The rationale for the development and administration of new vaccines, for example, for gonorrhoea and TB, could be promoted with reference to the need to counter AMR. Just as was done for typhoid, the case can be better made to rank and quantify the effectiveness of vaccines, and the potential results for particular disease burdens.

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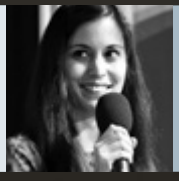

The seventh commandment

Improve the numbers, pay and recognition of people working in infectious disease

Improving the numbers, pay and recognition of people working in infectious disease is something which is easy to agree with. Whilst evidence exists that this has been partially achieved it is not a process which is complete, but it is something in which we, as researchers who apply for grant funding, together with the funding bodies, have influence.

Infectious disease is a broad and encompassing term and an umbrella for a multitude of different disciplines and professions. For the purposes of this article, and in order to map it to the remit of the antimicrobial resistance (AMR) review on which it is commenting, it includes all those working within the AMR field such as, in no particular order, social scientists, economists, clinicians, veterinarians, biologists, chemists, physicists, geographers, and all those in between and around these subject areas who are active within AMR and One Health topics. It will also focus on the university sector as this is arguably where most of the research into AMR is being carried out. The range of professions now working together to address AMR has increased as appreciation of the multidisciplinary nature of AMR has been cemented within the various funding mechanisms available to researchers. As funders have specifically called for One Health projects this has served to increase both the numbers and areas of expertise of individuals now investigating AMR.

A decade or two ago it was unusual to find specific funding calls for research aimed at addressing AMR. The potential of AMR to impact on human life, whether that be through medicine, farming or socio-economic routes was less well appreciated than it is now. These days it is challenging to keep track of the multiple funding calls designed to address various aspects of the AMR problem and the solutions required to fix it. It is also important that we see funding for the next generation of scientific leaders within the AMR field.

In the last couple of years there have been two AMR-specific doctoral training programmes rolled out within the UK. The Wellcome Trust Doctoral Training Centre in Antimicrobials and Antimicrobial Resistance, run through the University of Nottingham and the University of Birmingham, and the Medical Research Foundation (MRF) National PhD Training Programme in Antimicrobial Resistance Research run through the University of Bristol. Both aim to train the next generation of AMR investigators in multiple disciplines. Sustained yearly intake of students within these schemes, plus increasing numbers of students undertaking other AMR PhDs, will put us in a strong position to capitalize on the increasing numbers of postdoctoral positions becoming available in the AMR field.

For both early-career and established researchers the availability of current funds to support their research has increased substantially in recent years, resulting in a funding landscape that is quite complex and intertwined. Funds are available from the research councils within UK Research and Innovation (UKRI), the Department for Health and Social Care (DHSC) and Innovate UK, who administer their own funds, plus other specific ones such as the Grand Challenge Research Fund (GCRF), the Newton Fund and the Global AMR Innovation Fund (GAMRIF), which itself feeds into the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the Foundation for Innovative New Diagnostics (FIND) and the Global Antibiotic Research & Development Partnership (GARDP), amongst other initiatives. There are also multiple charities, including the Wellcome Trust and the Bill & Melinda Gates Foundation (which both also contribute to CARB-X), making significant contributions with dedicated AMR funding, networks and consortia. Other funds such as the Fleming Fund (a UK aid programme) and the Joint Programme Initiative on AMR (JPIAMR), itself funded by national funding bodies from a collective of 27 nations

(including the UK) from four continents, aim to catalyse overseas and international efforts, research, development, capacity-building and networking activities in order to improve the international response to AMR. The focus now put on AMR by funders means this list is by no means exhaustive and the identification of suitable sources of funding is a welcome but not insignificant task.

The increase in funding has been successful in leading to an increase in the numbers of researchers investigating AMR and, possibly because of this, has also catalysed the formation of multiple university-based AMR Centres and industry-based alliances such as the BEAM (**B**iotech companies in **E**urope combating **A**nti**M**icrobial resistance) Alliance and the AMR Alliance. Whether the funding has catalysed these centres by increasing the numbers of AMR researchers at an institution, or they have been set up as a response to attract the increased funding available is debatable but doesn't matter as long as they are productive. A productive AMR Centre which makes translational impact within any area of AMR is a good thing and naturally increases the recognition of all involved within it through reputation in what is now an extremely topical subject.

That just leaves pay, which has effectively been frozen, at least in the academic sector, for the last decade. With the increase in trained and talented individuals it is likely there will be increasing competition for AMR-focused research positions, and this is likely to continue. The opportunities to build careers within the AMR field are now more robust; it is recognized as a long-term issue which is not going to be fixed in the next ten years. However, and this is true of many disciplines within academia, we need to see these opportunities translated into increased job security for research and support staff and a reduction in short, fixed-term contracts. Therefore, while opportunities to negotiate better terms of employment are likely to increase, with more excellence within the pool of potential employees, employers will need to pay a premium and offer more competitive contracts to secure it. This is something that funders should consider when designing their next funding calls and which we should aim to optimize when we cost our next grant application – to fully recognize the individuals with the skills we want to attract.

We need to see these opportunities translated into increased job security for research and support staff

Conflicts of Interest

Roberts currently receives financial support from the MRF National PhD Training Programme in Antimicrobial Resistance, the Medical Research Council (MRC; Antimicrobial Resistance in a Global Context – a cross-council call in partnership with the Department of Health, and a Confidence in Concept Award), the Biotechnology and Biological Sciences Research Council (BBSRC; NPRONET Proof of Concept Award) and the Society for Applied Microbiology (International Capacity Building Fund and a Public Engagement Grant).

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The eighth commandment

Establish a Global Innovation Fund for early-stage and non-commercial research

Of all of the recommendations from the O'Neill AMR review, the one demonstrating significant progress must be push funding for preclinical research and development (R&D). Indeed, we can now say that all of the tools are in place today to achieve this goal. What remains to be done is to ensure sustainable funding for decades, as resistance demands eternal vigilance. Because of resistance, antimicrobial R&D must always press forward, funded sustainably over generations.

In the past couple of years, three major efforts have been launched: the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the Global Antibiotic Research & Development Partnership (GARDP) and the Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR) Impact Fund. Between them, these new organizations have already raised almost US$750 million in new funding for antibiotic R&D over a five-year period. All three are focused on the most dangerous drug-resistant bacteria, with global vision and strong collaborative instincts. The oldest of these three launched in July 2016, so the organizations are still maturing, but we can only be encouraged by the emergence of three well-funded organizations with complementary missions, working together in this endeavour. CARB-X received over 400 applications for funding in 2018 alone, including more than 100 applications that featured entirely new therapeutic classes against Gram-negative bacteria. Drug development requires many preclinical strategies, but the quality and quantity of the preclinical pipeline has exceeded our expectations, so long as these companies receive the funding necessary to move towards clinical trials and regulatory approval.

> Because of resistance, antimicrobial R&D must always press forward, funded sustainably over generations

In addition to new organizations, existing institutions have stepped up their efforts against drug-resistant infections. The Wellcome Trust has made a strategic commitment to research against drug-resistant infections, with several other key programmes. Significant increases in Government funding have occurred in the the USA, the European Union, India and elsewhere. In addition to these new funds, the world should be grateful for significant existing efforts from the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), the National Institute of Allergy and Infectious Diseases (NIAID), the Biomedical Advanced Research and Development Authority (BARDA) and the Innovative Medicines Initiative (IMI), together with other funders of basic research worldwide. NIAID alone supports hundreds of millions of dollars for research against drug-resistant infections.

While the AMR review called for US$2 billion in such push funding, we should not fixate on that funding estimate, but should carefully evaluate the funding needs of these organizations to see what funding can be efficiently deployed. The first step will be a careful inventory of existing research efforts. The AMR R&D Hub, created by the G20, may be well-situated to collect this data, complementing existing efforts. Other key stakeholders include the UN Interagency Coordination Group (IACG) on

AMR and the World Health Organization (WHO). Secondly, the combined pipeline should be evaluated to confirm whether the existing programmes are correctly focused and sufficiently funded. Finally, political advocacy will be required in order to reach the indicated level of funding and to sustain that funding for decades.

The preclinical funding landscape is without a doubt a ray of hope in an otherwise difficult field. But antibiotics face unique market challenges once the drug is approved, as was well documented in the AMR review and in the DRIVE-AB final report. Even if antibiotic development was fully subsidized, we still need market entry rewards to support the drug after regulatory approval. All of the push incentives described above are accelerating research, but without a market entry reward, the drugs accelerate into a wall upon regulatory approval. For most drugs, regulatory approval is a moment for commercial success. For antibiotics, the economic prospects are less sanguine, requiring market entry rewards in order to make our investments in push incentives result in successful drugs improving human health.

Network of major AMR development initiatives

	CARB-X	jpiamr	GARDP	repair impact fund	IMI ND4BB
BUDGET	US$ 502m (2016–21)	€234m (2012–24)	€270m (2017–23)	US$ 165m (2018–23)	€700m (2014–20)
PRODUCTS	Novel therapeutics, diagnostics, preventatives, devices	Novel therapeutics, diagnostics, surveillance, prevention, stewardship	Novel therapeutics, optimize antibiotics, develop combinations	Novel therapeutics, companion diagnostics	Novel therapeutics, diagnostics, economic models
PATHOGENS	High priority defined by WHO and CDC, largely Gram-negatives	WHO priority pathogens Member State national priorities	WHO priority pathogen list, especially Gram-negatives	High priority defined by WHO and CDC	Priority pathogens including pathogens on WHO priority list
STAGES OF DEVELOPMENT	Hit-to-lead through to end of Phase 1	Discovery research	Any stage of development to patient access	Lead optimization through to end of Phase 1	Whole value chain
GEOGRAPHY	Global	Global	Global	Europe & USA	Global
FUNDING INSTRUMENTS	Non-dilutive funding and expert support	Research project grants, networks, virtual research institute	Sponsor role (preclinical studies & clinical trials)	Convertible loans and royalty-based	Financial, in-kind and expertise support
FUNDING ALLOTMENTS	Flexible, with milestones; >30% cost share	Direct funding €1m to 5m	Direct funding and flexible partnerships	US$ 1m to 15m	Direct funding, grants of €4.4 to 211m (50 per cent in-kind contribution)
CONDITIONS	Stewardship and market access requirements		Stewardship and access. consider in/out licensing	Stewardship and access requirements (in progress)	Limited compensation when value generated

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The preclinical funding landscape is without a doubt a ray of hope in an otherwise difficult field

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Executive Director of
Combating Antibiotic Resistant Bacteria
Biopharmaceutical Accelerator

The ninth commandment

Better incentives to promote investment for new drugs and improving existing ones

Background

Antibiotics have a crucial role in fighting bacterial infections and are key to facilitating important medical procedures, such as organ transplants, medical devices, chemotherapies and joint replacement surgery. The emergence of antimicrobial resistance (AMR) across the entire spectrum of bacterial pathogens threatens the very foundation of modern healthcare. Yet, effort dedicated to antibiotic research is clearly far less than for medicines aimed at non-communicable diseases, such as cancer, diabetes and respiratory diseases.

In his 2016 policy paper on strategies to conquer AMR, O'Neill's 'ninth commandment' is 'better incentives to promote investment for new drugs and improving existing ones' (O'Neill 2016). The overarching goal of this proposal is to boost private sector investment in antibiotic drug development by improving returns on investment. Manufacturers of antibiotics have a different and more challenging commercial environment than those making drugs aimed to treat non-communicable diseases. Firstly, a new antibiotic entering the market will be competing against much cheaper generics which are just as effective against most infections until resistance occurs. Secondly, the new drug will appropriately be held in reserve as a healthcare strategy to delay the occurrence of AMR strains.

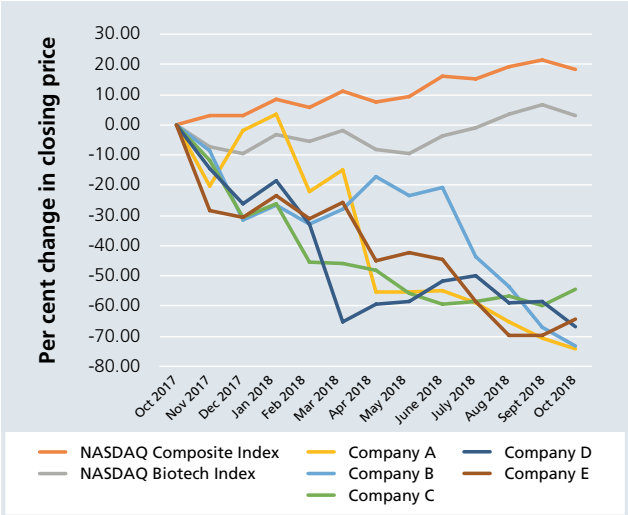


Figure 1 *Percentage change in closing stock price of antibacterial companies with recently launched or late-stage assets compared to NASDAQ indices 6 October 2017 to 5 October 2018.*

To counter these obstacles to commercialization, O'Neill's paper recommends the implementation of a global system of financial incentives which would reward companies when their antibiotics successfully enter the market. On the 'pull' side of the equation, governments should support early- and late-stage research as well as institute national purchasing arrangements to build stockpiles of new antibiotics, thereby guaranteeing market stability. O'Neill projected that market-driven incentive awards of US$1.6 billion per year would have a material impact – a modest sum given that the long-term economic impact of AMR on the world healthcare system has been estimated to be in the trillions of dollars.

Crisis in research and development (R&D) investment

Unfortunately, in a recent update on the implementation status of O'Neill's ten proposals, as written by himself, the 'ninth commandment' had achieved no real progress (O'Neill 2018). We agree with this assessment and, based on recent events, conclude that the lack of significant 'pull' incentives further jeopardizes the success of this area. O'Neill also expressed concern about the withdrawal of

several large pharmaceutical companies from the antimicrobial area – a trend which regrettably continues. Since 2016, two more large pharmaceutical companies have exited antibacterial R&D. In July 2018, Sanofi transferred its entire antibacterial research group and their projects to the biotechnology company Evotec. In the same month, Novartis announced its decision to close its California-based antibacterial unit and laid off 140 employees. Subsequently, Novartis out-licensed three of their most advanced programmes to Boston Pharmaceuticals, another biotechnology company.

Over the last year, antibacterial research seems to have been losing investor interest too. Five antibacterial-focused biotechnology companies that have recently launched or registered an antibiotic, or have an antibiotic in Phase III, have posted a loss of their stock value ranging between 50% and 75% compared with the stock exchange in which they trade, which has increased by approximately 20% (and approximately 3%-5% for biotechnology companies) (*Figure 1; data from Yahoo Finance, accessed 6 October 2018*).

Non-profit and Government funding initiatives, such as the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), Innovative Medicines Initiative (IMI) AMR Accelerator Programme, the TB Alliance and the US Biomedical Advanced Research and Development Authority (BARDA), now play essential roles in sustaining industrial antibacterial research by funding to support translational preclinical and clinical studies ('push incentives'). Essentially, these public–private partnerships (PPPs) underpin most of the assets in the current antibacterial R&D pipeline. However, 'pull' incentives are also needed. Without 'pull' incentives, as proposed by the O'Neill report, the sustainability of this pipeline remains fragile and delivery of new treatments for multidrug-resistant infections remains at risk.

How innovative is the global antimicrobial drug pipeline?

Given the slow progress of implementing market-driven incentives, what is the status of innovation in global antimicrobial drug development? Accurately measuring innovation in any industry is a highly complex task. The first and most crucial step is deciding how to define an innovative outcome or product. Novelty in antimicrobial drug discovery is essential to overcome AMR, and innovation can take multiple forms, such as extending the lives of existing antibiotics through new re-formulations, combinations and/or drug delivery systems. One could also develop new drug entities that overcome resistance mutations in existing targets through a novel molecular action such as the compound binding at a different site on the bacterial protein target.

To obtain a rough snapshot of biotechnology and pharmaceutical industry innovation in antimicrobials, we used Pharmaprojects, a comprehensive commercial database of global drug development activities (Citeline Copyright © 2018 Informa PLC). We collected data on all active, pre-launch, antimicrobial projects (i.e., preclinical, Phase I to III) by first using 'Infectious Disease' as the category of disease then manually filtering out non-bacterial projects. For the purposes of this overview analysis, we included all Gram-negative and Gram-positive bacterial infections and tuberculosis where the AMR threat is the greatest. We then manually reviewed the '*Mechanisms of Action*', '*Biological Target*', and '*Overview*' categories for target novelty. Projects with undisclosed targets were omitted from the analysis.

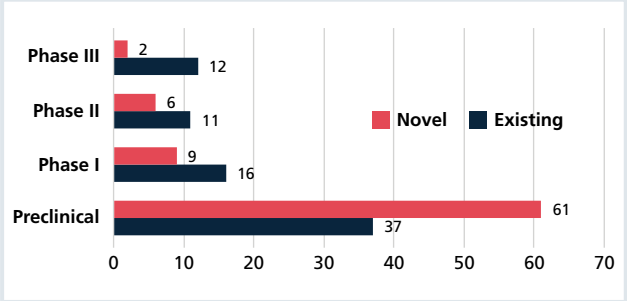
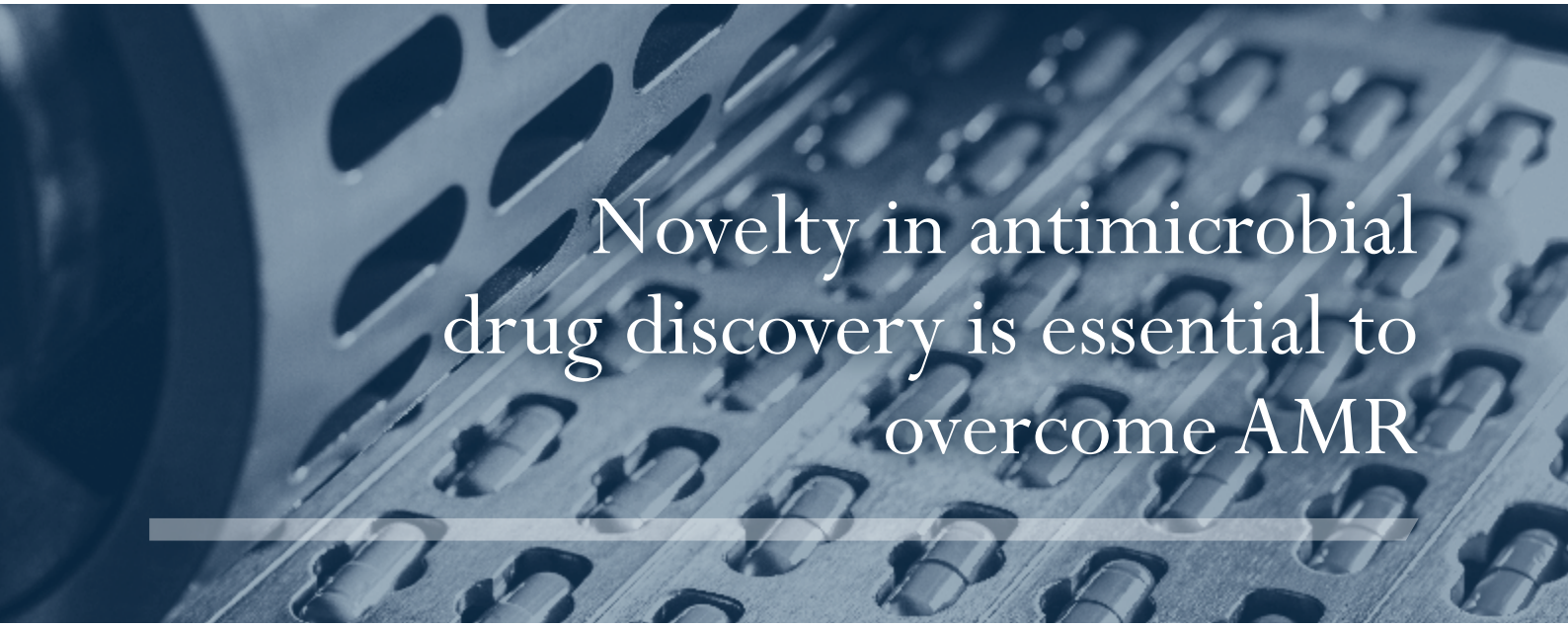


Figure 2 *Distribution of active antimicrobial drug discovery projects with new or existing targets by development phase. Data from Pharmaprojects (**https://pipeline.citeline.com/CpLogin.aspx**, accessed 23 September 2018).*

Figure 2 shows the distributions of projects involving either existing or novel targets by preclinical and clinical phase. For Phases I to III, there were 56 projects for new and existing targets which closely corresponds to the recent analysis of the global clinical antibacterial pipeline by Theuretzbacher *et al*. (2018). As expected, clinical phases are dominated by drugs against existing targets. For preclinical projects as well as some in Phase I and II, we see



somewhat of a trend towards novel targets. This could be due to multiple factors including promising new science, increasing investment in AMR-centric biotechnologies and exhaustion of opportunities for improving the formulation, chemical design and delivery of classical antibiotics.

However, optimism about seeing future abundance of new drugs in the preclinical phase with novel mechanisms of action needs to be tempered by the fact that project attrition rates increase dramatically as new chemical entities (NCEs) progress through and into clinical trials. The overall Phase I–III pipeline is very sparse in terms of projects and needs substantial reinforcement. Much of antimicrobial drug development seems to occur in the biotechnology sector and those companies have relatively shallow pipelines of one or a few projects.

We also looked at the kinds of novel targets progressed to clinical Phases I, II and/or III. *Staphylococcus aureus*, *Clostridium difficile* and TB infections were the dominant indications for new targets. There is a significant lack of both systemic antibiotics and novel mechanism of action antibiotics against Gram-negative infections. Most novel targets are still encoded by the genome of the pathogen, as are the targets of existing launched drugs. While targeting the pathogen directly is an effective near- to mid-term therapeutic strategy, in the longer term of clinical use AMR is still likely to emerge against these drugs as the pathogens mutate and evolve ways to evade such therapeutics. However, several new modalities were evident which have the potential to make AMR emergency less likely, such as bacteriophages, microbiome-based and human host-based therapeutics. In the face of challenges in traditional antibacterial research (small molecules targeting essential bacterial targets) we suggest that more investment in alternative approaches is warranted. As an example, targeting human host factors involved with bacterial and/or TB infections might lead to novel therapeutics that could be used in combination with direct-acting antimicrobials (Wang *et al*. 2018).

Conclusion

While innovation in novel antibacterials is occurring, the pipeline is nascent and requires strong financial 'pull' to deliver even a few new medicines in coming years. Introduction of the incentives proposed by O'Neill remains the key priority to create a sustainable approach to the growing global challenge of AMR. Without them we risk a continued downturn in investment in the area which risks the progress of the pipeline created by PPPs and delivery of urgently needed medicines to patients. We are very encouraged by the recent statements made by the US FDA Commissioner Scott Gottlieb supporting the need for 'pull' incentives and proposing a new funding model for consideration (Gottlieb 2018). The global dialogue on the need for incentives remains substantial but this needs to be translated to action at national and international levels.

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Stephen J. Baker [2]
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The tenth commandment

Build a global coalition for real action – via the G20 and the UN

As O'Neill reflects on his assessment of the last two years since the launch of his review on antimicrobial resistance (AMR) (O'Neill 2018), we need 'action not words' to tackle rising drug resistance. This sentiment applies to all ten of his 'commandments', but takes on particular significance when we consider the last of his recommendations: 'build a global coalition for real action'.

Of course, it is one thing to call for action and quite another to achieve it – particularly when the actions required are as ambitious as the programme set out by O'Neill. The thrust of O'Neill's tenth recommendation was that sustainable delivery of the other nine would require new structures that go beyond governance mechanisms already in place, as well as a new kind of framework to guide and sustain global delivery. Yet while we have seen some important developments in thinking on global AMR governance, two years on from the O'Neill review we are yet to see the development of the mechanisms we so vitally need.

As the AMR review suggested, we believe that the next steps for AMR governance will require global leadership by the United Nations (UN) and the G20. Undeniably, important progress has been already made – over the last two years the UN and G20 have both played roles in advancing discussions about the global response to AMR.

Looking towards the UN, the convening of the High-Level Meeting on AMR in 2016 was arguably the most significant development to date in AMR's (notable) rise up the global agenda in recent years. The September 2016 meeting was only the fourth time in history that a health topic has been discussed by the General Assembly. This meeting not only recognized AMR as a fundamental and long-term threat to human health, but also as a threat to sustainable food production and the wider global Sustainable Development Goals (SDGs). In response, the then Secretary-General established an *ad hoc* Interagency Coordination Group (IACG) with the aim of providing practical guidance on the future approaches needed to sustain effective global action against AMR. In the spring of next year, the IACG will provide their final recommendations to the Secretary-General. This milestone will provide a springboard for further action and debate at the UN on how to establish a successful and sustainable global response to AMR.

At the G20 level, AMR has featured consistently in discussions since 2015, reflecting the recognition of the major negative impact that it could have on global economic prosperity. Successive statements by the leaders and health ministers of the G20 have made high-level commitments to tackle AMR through the leadership of this group in implementing multi-sectoral AMR national action plans (NAPs). There has also been a pledge to support other nations alongside ongoing efforts by the Tripartite – a collaboration between the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the WHO to take collective action to minimize the emergence and spread of AMR – to deliver their own action plans. Further to this, under German leadership in 2017, G20 leaders supported the establishment of a global 'R&D Collaboration Hub' for AMR (G20 2017), which has recently begun its work. But while it is encouraging – and promising for the future – that AMR has remained on the G20 agenda, the group has not so far delivered the type of ambitious, transformative intervention (particularly in respect of antibiotic R&D) which O'Neill clearly envisaged that it could.

Thus, it can be seen that the engagement of the UN and G20 over the last two years has clearly driven significant steps in the emergence of a more ambitious global

response to AMR. That said, there remains much more to do to draw on the full potential of the involvement of these new players as we develop and deliver ambitious new mechanisms that ensure effective and sustainable global action on AMR.

A successful response to the uniquely global and multi-sectoral threat of AMR entirely depends upon achieving global collaboration and cooperation that transcends the barriers that often exist between the human health community and the other elements of the One Health landscape. The manner in which international institutions such as the UN, WHO, FAO and OIE have mobilized to date has been commendable, and through their joint work in the Tripartite collaboration they have recently committed to deepening their cooperation on AMR (FAO 2018). The Tripartite will unquestionably have a central role to play in any future global AMR coalition as they possess unique, well-established mandates, and global reach. Moreover, there is a wealth of experience in AMR action across these organizations – as well as the UN more widely – which should be integrated into any future approach to AMR governance.

However, we now need to move decisively towards establishing new ways of working which push the global community to raise levels of ambition and to go beyond the Tripartite members' established individual remits and delivery mechanisms. As it stands, there are gaps in the current approach to AMR which we would have the opportunity to fill as part of a new governance system. Of particular note is the low level of integration into the above-mentioned initiatives as yet achieved for work on the environmental impact of AMR. Inclusion of the UN Environment Programme (UNEP) alongside the existing Tripartite in any ongoing UN AMR coalition would be a welcome step towards addressing this gap. More generally, any future AMR response mechanism must prioritize enhanced coordination across work on human, animal and environmental issues.

Crucially, the IACG is already considering precisely these issues as part of its work by exploring options for how the global governance system for AMR might work from 2019 and beyond. Some of the ideas generated by the IACG at a cross-stakeholder workshop have already been the subject of consultation (Rochford *et al*. 2018), including the question of whether a future structure should be supported by a new multi-sector, multi-stakeholder Global Steering Board, and an advisory and time-limited High-Level AMR Commission of cross-sector experts. More ambitiously still, it is suggested that such an arrangement might have an international legal agreement at its core as a means to hold countries and industries to account and command effective action.

The question of whether such a legal agreement is politically feasible is as yet untested; however, given the fundamental collective action problems we face with AMR, perhaps this is the only way forward that binds countries into reporting, reviewing and ramping up progress to a consistent standard. Such proposals are bound to have vocal critics but warrant serious discussion and debate in the months ahead.

The role of the UN in such a future landscape will ultimately be to ensure continued engagement with AMR in two major ways. Firstly, it can act to promote continued (and deeper) cooperation between key agencies such as the Tripartite and UNEP. In doing so, it can also establish a mandate for the wider 'family' of UN agencies – which includes significant, high-profile organizations such as the UN Children's Fund (UNICEF), as well as a diverse set of less

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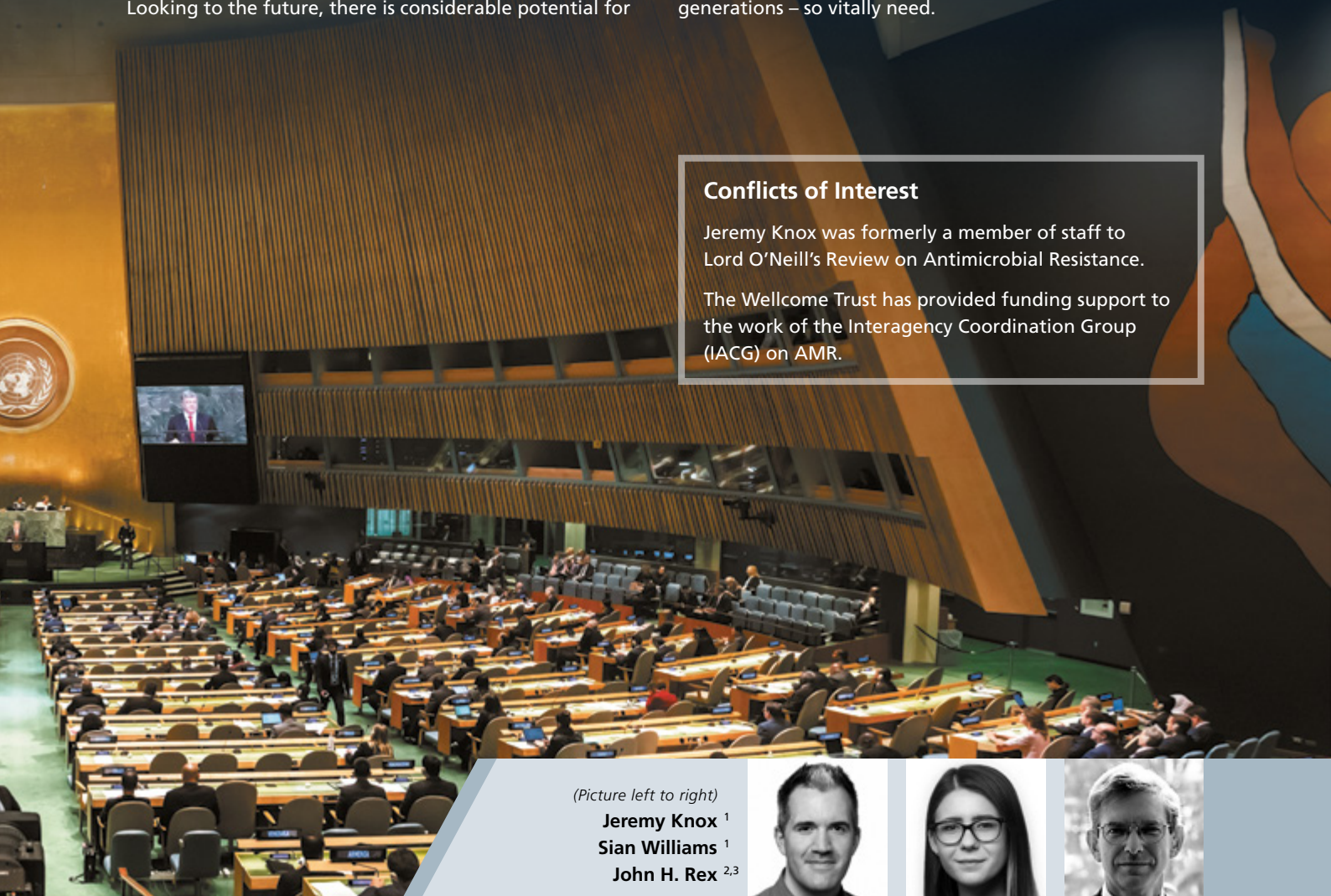
high-profile bodies whose remits are sensitive to the impact of AMR – to bring AMR-related activities into the mainstream of their work. Secondly, it can provide an unrivalled forum for an open dialogue (and consensus-building) with Member States, and accordingly the development of a broad, comprehensive mandate for action. Ultimately it is at country level where most action must be taken, and so it will be vital to ensure countries are directly engaged and supported if we are to make progress in all regions of the world.

And what of the other explicit element of O'Neill's 'global coalition' recommendation, the G20? With no established precedent for the group's engagement with health issues, there is no clear template for the role of the G20 in a global coalition for action on AMR. Although the G20 is inevitably far from representative of the wider global community, it nonetheless represents some of the largest and most impactful markets for antibiotic consumption and is the established source for innovation of new antibiotics. Hence, commitment by its leaders to prioritize and show leadership on developing comprehensive plans to tackle AMR should be regarded as significant. Looking to the future, there is considerable potential for the G20 to go further in addressing the challenges of market interventions to support antibiotic development – an area in which they are well-placed to address vexed issues of implementation and financing.

Finally, and perhaps most importantly, any successful action-oriented coalition against AMR must also consider the source of its mandate to create change. Implicit in O'Neill's call for a 'global coalition' is the need to galvanize a true global movement to tackle AMR, based on sustained political support. This depends upon more than just having the right mechanisms in place to drive progress and facilitate accountability; it requires a far broader base of political buy-in and public support than we have seen to date. Without a clear public mandate, and a renewal of the kind of bold political leadership which saw the commissioning of O'Neill's review on AMR in the first place, the 'global coalition' on AMR will be destined to run out of steam. The global health community must therefore seize the unprecedented opportunities that will present themselves through the UN and IACG in the months ahead to deliver the sustained, effective response to drug-resistant infections that we – and future generations – so vitally need.



Conflicts of Interest

Jeremy Knox was formerly a member of staff to Lord O'Neill's Review on Antimicrobial Resistance.

The Wellcome Trust has provided funding support to the work of the Interagency Coordination Group (IACG) on AMR.

(Picture left to right)

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We would like to warmly welcome the following

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Role of community pharmacists in controlling antimicrobial resistance

Community pharmacists in developing countries are the healthcare entry point for members of the public to access pharmaceutical services.

They usually dispense medicines to patients with prescriptions, but also sell them without prescriptions when legally permitted. It has been estimated that approximately 80% of antibiotics are used in the 'community' – either prescribed or bought without a prescription. These types of pharmacies are quite popular in countries such as Nepal (my home), as they have become the easiest and cheapest way for patients to obtain medicines for general diseases. Although many developing countries have laws regarding restriction of distribution of antibiotics, the lack of implementation of them simply aggravates the problem of antimicrobial resistance (AMR).

A crucial role is played by the community pharmacist in the rational use of antibiotics and are often operated by non-qualified 'pharmacists'. They desperately need training and education on the appropriate use of antibiotics as they are best positioned to lead in changing customer attitude towards consumption of antibiotics. Moreover, they should be regularly updated with new antibiotic usage, guidance and patterns of AMR. The irrational use of antibiotics is highest amongst communities in developing countries and broad-spectrum antibiotics, such as amoxicillin and azithromycin, are still widely dispensed without a prescription.

The overuse, misuse and underuse of antibiotics contributes to the spread of antimicrobial resistance. Awareness and knowledge of this in the community, requires education, communication and training. The community pharmacist could play a vital role here. They should counsel the patient on how to take the full dose of medicine, with relation to meal and time intervals. They should ensure packaging, labelling and physical appearance are properly checked and that storage condition instructions are abided by and passed on to the patient.

The community pharmacist needs to debunk the misconceptions of antibiotic treatment of non-bacterial infections. The Community Pharmacy Association of Thailand worked with the slogan "*Mirror, mirror on the wall, do I need antibiotics at all*?" to prevent the unnecessary use of antibiotics for viral infections. In Spain, a communication campaign was organized with the slogan "*Do not ask us for antibiotics but for information*" to discourage the use of antibiotics without proper prescription. Other health promotion programmes, like Canada's, *Do bugs need drugs*?, have focused on proper handwashing techniques or the importance and safety of vaccines to increase the rate of vaccination. They have all proven to be a highly successful strategy to get the public behind AMR prevention.

Implementation of strict rules and regulations, policies prohibiting the sale of antibiotics without prescription, public awareness, counselling of patients and immunization programmes will help to reduce the ongoing burden of silently spreading superbugs.

The community pharmacist has a public duty, not just a role.

Binod Rayamajhee

Works for the Department of Infectious Diseases and Immunology and the Kathmandu Research Institute for Biological Sciences in Nepal

Anticipation of what's to come

The year ahead will bring big changes; we will be leaving the EU, there will be a UK spending review with implications for research and education budgets, and there will be further visibility of UK Research and Innovation's (UKRI) strategy for public research funding in action.

Despite all these changes, it will be the people and the science, as always, that will power our community and give us focus.

A recent example of people coming together to bring out the best of bioscience was in Biology Week. Now in its seventh year, the week of activity harnessed and amplified enthusiasm and support for the biosciences, and showcased the strengths of our biology students, researchers, professionals, policymakers and many more.

This year, more than 100 events took place across the UK and in other parts of the world. The RSB head office ran a debate at the Royal Institution to a packed auditorium, a panel discussion on improving accessibility and diversity, our Annual Awards ceremony and a reception in the Houses of Parliament. All of these events took place alongside our annual favourite species poll, our flagship social media campaign **#iamabiologist**, and our BioArtAttack competition.

We also launched our current affairs-style documentary in partnership with ITN Productions. Anchored by Natasha Kaplinsky, the 100 minute programme attracted the involvement of 17 UK-based bioscience research institutions and organizations, each highlighting the work they are doing towards the apt theme of *Addressing Global Challenges*, you can see their stories on our website.

A showcase of the programme was warmly received at The Francis Crick Institute as part of our Annual Awards

Mark Downs CSci FRSB
Chief Executive of the Royal Society of Biology

Fostering enthusiasm for biology and providing support for bioscientists doesn't end with Biology Week

ceremony, which also celebrated the winners of our Photography competition, our Nancy Rothwell specimen drawing competition and our Outreach and Engagement Award winners too.

Biology Week's social media campaign **#iamabiologist** set out to highlight the diversity of people and professions within the biosciences. More than 2,500 people took part across the globe, with biologists of all ages and career stages taking part in countries such as South Africa, Zimbabwe, Nigeria, Australia, Thailand, Peru and from across the United States, as well as throughout the UK.

Fostering enthusiasm for biology and providing support for bioscientists didn't end with Biology Week. At the end of October, we held our Biosciences Career Day at Manchester Metropolitan University. Over 200 students and recent graduates attending heard from bioscience professionals, had help developing their CV writing and interview skills, and were able to network with potential employers.

In November we embarked on a new initiative – we organized our first-ever biosciences Outreach and Engagement symposium, featuring 12 jam-packed sessions for those new to outreach or looking to brush up on their skills.

The symposium was held in partnership with a number of our member organizations and the University of Birmingham, and brought together early career researchers and science communication professionals from across the UK to share best practice, discuss challenges and opportunities, and also build and strengthen networks.

This wide portfolio of activities and events is underpinned by the same set of fundamental goals – to support and strengthen the biosciences community, improve

professionalism and provide a unified voice for our membership.

These goals will remain central to our work as we begin to explore the unchartered waters of post-Brexit UK.

We will continue to convene and gather concerns and present these to Government in relation to the future research environment, as well as ongoing UK policy work for regulation, environment and health. Ensuring that scientists can collaborate internationally, and that the knowledge generated by science can be put to good use, are bedrock concerns of our policy activity and we will continue to drive these forward.

Next year we celebrate our tenth anniversary, and we will be marking this milestone with another wide-reaching and diverse programme of events and initiatives.

We hope both our individual members and member organizations will join us in celebrating how far we have come as an organization since 2009, and help us to continue to showcase the excellence of the biosciences here in the UK.

Plumbing the depths – genetic resources in the high seas

You may recall an article in *Microbiologist* last March that introduced Access and Benefit Sharing (ABS), the idea that if a researcher from one country uses a genetic resource from another (e.g. from microbes, plants or animals in the environment), then consent should be given and there should be an opportunity to share the benefits (e.g. royalties or shared training of researchers). The Nagoya Protocol is the international agreement that sets out how countries can enshrine this concept into law. As of writing this article, 107 countries are party (have agreed) to the protocol.

This agreement obviously has implications for both basic and applied research, which is why policymakers continue to argue over its various complexities, such as how this applies to sequence data (SfAM published its position on this issue last year). Meanwhile, a related issue steadily approaches from the horizon: how access and benefit sharing applies to genetic resources in the high seas.

Regions such as this are known as Areas Beyond National Jurisdiction (ABNJ) – meaning that no one country is responsible for what goes on there. As such, the high seas have historically been seen as a region of open access and freedom, raising concerns over how to ensure its resources are used responsibly and equitably. A classic example of this is the management of deep-sea mining for metals. International political wrangling in the 1970s and 1980s resulted in the 1982 United Nations Convention on the Law of the Sea (UNCLOS) declaring the seabed and its mineral resources as the 'common heritage of mankind'. The International Seabed Authority (ISA) was consequently set up to regulate activities that explore and exploit mineral resources on the sea floor.

Although deep-sea mining activities aren't exactly ubiquitous, the rapid pace of advancing technology will soon make routine mining operations possible, creating a lot of work for the ISA. Microbiologists are similarly poised to explore the oceans more readily, enabled by new technologies including autonomous vehicles and next-generation sequencing. Exciting potential discoveries include new medicines, bioplastics and foods. However, unlike for ocean mineral deposits, there are no international rules on the use of genetic resources (e.g. bacterial DNA) in ABNJ. Unbridled access to the various flora and fauna of the ocean could be a boon to the scientific community – although it may also spell trouble for the health of ocean ecosystems.

Chris Brown
Policy & Public Affairs Manager of the Society for Applied Microbiology

Policymakers now have their eye on marine genetic resources. International negotiations began in September on a proposed agreement under UNCLOS for the conservation and sustainable use of ocean biodiversity, otherwise known as BBNJ – Biodiversity Beyond National Jurisdiction. While many scientists will surely agree that research and development activities should avoid damaging the very ecosystems they are studying, hardly anyone in the scientific community will be a fan of regulations that place a burden on researchers. A delicate balance will be required.

An agreement is likely to be years away, but now is the time for the scientific community to make its voice heard. Networks such as the Deep-Ocean Stewardship Initiative (DOSI) have already begun to advocate a science-based approach to BBNJ. A workshop held by DOSI this April highlighted the potential benefits that could be realized through an international agreement, such as data sharing and coordinated scientific training. Potential hurdles to overcome were also discussed, for instance the need to standardize data collection. The team at SfAM will be working to make sure microbiology is put firmly on the agenda. We have recently published a policy briefing on the marine microbiome, with which we will raise awareness among policymakers of the importance of preserving marine ecosystems and the potential economic benefits of research on aquatic microbes. Achieving success in this arena relies on the expertise and continued engagement of microbiologists. If you would like to get involved, or would just like to know more about this topic, please do get in touch or visit the SfAM website.

The preclinical funding landscape is without a doubt a ray of hope in an otherwise difficult field

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Rapid detection of sleeping sickness and anti-malarial drugs

Human African Trypanosomiasis (HAT) or sleeping sickness is a life-threatening neglected tropical disease affecting rural populations in sub-Saharan Africa. In West and Central Africa, the chronic form of sleeping sickness is caused by *Trypanosoma brucei gambiense*, a protozoan parasite. HAT causes severe neurological disorders often leading to death if not treated. The HAT Sero K-Set is a fast and highly specific test that is stable at ambient temperature and can be performed after minimal training, therefore perfectly suitable in primary health care centres for routine HAT screening.

Malaria is a life-threatening disease caused by parasites of the genus *Plasmodium* that are transmitted to people through the bites of infected mosquitoes. Even though most malaria cases and deaths occur in sub-Saharan Africa, Asia and Latin America, to a lesser extent the Middle East and parts of Europe are also affected. International travellers from non-endemic areas are at high risk of malaria as they lack immunity. Protection against mosquito bites represents the first line of defence for malaria prevention but it can also be prevented through the administration of anti-malarial drugs such as Proguanil and Mefloquine. During treatment monitoring drug intake is

essential especially regarding issues of emerging resistance. Drug presence can easily be monitored in urine samples using either the PG-Strip or MQ-Strip.

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Cherwell enhances quality management system

Cherwell Laboratories, UK-based manufacturer of Redipor® prepared media and supplier of environmental monitoring solutions has successfully completed the migration of its quality management system to the new ISO9001:2015 version. This enhancement affirms that Cherwell operates to stringent quality assurance and manufacturing standards, enabling its customers to have complete confidence in the company's products.

Cherwell's clients are mainly within the pharmaceutical sector, operating to the rigorous standards laid out in Good Manufacturing Practice (GMP). These customers demand high quality and as such any supplier must have robust procedures and processes in place. The 2015 version of ISO9001 quality management places greater emphasis on the leadership of the business and risk assessment to understand issues that could affect the business.

Cherwell's product offering includes the Redipor® range of prepared media which it has been manufacturing for over 30 years. Developed to service industrial markets, the range offers flexibility, reliability and choice for users and includes a selection of petri dishes, settle plates, bottled media, injection vials and DIN bottles, broth bags and ampoules. Cherwell has a strong understanding of users' needs and an ability to offer bespoke products as a solution to help resolve issues.

Visit **www.cherwell-labs.co.uk** for more information about Cherwell's Redipor® range of media, SAS air sampler product range and environmental monitoring accessories.

Further Information

Visit: **www.cherwell-labs.co.uk**
Tel: **+44 (0)1869 355500**
Email: **sales@cherwell-labs.co.uk**

To Automate or Not to Automate (your media preparation); that is the question

Automated media preparation in-house using automated preparation equipment allows preparation, sterilization and dispensing to be performed quickly, flexibly and efficiently.

Media Preparation

Using a preparator such as the Masterclave 10, rather than a standard autoclave, provides a clear advantage. Effective sterilization is ensured as the temperature of the actual media is measured. Media can be maintained at a specific temperature or cooled to allow dispensing. This can help to reduce the risk of burns or scalds. To eliminate hot spots and ensure thorough mixing, media is continuously stirred without introducing air bubbles.

Plate Pouring

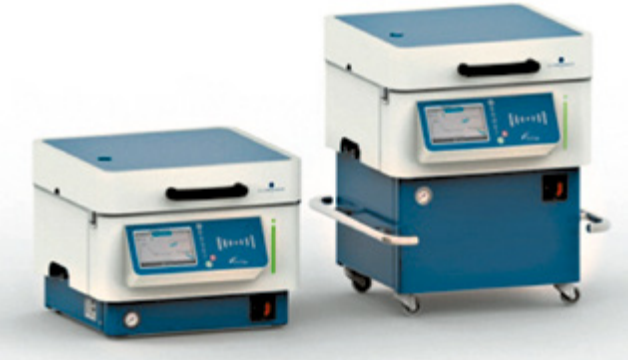
Processed sterile media can then be dispensed directly from the Masterclave 10 to the APS One, an automated plate pourer that allows prepared agar plates to be stacked ready for use. Over 700 plates can be dispensed in an hour. For traceability, operator names and batch numbers can be entered and it's possible to add a chart recorder or barcode reader.

There is a perception that automated media preparators are expensive. However when you consider the amount of time they save and the reduced chance of contamination, they are the very best way of producing consistent, high quality culture media.

Further Information

Visit: **www.dwscientific.co.uk**
Tel: **+44 (0)1274 595728**
Email: **sales@dwscientific.co.uk**

Masterclave 10 and 20 Media Preparators



One-day Food Testing

Detection of food pathogens in a single day
Control in IV Range

GPS™ (**genetic PCR solutions™**, a brand of Genetic Analysis Strategies SL.) has developed a protocol for foodborne pathogen control that allows users to obtain results in a single working day. Time of each step has been reduced and the procedure has been simplified and optimized. The method is easy, safe and fast.

- **Minimum enrichment times**. Validations with different kind of food samples by spiking <10 cells. *Salmonella enterica* 8 hours, *Escherichia coli* 8 hours, *Listeria monocytogenes* 12 hours.
- **FastExt®**. GPS™ rapid DNA extraction (<20 min) from Peptone Broth and Fraser media pre-enrichments, eliminates PCR inhibitors, and validated in different matrices (vegetables, meat, dairy, cereals, and fruits).
- **Pathogen panel**. All qPCRs run with the same protocol (temperature and time), allowing all pathogens to be tested simultaneously in single-plex at very low cost. Avoid false negatives!
- **MONODOSE**, GPS™ Innovation. Ready-to-use PCR tubes contains all the reagents needed to perform the detection test for each specific pathogen. Just add the sample!
- **Fast-Cycling, qPCR in 35 min***. GPS™ has optimized its reagents to use a thermo-cycling protocol with very short reaction times (8 min). *, qPCR total time depends on your thermocycler ramp rates.

Further Information

Visit: **www.geneticpcr.com**
Tel: **+44 (0)965 429 901**
Email: **info@geneticpcr.com**

Environmental swabbing for Norovirus?

In a study presented at the recent European Society for Clinical Virology, it has been demonstrated that MWE's NRS II™ Transwab® can recover Norovirus GII from simulated food contact surfaces including stainless steel and polypropylene.

Norovirus causes 18% of diarrheal disease globally. With its high infectivity and persistence, particularly in the context of the healthcare and hospitality professions, it is essential to monitor its presence in the environment. NRS II™ Transwab® is a premoistened sampling swab device, with a neutralising solution to prevent any traces of antimicrobial reagents interfering with the survival of pathogens, including viruses.

Reference

D'Agistino, M., 2018, Environmental Sampling for Norovirus GII Using NRS II™ Transwab®, *European Society for Clinical Virology 2018*, Athens Poster P106

Further Information

Visit: **www.mwe.co.uk**
Tel: **+44 (0)1225 810361**
Email: **sales@mwe.co.uk**

Newly isolated intestinal microbiota strains added to the NCIMB reference collection

Researchers from the Host-Microbiota Interactions Laboratory at the Wellcome Sanger Institute have added 20 strains to NCIMB's reference collection, including a number of novel species and genera.

This research group studies the intestinal microbiota, and the strains they have deposited in the collection are all strict anaerobes that have been isolated from human faecal samples. The strains are from a number of different families and genera including *Bacteroides*, *Enterococcus*, *Escherichia*, *Propionibacterium*, *Sarcina*, *Bifidobacterium*, *Gordonibacter*, *Alistipes*, *Pediococcus*, *Lactobacillus* and *Clostridiaceae*.

These strains are an exciting addition to the NCIMB collection. The work that this research group is doing in culturing and isolating gut bacteria is making a significant contribution to the understanding of gut microbiota and its compositional diversity, so we are delighted to be able to make the strains they have deposited available to the wider research community.

NCIMB manages the National Collection of Industrial, Food and Marine Bacteria: a reference collection of ACDP hazard group 1 and 2 microorganisms that includes many environmentally important and industrially useful bacteria, plasmids and bacteriophages. The collection is continuously expanding as a result of new accessions from the international research community.

To purchase strains, or for information on how to deposit strains with NCIMB, contact enquiries@ncimb.com or visit our website www.ncimb.com.

Further Information

Visit: **www.ncimb.com**
Tel: **+44 (0)1224 711 100**
Email: **enquiries@ncimb.com**

NCTC: A member of the UK Biological Resource Centre Network (UKBRCN)

The National Collection of Type Cultures (NCTC) is one of four Culture Collections operated by Public Health England. Founded in 1920, it is the longest-established collection of its type, and serves as a United Nations Educational, Scientific and Cultural Organization (UNESCO) Microbial Resource Centre (MIRCEN).

NCTC holds almost 6000 type and reference bacterial strains, many of medical, scientific and veterinary importance. Our strains support academic, health, food and veterinary institutions and are used in microbiology laboratories and research institutes worldwide. All strains are available in a freeze-dried format and DNA from over 150 strains is available via the online catalogue.

NCTC is a dynamic collection and this year alone 150 new strains have been added to the collection. To keep up to date with NCTC news and developments, sign-up to our mailing list to receive newsletters and promotions by email. The first 50 to sign up will receive a Cultures Collections goodie bag and a 20% discount for their institution's next order.

www.phe-culturecollections.org.uk/signup

Further Information

Visit: **www.phe-culturecollections.org.uk**
Tel: **+44 (0)1980 612512**
Email: **CultureCollections.BusinessE@phe.gov.uk**

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