When the drugs won't work

Antimicrobial resistance and the future of medicine

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The International Longevity Centre – UK (ILC-UK) is a futures organisation focussed on some of the biggest challenges facing Government and society in the context of demographic change.

We ask difficult questions and present new solutions to the challenges and opportunities of ageing. We undertake research and policy analysis and create a forum for debate and action.

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Preface

The Jack Watters debate: Tackling antimicrobial resistance in an ageing society, took place on the 16th November 2016 at the Old Operating Theatre Museum in London.

This event was dedicated to a long term supporter of the ILC-UK and a pioneer in championing the health and well-being of ageing people, Dr. Jack Watters.

The debate was chaired by Baroness Sally Greengross (Chief Executive, ILC-UK) and saw the participation of:

- **Professor David Salisbury CB**, *Associate Fellow, Centre on Global Health Security Chatham House*
- **Matthew Edwards**, *Head of Mortality and Longevity, Towers Watson*
- **Michelle Bresnahan**, *Founder, A Life for a Cure*
- **Dr Gina Radford**, *Deputy Chief Medical Officer*

Jack Watters served as Pfizer US Vice President for External Medical Affairs. In a pharmaceutical career spanning more than thirty years, Jack pioneered the landmark Diflucan Partnership Programme; championed the 'Get Old' campaign to promote positive attitudes and approaches to ageing, and worked tirelessly in the fields of human rights, HIV/AIDS and ageing.

To celebrate Jack's life and contribution to public health advancements around the world, the ILC-UK organised this special debate on one of the greatest challenges of the 21st century: the threat posed to medicine by the rise of antimicrobial resistance. Fittingly held in the oldest operating theatre in Europe, the debate focused on what must be done to prevent (in the words of Lord O'Neill, Chair of the UK's Review on Antimicrobial Resistance) medicine being plunged '*back into the dark ages*'.

Senior policymakers and patient group representatives discussed the UK, and global challenge posed by antimicrobial resistance; the specific risk posed to healthy longevity; and what Government and civil society can do to meet these challenges. This information report contains a summary of what was discussed, and provides a resource for those interested in how they can help to prevent the rise of antimicrobial resistance.

When the drugs won't work: Antimicrobial resistance and the future of medicine

'The world could soon be "cast back into the dark ages of medicine" unless action is taken to tackle the growing threat of resistance to antibiotics.'

David Cameron, 2014

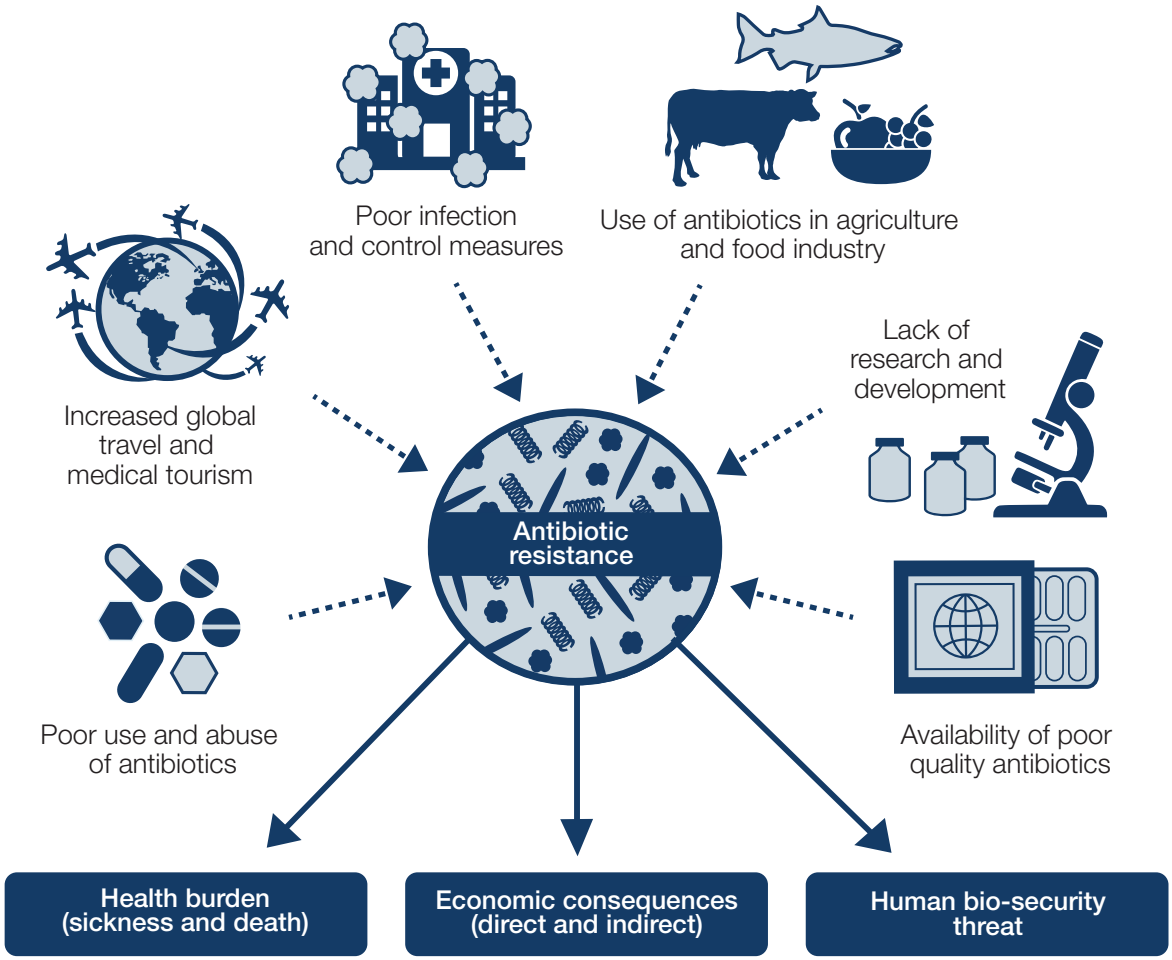
1. Introduction

On the 21st September 2016, the UN dedicated a day to a high-level discussion on an issue Secretary General Ban Ki-moon warned 'will undermine sustainable food production, put the sustainable development goals in jeopardy and make providing high-quality universal health coverage more difficult, if not impossible[1]'.

The UN's meeting on antimicrobial resistance (AMR) was only the fourth in its history to be held on a health issue, an issue which has been described by senior medical professionals as 'an unprecedented threat to human health[2]'. On 16th November 2016, the International Longevity Centre – UK (ILC-UK) assembled policy makers, medical professionals, industry and patient group representatives to consider the role of supranational organisations, Governments, medical professionals and individuals in preventing the rise of AMR.

This information resource seeks to provide an introduction to AMR: what it is, how it occurs, and the nature of the threat it poses to humanity and modern medicine. It will summarise what was discussed at the Jack Watters debate, and will conclude by exploring what each of us, either as policy makers, medical innovators or private individuals can do to prevent medicine being 'plunged back into the dark ages[3]'.

Fig 1: Influences of Antibiotic resistance[4]



[1] Ban Ki-moon, 21st September 2016, High-Level meeting on Antimicrobial Resistance, UN Headquarters. For more information see http://www.un.org/pga/71/event-latest/high-level-meeting-on-antimicrobial-resistance/
[2] M. Dryden, '*Case study: Surgihoney Reactive Oxygen (SHRO)*', p24, IFoA Longevity Bulletin Issue 08, May 2016.
[3] David Cameron, https://amr-review.org/home.html.
[4] Adapted from I. Holanec, *'What you need to know about antibiotic resistance'*, p12, IFoA Longevity Bulletin Issue 08, May 2016.

2. What is antimicrobial resistance?

Antimicrobial resistance is a natural phenomenon, a product of evolutionary selective pressure. Mutations can occur when bacteria reproduce through the process of binary fission, i.e. when a bacteria cell divides into two new cells, containing the same genetic material as the parent cell.

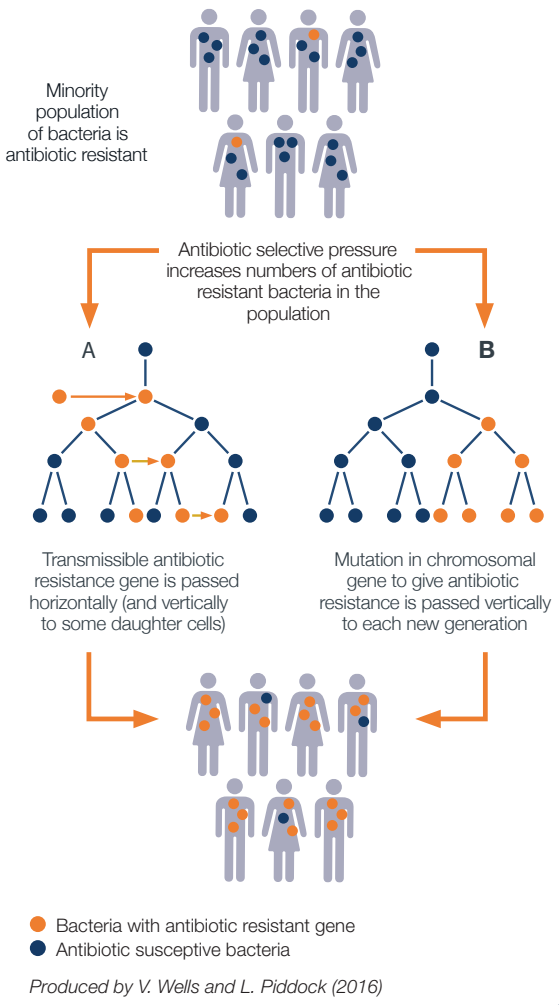
Some of these mutations can confer resistance to one or more types of antibiotic; as Wells and Piddock explain, 'In antibiotic-susceptible populations of millions of bacteria, occasionally a few may be drug-resistant. In the presence of an antibiotic, all of the susceptible bacteria die, allowing drug resistant bacteria to proliferate. These can reach huge numbers within just one day[5]'.

As well as proliferating through reproduction, bacteria can also transmit resistance genes via small cell elements called plasmids; these are mobile elements which can transfer genetic material between bacterium, and between very distantly related bacteria. Figure 2 illustrates the manner in which AMR arises and is passed on and around bacterial populations.

Selective pressure has ensured that different bacteria have developed resistance to every type of known antibiotic. Figure 2 illustrates the period of time between each new antibiotic discovery, and the first instances of resistance to that type of antibiotic. Antimicrobial resistance is a natural, and inevitable phenomenon.

[5] V. Wells and L. Piddock, '*How antibiotic resistance emerges*', p5, IFoA Longevity Bulletin Issue 08, May 2016.

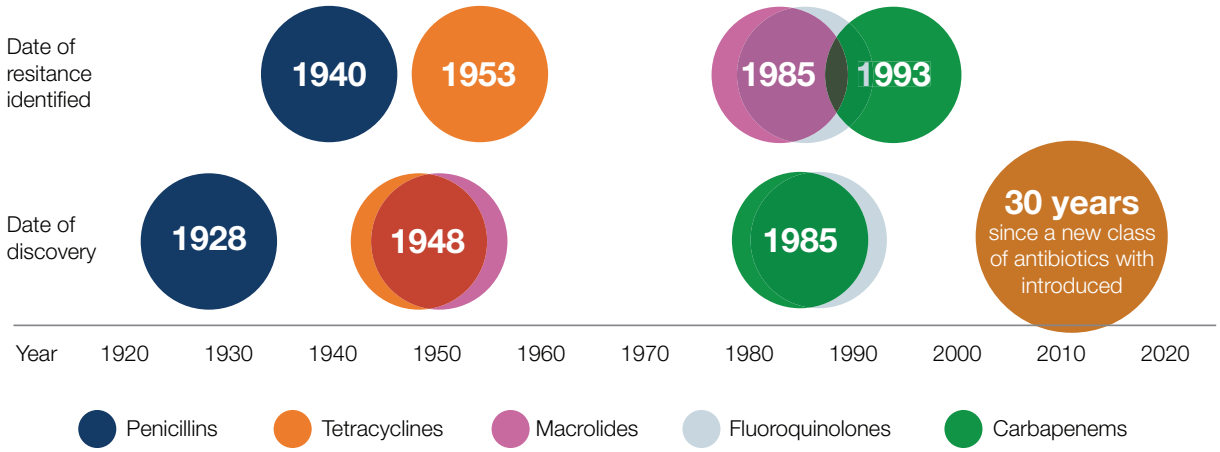
Fig 2: How antibiotic resistance arises and spreads in bacterial populations



Produced by V. Wells and L. Piddock (2016)

'In the presence of an antibiotic, all of the susceptible bacteria die, allowing drug resistant bacteria to proliferate. These can reach huge numbers within just one day.[4]'

Fig 3: Timeline of antibiotic discovery and subsquent resistance



Source: Perry and Woolhouse (2016)

However, as Perry and Woolhouse note, 'Resistance is fuelled by inappropriate antibiotic use, unnecessarily prolonged antibiotic courses and the use of untargeted antibiotic treatment[6]'. If a course of treatment is not finished, a small population of bacteria can persist, and reproduce; Sir Alexander Fleming warned of such dangers in 1946, claiming 'The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin resistant organism[7]'. Also, the more antibiotics are used, the greater the selection pressure for bacteria to develop genes to resist antibiotic treatment.

Recently, global consumption of antibiotics has increased dramatically. Between 2000 and 2010, global consumption rose by 36%[8], with Van Boeckel et. al attributing this rise 'largely as a result of increased access in the developing economies of Brazil, Russia, India, China and South Africa[9]'.

Furthermore, colistin, the so-called last line of defence, the antibiotic reserved for when all other antibiotic treatments have failed, is also being used more commonly. Originally not administered at all, given its potential to cause kidney damage, a Freedom of Information request issued to Public Health England in February 2017 found that prescriptions of colistin rose by 40% between 2014 and 2015, from 346,143 doses to 485,024 doses[10].

Between 2000 and 2010, global consumption of antibiotics rose by 36%.

Prescriptions of colistin rose by 40% between 2014 and 2015.

[6] M. Perry and M. Woolhouse, '*Clinical implications of antimicrobial resistance*', p7, IFoA Longevity Bulletin Issue 08, May 2016.
[7] The World Weekly, 21 September 2016, http://www.theworldweekly.com/reader/view/storyline/2016-09-21/the-world-launches-a-landmark-drive-to-save-mankind-from-the-post-antibiotic-apocalypse/9088
[8] See T.P. Van Boeckel, S. Gandra, A. Ashok, Q. Caudron, B.T. Grenfell, S.A. Levin, and R. Laxminarayan, '*Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data*'. Lancet Infect. Dis. 14, 2014.
[9] M. Perry and M. Woolhouse, op. cit., p7.
[10] The Bureau of Investigative Journalism, 24th February 2017 https://www.thebureauinvestigates.com/stories/2017-02-24/colistin-antibi-

Colistin is also used in the agricultural industry, to promote muscle growth amongst livestock. Global demand for colistin in agriculture is predicted to reach 165,000 tonnes by 2021. Around 8000 tonnes of the drug were given to farm animals each year in China alone[11], the country where the first instance of colistin resistance was detected.

Around 8000 tonnes of the antibiotics are given to farm animals in China each year.

otic-resistance-superbugs-hospitals

[11] See Y. Liu,Y. Wang, T. Walsh, L. Xian, R. Zhang, J. Spencer, Y. Doi, G. Tian, B. Dong, X. Huang, L. Yu, D. Gu, H. Ren, BS, Xiaojie Chen, MS, Luchao Lv, MS, Dandan He, MS, Hongwei Zhou, PhD, Prof Zisen Liang, MS, Prof Jian-Hua Liu, Prof Jian-Hua Prof Jian-Hua Liu, Prof Jianzhong Shen, '*Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study*', The Lancet, 16:2, 2015.

3. The Threat

In 2015, research published in the Lancet confirmed the first recorded cases of plasmid-mediated colistin resistance in samples taken from products on the Chinese chicken and pork market[12]. They also recorded evidence of the colistin resistant gene mcr-1 in patients with infections in two hospitals in Guangdong and Zhejiang provinces. In 2017, the same research team found that around 1% of hospital patients in two hospitals in Zhejiang and Guangdong exhibited colistin resistance, even though they had never been exposed to the drug.

They also discovered that mcr-1 is proliferating beyond farms via flies and birds, and concluded that the DNA sequences of bacteria from farms, supermarket meat products and humans was so similar that colistin resistance must have spread first to the poultry sector, and then to humans.

Already, drug-resistant infections are estimated to account for around 700,000 deaths per year[13], with: 200,000 deaths globally from multidrug-resistant tuberculosis[14]; around 50,000 deaths per year in Europe and the US[15] and 60,000 new born deaths from antibiotic-resistant neonatal infections in India alone[16]. However, if colistin, and the broader family of last defence antibiotics known as polymyxins are rendered redundant by AMR, the consequences are catastrophic.

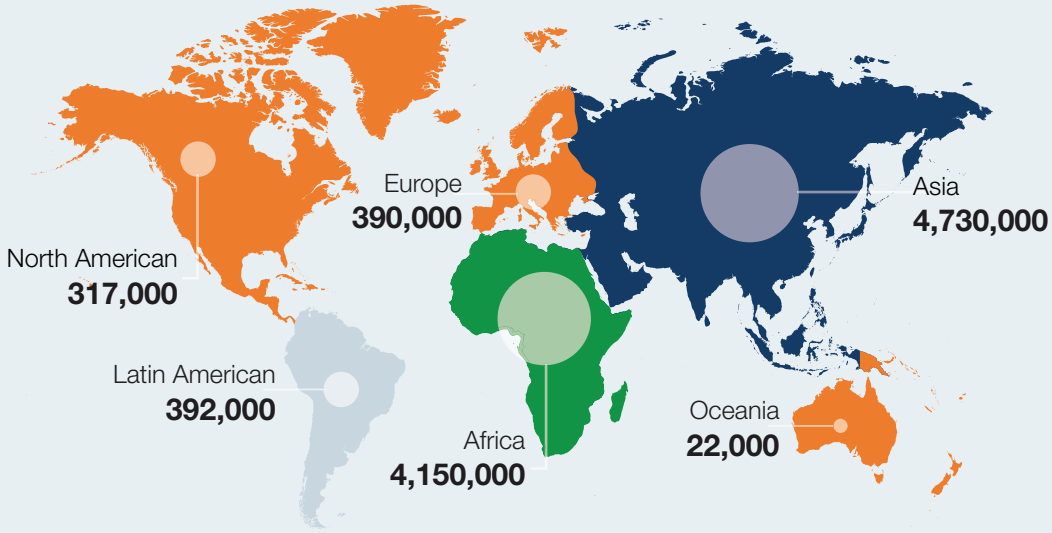
The Review on Antimicrobial Resistance, chaired by Lord O'Neil, in conjunction with Rand Europe and KPMG projected that by 2050, global mortalities due to AMR could reach 10,000,000, and cost the global economy £66 trillion in lost productivity[17], through increasing the fatality rate of infectious diseases such as pneumonia and TB; through infections acquired whilst receiving cancer treatments such as chemotherapy; and through infections acquired during routine surgical procedures.

Drug-resistant infections are estimated to account for:

- **Around 700,000 deaths per year.**
- **200,000 deaths globally from multidrug-resistant tuberculosis.**
- **Around 50,000 deaths per year in Europe and the US.**
- **In India 60,000 new born deaths from antibiotic-resistant neonatal infections per year.**

[12] Ibid.
[13] See The Review on Antimicrobial Resistance's 'Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations', 2014, https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf
[14] WHO, Tuberculosis Factsheet, Online, Available at: http://www.who.int/mediacentre/ factsheets/fs104/en
[15] Dame Sally Davies, Chief Medical Officer, Foreword, IFoA Longevity Bulletin Issue 08, May 2016.
[16] Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance – the need for global solutions, The Lancet Infectious Diseases 2013; 13: p.1057-98.).
[17] See The Review on Antimicrobial Resistance, 'Tackling drug-resistant infections globally: Final report and recommendations', 2016, https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

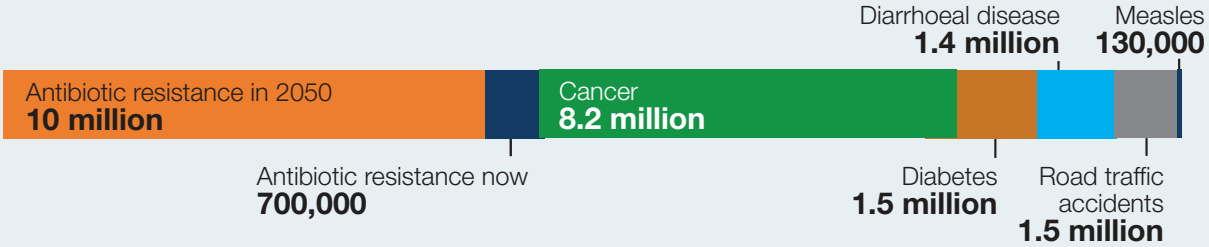
Fig 4: Death attributable to antimicrobial resistance every year by 2050



Source: Review on Antimicrobial resistance 2014

This would make antibiotic resistance the single greatest cause of death by 2050, ahead of cancer, diabetes and diarrhoeal disease.

Fig 5: Death attributable to antimicrobial resistance every year compared to other major causes of death



Source: Review on Antimicrobial Resistance 2014

Matthew Edwards, Head of Mortality and Longevity at Towers Watson informed the Jack Watters debate that Dame Sally Davies, England's Chief Medical Officer's concern that 'the recent era of material mortality improvements will give way to many years of material mortality worsening[18]' is well founded. In fact, by his calculations, 'the magnitude of the problem is sufficient to, at worse (a 'plausible' worst rather than a 1-in-200 year extreme event), largely zeroise or even negate[19]' longevity improvements made since the mid-20th century.

It is for these reasons that AMR has been described as 'an unprecedented threat to human health', and why the UK Government's latest official emergency risk assessment compiled by the Secretariat for Civil Contingencies, the National Risk Registry (NRR), has a section dedicated to AMR. It notes that

The latest NRR notes that the most 'significant civil emergency risk' is pandemic influenza, and that such an event would become more serious without effective treatments.

[18] Dame Sally Davies, op. cit.
[19] M. Edwards, 'Antibiotic resistance and longevity improvements', p16, IFoA Longevity Bulletin Issue 08, May 2016.

the reason AMR is not included in the main risk matrix is because it represents a longer-term issue, not confined to a single event. The 2015 NRR lists the most 'significant civil emergency risk' as pandemic influenza, and also notes that 'influenza pandemics would become more serious without effective treatments', in light of AMR; presumably due to the risk of secondary infections occurring, such as ear and sinus infections.

Overall relative impact score					
5				Pandemic influenza	
4			Coastal flooding Widespread electricity failure		
3		Major transport accidents Major industrial accidents	Effusive volcanic eruption Emergency infectious diseases Inland flodding	Severe space weather Low temperature and heavy snow Heatwave Poor air quailty events	
2		Public disorder Severe wildfires	Animal diseases Drought	Explosive volcanic eruption Storms and gales	
1			Disruptive industrial action		
	Between 1 in 20,000 and 1 in 2,000	Between 1 in 2,000 and 1 in 200	Between 1 in 200 and 1 in 20	Between 1 in 20 and 1 in 2	Greater than 1 in 3
Relative likelihood of occurring the next five years					

Fig 6: National Risk Register of Civil Emergencies 2016

Source: National Risk Register of Civil Emergencies 2016

It is this level of threat that has also prompted action from the G8 group of nations, the UN, and the WHO.

4. What can I do?

4.1 Governments and supranational organisations

The United Nations have devised and published the UN Action Plan on AMR, which commits nations to:

- Develop surveillance and regulatory systems on the use and sales of antimicrobial medicines for humans and animals
- Encourage innovative ways to develop new antibiotics, and improve rapid diagnostics
- Educate health professionals and the public on how to prevent drug resistant infections

Some Governments and supranational organisations have already begun to work towards realising the action plan. The World Health Organisation, in response to their 2014 report on AMR worldwide have committed to implement a surveillance and regulatory system to measure trends and identify problem pathogens early.

In terms of improving rapid diagnostics, prizes such as the Longitude Prize in the UK and similar prize funds in the US and across the EU have been founded to incentivise the creation of a test to quickly identify the cause of an infection and determine whether to use antibiotics and if so which types. It is hoped that such tests could dramatically reduce global antibiotic consumption if deployed successfully.

Governments are also taking measures to address areas of concern particular to their own nation. For example, China has banned the use of colistin in the agricultural sector from April 2017, and the UK has set its own target to reduce inappropriate prescriptions and the incidence of high risk bacterial infections in hospitals by 50% by 2020, and to reduce the level of antibiotic use in the agricultural sector to 50mg/kg by 2020; this would represent a 10.7% reduction in antibiotic usage in food producing animals from 2015 levels (56mg/kg)[20].

However, the O'Neil Review's final recommendations placed a number of demands on Governments to encourage the development of new antibiotics. Whilst Governments have committed funding to AMR non-commercial R&D, through initiatives such as the BARDA biopharmaceutical Accelerator in the US, and the EU's Innovative Medicines Initiative (IMI), the Review called for the establishment of a global innovation fund endowed with $2 billion over a five year period. The Review suggested that such funds should aim to fund around 15 licensed antibiotics per decade, which should aim to encompass two new broad spectrum classes and two new targeted therapeutic classes every ten years.

The O'Neil Review's final report also emphasised the role of vaccines in reducing the need for antibiotic use and reducing global consumption. The WHO have calculated that if the coverage of existing vaccines was increased, millions of days of antibiotic use could be prevented.

China has banned the use of colistin in the agricultural sector from April 2017.

[20]Veterinary Antimicrobial Resistance and Sales Surveillance 2015, Veterinary Medicines Directorate, 2016, https://www.gov.uk/government/publications/veterinary-antimicrobial-resistance-and-sales-surveillance-2015

For example, if every child in the world was vaccinated against streptococcus pneumoniae, an estimated 11 million days of antibiotic use would be saved each year. Similarly, if flu vaccination rates increased, antibiotic use would also be reduced, as antibiotics are often taken unnecessarily when individuals present with symptoms such as fever that can be caused by a virus. Additionally, secondary infections arising from influenza, such as sinus and ear infections, require antibiotic treatment; therefore, reducing flu rates can reduce the need to treat such secondary infections.

The WHO also notes that the development of new vaccines to protect against common diseases such as group A streptococcus, and diseases which are now frequently drug resistant such as multi-drug resistant tuberculosis (MDR-TB) could also reduce antibiotic usage. The O'Neil Review has recommended that Governments incentivise the creation of new vaccines through pledging Advanced Market Commitments (a commitment to purchase certain quantities of vaccine in advance to ensure a viable market), and/or provide market entry rewards.

As for expanding vaccine coverage, at the Jack Watters debate, Professor David Salisbury, Associate Fellow at the Centre on Global Health Security at Chatham House claimed that there 'is no debate' as to whether more should be done to increase the coverage rate of a wide range of vaccines, across the life course.

Fig 6: Opportunities for future vaccinations

Vaccines:

- **Respiratory Syncytial Virus**
- **Staphylococcus aureus**
- **Clostridium difficile**
- **Escherichia coli**
- **Norovirus (Children, at risk groups and older people)**
- **Pseudomonas**
- **Klebsiella**
- **Alzheimer's**
- **Diabetes**
- **Cancer**

Source: Presented by Professor David Salisbury at the Jack Watters debate

The O'Neil Review notes that vaccine programmes often 'save society more than 10 times their original cost[21]', and are an effective way of protecting against vaccine preventable diseases, in addition to reducing antibiotic consumption. Policymakers can seek to increase coverage rates of current vaccines through ensuring that a wider range of vaccines are made available on the NHS, and by investing in public health campaigns to highlight the importance of immunisation throughout the life course.

[21] F. Zhou, A. Shefer, J. Wenger et al, '*Economic evaluation of the routine childhood immunization program in the United States*', Pediatrics, 133:4, 2009.

4.2 Medical Professionals

Whilst the medical professional currently lacks a comprehensive diagnostic tool to determine whether antibiotics should be used, and if so which type, healthcare workers are being called upon to consider their roles as stewards of antibiotics. Ó Gráda notes that if all European medics reduced the use of antibiotics to Dutch consumption levels, Europe-wide usage would be cut by almost 50%[22].

Also, ensuring that thorough infection control strategies are in place in healthcare settings is also key; a study of antibiotic usage in the Grampian region of Scotland found a 50% reduction in the prevalence of MRSA following the introduction of stewardship education and infection control strategies[23].

Healthcare workers can also continue to inform and educate their patients about the importance of finishing all courses of antibiotics, and challenging patients who request antibiotics to treat symptoms not caused by bacterial infection. Healthcare workers also have a role to play in informing their patients about the benefits of immunisation, to help increase vaccine coverage rates and ultimately reduce antibiotic usage.

Grampian region of Scotland found a 50% reduction in the prevalence of MRSA in hospitals following the introduction of stewardship education and infection control strategies.

[22] C. Ó Gráda, '*Economic implications of antibiotic resistance: not all gloom and doom*', p19, IFoA Longevity Bulletin Issue 08, May 2016.

[23] T. Lawes, J.M Lopez-Lozano, C.A. Nebot, G Macartney, R. Subbarao-Sharma, C.R Dare, K.D. Wares, I.M Gould, '*Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant Staphylococcus aureus infections across a region of Scotland: a non-linear time-series study*', Lancet Infect. Dis. 15, 2015.

4.3 Individuals

Each of us can take steps to help prevent the rise of AMR. Being conscious of when antibiotics should not be taken, e.g. to treat symptoms caused by viruses, and completing a course of antibiotics if they are taken can help to reduce usage, and prevent bacterial remnants from persisting.

At the Jack Watters debate, Dr Gina Radford, Deputy Chief Medical Officer also reminded guests of the importance of practicing good hygiene to reduce the risk of infection. Dr Radford informed attendees

'On a day to day basis, you should wash your hands with soap and water for the length of one verse of God Save the Queen, or two times through Happy Birthday. I can absolutely guarantee that most of us don't do that. I know because I have observed, and I have observed myself. We don't do some of this stuff, and we are not practising just some of the most basic hygiene'.

"Remember the importance of practicing good hygiene to reduce the risk of infection."

Dr Gina Radford, Deputy Chief Medical Officer

Individuals can also check to see if they are eligible for vaccinations provided on the NHS, such as the seasonal influenza vaccine, or, where available, can look to book a private appointment with their GP practice or local pharmacist. Michelle Bresnaham, founder of 'A life for a cure', an advocacy group promoting uptake of meningitis vaccines, reminded attendees of the Jack Watters debate that as well as helping to reduce antibiotic usage, raising awareness about the benefits of life course immunisation also protects against the burden of disease at all ages.

Like all great challenges that demand a global response, AMR requires a coordinated response at every level, from supranational organisations, to national Governments, to hospitals and to individual members of the public. Through each of these actors being aware of how their actions can either accelerate the rise of AMR or help to prevent it, we may yet be able to confront this unprecedented threat to human health, and prevent medical practice from being plunged back into the dark ages.

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