Sustaining global action on antimicrobial resistance

Foreword

As I write this, almost a year has passed since the United Nations General Assembly (UNGA) high-level meeting on antimicrobial resistance (AMR). The landmark UNGA Political Declaration demonstrated that understanding of the global AMR threat in humans, animals, agriculture and the environment has now reached the highest levels. The declaration also called for the establishment of an ad hoc Inter-Agency Coordination Group (IACG), of which I am one of the three co-convenors. Since being established in March 2017, the IACG has published a Framework for Action[1] and has been developing its work plan for how to respond best to the challenge that drug-resistant infections pose to humanity. The IACG will provide details on progress made and recommendations on next steps in its report back to the UN Secretary-General during the 73rd session of the UNGA, culminating in September 2019.

The UK's independent Review on Antimicrobial Resistance, led by Lord O'Neill, found that drug-resistant infections already cause around 700,000 deaths worldwide each year. If AMR continues to emerge and spread at the current rate, then the enormous benefits antibiotics have provided to society will be seriously eroded. The O'Neill Review predicted that such a scenario would cause up to 10 million deaths a year globally by 2050, but set out a roadmap for how such a situation could be controlled through national and international efforts.

While AMR is a natural phenomenon, and all antibiotic use contributes to the development of drug resistance, it is inappropriate antibiotic use that is of greatest concern, and this is something that *can* be addressed. Beyond discovering new antibiotics and alternative therapies, we must commit sufficient resources to getting the balance right between, on the one hand, preserving the effectiveness of existing antibiotics by reducing their inappropriate use, and on the other, ensuring that they are accessible to all who need them.

As reported at the World Health Assembly this year, there has been good progress on developing National Action Plans (NAPs) on AMR: 67 countries had one with a further 62 in development, covering 90 per cent of the world's population[2]. We now need to shift the focus to ensure these plans are implemented. AMR is one of the most complex health and economic threats facing society today and will be for the foreseeable future, but as this pamphlet shows, much progress can be made in a year – and we need to continue to do more.

Producing this pamphlet and distributing it at the 21 September 2017 UNGA AMR side event is just one of the ways Wellcome and the UN Foundation are supporting the IACG. They are also joining with the governments of the UK and Thailand at another call to action in Berlin in October 2017. There and elsewhere, all stakeholders will be encouraged to do what they can to address AMR. We must continue to deliver the advances needed to maintain antibiotic effectiveness and quell this major threat to health, prosperity and the UN's Sustainable Development Goals (SDGs).

Professor Dame Sally Davies
Chief Medical Officer for England

September 2017

Global governance update

Worldwide action to control AMR gained a historic boost at the UNGA on 21 September 2016. There, for the first time, UN member states unanimously committed to taking a collaborative and holistic approach to tackling AMR. They called on all sectors, encompassing human health, animal health and agriculture, to address the root causes of AMR and mitigate what could be a major public health crisis. Their Political Declaration on AMR builds on important commitments made by the governing bodies of the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) in 2015.

"AMR poses a formidable threat to the attainment of the SDGs, and in particular our ability to ensure good health and wellbeing, to maintain clean water and sustainable food production, and to eliminate poverty. Member states recognised this last year at the UNGA. While countries must be in the driver's seat, it is incumbent on all of us, across all sectors, to work together to address this challenge."

Dr Jeremy Farrar
Director of Wellcome

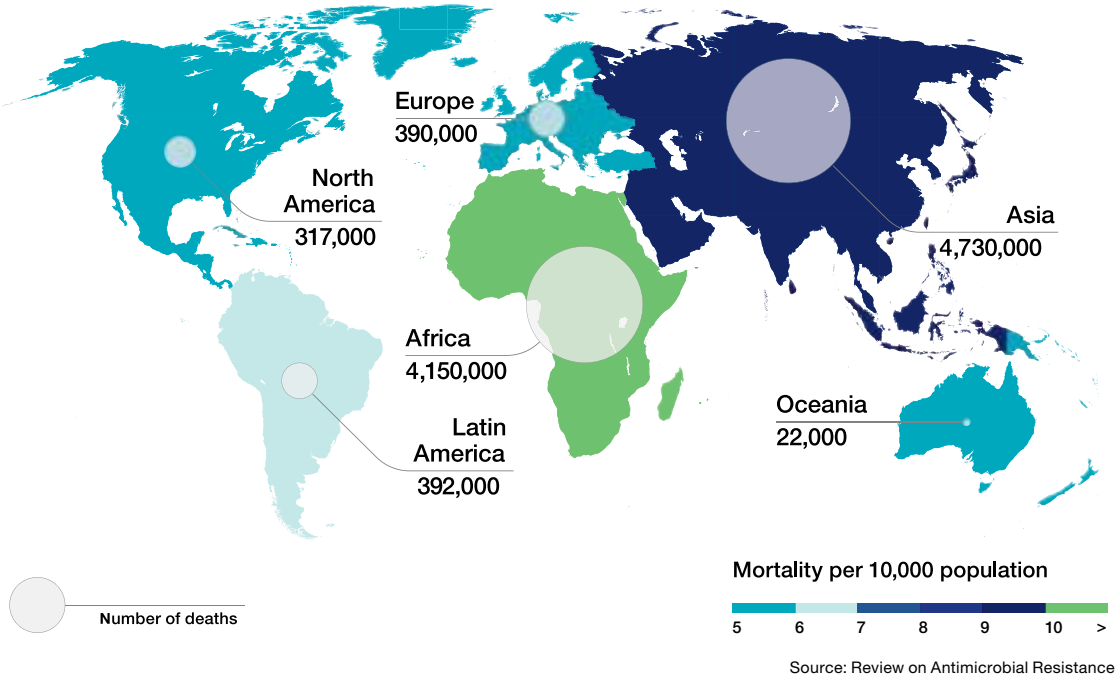
The Political Declaration noted that the SDGs will only be achieved if AMR is tackled. It also outlined several global governance responses, including calling upon the WHO, FAO and OIE to finalise a global development and stewardship framework. Another key action it specified was to establish the IACG on AMR, co-chaired by the UN Deputy Secretary-General and the Director-General of the WHO, whose mandate would be to provide practical guidance for ensuring sustained effective global action to address AMR. The IACG was officially founded on 17 March 2017, incorporating 27 organisations and 15 independent experts. Three conveners were appointed to direct the group's work – Professor Junshi Chen, Professor Dame Sally Davies and Ms Martha Gyansa-Lutterodt. The IACG will produce a report to present to the UN Secretary-General during the 73rd session of the UNGA in 2018 and 2019.

The IACG held its first meeting in New York on 2–3 May 2017, followed by a teleconference on 30 June. It has adopted a Framework for Action, based on over 150 interviews[7]. The Framework establishes a comprehensive view on 14 different issues mapped against the SDGs and the WHO's Global Action Plan (GAP) on AMR, and presents five levers that can help address them. A second teleconference and a face-to-face meeting, held in September and October 2017 respectively, will build on this.

The Framework also underpins the IACG's work plan for 2017–19, which is available online, and its five primary objectives:

1. To support the implementation of the UNGA Political Declaration and the GAP and link them to the SDGs by championing and advocating for action against AMR at the highest political level.
2. To coordinate mapping of the actions being taken by UN agencies – and other organisations and key stakeholders – towards achieving measurable results, and to identify opportunities for collaboration, as well as gaps, redundancies and duplication.

Deaths attributable to AMR every year by 2050



Source: Review on Antimicrobial Resistance

3. To promote, plan and facilitate collaborative action to align activities so that gaps are closed and resources are optimally distributed.
4. To explore the feasibility of developing global goals and ambitions related to AMR for UN agencies, component members and, where appropriate, other stakeholders, for priorities set out in the declaration.
5. To report regularly on progress and on IACG meetings and issue a full report to the Secretary-General during the 73rd session of the UNGA, keeping member states, stakeholders and the governing bodies of the FAO, OIE and WHO fully apprised of progress.

The IACG will require support from stakeholders across the global community to fulfil this plan.

The IACG's establishment also follows calls for collective action from other stakeholders.

The G20's leading economies have also agreed to work together to tackle AMR. On 19 May 2017, health ministers from the G20 countries made recommendations that were then adopted on 8 July 2017[4]. These aims include having NAPs based on the One Health approach (see page 12) well underway by the end of 2018.

The leaders of the G20 countries have also highlighted the importance of fostering R&D, in particular for priority pathogens as identified by the WHO and for tuberculosis. A key element of this will be the Global AMR R&D Hub, recently launched under Germany's leadership of the G20.

Meanwhile, the WHO continues its own efforts to facilitate implementation of the GAP, having held several meetings across the world over the past year. For example, at the WHO headquarters in Geneva experts came together on 8–9 June 2017 to discuss indicators for monitoring and evaluating country and global efforts to tackle AMR. Also in Geneva, another expert consultation meeting on health workforce and AMR education was held on 23–24 March 2017. Following that, a subcommunity on Health Workforce AMR Education and Training has been established that has created a list of 91 available educational tools.

Epidemiological update

Drug-resistant infections have continued to emerge and spread throughout the world over the last 12 months. Many strains of bacteria are increasingly displaying resistance to combinations of commonly used and last-resort antibiotics. The WHO is particularly concerned about resistance among ESKAPE pathogens: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* *Pseudomonas aeruginosa* and *Enterobacter* species, such as *Escherichia coli*[5].

A report published in January 2017 by the European Centre for Disease Prevention and Control (ECDC) surveyed AMR trends for the period 2012–15[6]. It found that more than one-third of *K. pneumoniae* isolates showed resistance to at least one antimicrobial class. Resistance levels and the proportion of *K. pneumoniae* bacteria possessing enzymes that confer resistance to many highly effective antibiotic classes are increasing[7]. Similarly, more than half of *E. coli* isolates showed resistance to at least one antimicrobial class, with resistance levels increasing. Additionally, the ECDC reported high percentages of antibiotic-resistant *P. aeruginosa* in Eastern and South-eastern Europe in 2015, with 14.9 per cent of isolates resistant to at least three antimicrobial groups; 5.5 per cent were resistant to all five groups tested. However, *P. aeruginosa* resistance to fluoroquinolones and aminoglycosides is decreasing, while resistance to carbapenems did not significantly increase. In an ECDC report published in November 2016, nine countries also reported resistance in ten or more *Acinetobacter* strains[8].

Another significant epidemiological finding from the past year was a 70-year-old woman from Nevada dying in September 2016 from systemic inflammatory response syndrome (SIRS) caused by *K. pneumoniae* unresponsive to antibiotic treatment. The woman had been repeatedly hospitalised in India for a hip injury before returning to the USA. Isolates from the patient showed that the strain was resistant to 26 antibiotics[9]. The situation in India also drew attention when a study of 18 poultry farms in the Punjab found resistance to 10 out of 11 antibiotics that were tested[10].

A similar theme has emerged in Europe, as a new gene conferring resistance to the last-resort antibiotic colistin has been found in *Enterobacter* from pigs in Italy, Spain and Belgium[11]. This follows findings published in January 2017 documenting the proliferation of resistance genes across Chinese clinical settings[12]. The studies detected low levels of several *E. coli* strains with resistance genes at several institutions in different provinces. The news is concerning due to the imminent release of colistin for clinical use in China.

In South Africa, a form of tuberculosis that is resistant to at least four front-line antibiotics has been reported to be spreading primarily from person to person[13]. This is significant, because it had previously been thought that patients mainly acquired extensively drug-resistant tuberculosis due to inadequate treatment.

Meanwhile, the WHO Gonococcal Antimicrobial Surveillance Programme (GASP) published data in July 2017 showing widespread resistance among gonorrhoeal infections[14]. And in Australia, the CARAlert system flagged more than 1,000 cases of bacteria resistant to last-resort antibiotics between March 2016 and March 2017[15].

These developments, coming in just the past 12 months, underline the central truth of drug-resistant infections: that they are already inflicting a cruel burden on individuals and more broadly on global health today. This truth is destined to become only more profound tomorrow without better surveillance and awareness of increasing resistance.

Dr Jeremy Farrar
Director of Wellcome

Progress with development of National Action Plans

The WHO highlighted AMR as a "serious, global threat" in April 2014. In 2015 the World Health Assembly, the governing body of all member states of the WHO, then launched its GAP, which urged member countries to develop corresponding NAPs by May 2017. The development of these plans has attracted broad attention because of AMR's deep implications, particularly its potential to threaten economic prosperity and undermine the UN's SDGs.

Included in the GAP's strategic objectives is the call to combat AMR by encouraging less reliance on antibiotics, and in the process preserve equitable access to the medicines needed to treat serious infections. The objectives seek to reduce reliance through better hygiene and other infection prevention and control (IPC) measures, and also by developing alternatives – such as vaccines. It is also important to develop improved surveillance of antibiotic use and for the appearance and spread of drug-resistant infections.

As part of its worldwide efforts, the WHO established the Global Antimicrobial Resistance Surveillance System (GLASS), whose first formal call for data ran from April 2016 to July 2017. And in an effort to monitor the GAP, the 'tripartite' organisations collaborating on One Health – the WHO, FAO and OIE – are developing a joint monitoring and evaluation approach. This will monitor, and evaluate how to improve, the process of GAP implementation, and also monitor and evaluate the results in terms of expected outcomes and impact on AMR.

More advanced economies are also assisting low- and middle-income countries (LMICs) to develop the necessary infrastructure for surveillance. For example, three scoping studies on strengthening surveillance capacity, enabled by the UK-based Fleming Fund, announced their results in March 2017[16].

Wellcome has analysed responses to the WHO country self-assessment questionnaire on NAPs. Of the 151 countries (out of 195 WHO member states) that responded:

85% of countries are developing or have developed NAPs

52% of countries have a fully developed plan that addresses the full One Health spectrum of animal, human and environmental sectors

52% of LMICs have national-level measures in place on IPC in human healthcare, but just 7 per cent have a national surveillance system for AMR in animals and foods

19% of countries have a multisectoral AMR action plan approved that reflects the GAP objectives and which features an operational plan and monitoring arrangements

5% only 5 per cent of countries have a multisectoral AMR action plan that has been implemented with identified funding sources and monitoring processes in place.

For example, in 2012 Vietnam started monitoring the sale and use of antimicrobial products through the VINARES project[17]. While this was followed in 2013 by a NAP[18], in October 2016 the SEA-EU-NET II project concluded that "In reality, the implementation of the action plan is limited", though its report went on to add that "there is interest for further commitment by the Vietnam government"[19]. Elsewhere, other more recent efforts have emulated the WHO GAP more closely, such as the Philippines' launch of its One Health-based NAP in November 2015[20].

With the UNGA recognising in 2016 of the need for coordinated action, further important steps followed. One key achievement came in April 2017, when India published a NAP including a declaration of goals and objectives created jointly between government departments[21]. Other recent activities include Fiji building on the NAP it launched in 2015 by investigating the understanding of antimicrobial stewardship among retail and hospital pharmacists[22].

Regionally, in July 2017 the European Union adopted its second action plan against AMR[23]. Also, between 2016 and 2018 the Global Antibiotic Resistance Partnership (GARP), which includes countries in Africa and Asia, intends to expand its membership from eight to 14 countries[24].

Thailand case study

In Thailand, AMR is estimated to have caused 38,000 deaths and an economic loss of $1.2 billion in 2010, thanks in part to excessive antibiotic use[25]. Having previously addressed AMR with fragmented approaches, the country developed a national strategic plan at the end of 2015. The draft plan was discussed by several hundred stakeholders before the Thai government endorsed it in August 2016. The final version comprises six strategic actions and five targets. It promotes evidence-based decisions on antimicrobial use by clinicians, policy makers, the general public and veterinarians. It aims to monitor progress on antibiotic usage patterns in humans and animals using similar surveillance systems to Europe, including a module in the national health and welfare survey. In setting up this plan, Thailand has provided a strong model for how governments can engage with and drive change across multiple sectors.

Steps by industry

The world relies on industrial companies to develop, produce and sell antibiotics and diagnostic equipment for identifying infections. These companies therefore play a vital role in combating AMR, and over the past year several events have shaped their contribution:

- In May 2017, the signatory companies to the 2016 Davos Declaration on Combating Antimicrobial Resistance – more than 100 in total – established the AMR Industry Alliance for pharmaceutical, biotech and diagnostic companies. Hosted and supported by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the Alliance will develop a mechanism to track progress, identify gaps and set targets on combating AMR, reporting first in 2018.
- Also in May 2017, the US Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) held a two-day meeting on facing the AMR challenge. There, Elanco Animal Health president Jeff Simmons discussed how labelling changes can be used to narrow the use of medically important antimicrobial drugs in food-producing animals so that they are used only to fight disease and only with veterinary oversight[26].
- In August 2017, the Netherlands-based Access to Medicine Foundation published its methodology for evaluating how companies are responding to the increase in AMR. It will assess R&D, manufacturing, production, and appropriate access and stewardship of antimicrobials with 30 companies falling within its scope, reporting back its initial findings in early 2018.

Strong industry support is especially welcome because poor financial incentives have historically diminished interest in antibiotic development, intensifying AMR concerns. Innovative new antibiotics are typically left as a last resort and therefore sell in low volumes, hampering companies' potential incomes.

$65.6m

worth of funding for 18 antibiotic and diagnostic R&D projects allocated through CARB-X partnerships to date

The diagnostic industry is similarly challenged because identifying a bacterial infection is usually more costly than prescribing antibiotics on an essentially precautionary basis. Steps taken over the past year to help industry overcome these hurdles in a sustained way that continues to fight the evolution of resistance include:

- The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), set up by the US government and Wellcome in July 2016 to drive antibacterial products into development. Since CARB-X's launch, two rounds of funding have provided up to $65.6m for 18 antibiotic and diagnostic R&D projects in India, Ireland, France, Switzerland, the USA and UK.
- The DRIVE-AB project, funded by Europe's Innovative Medicines Initiative (IMI), which has explored the issue of incentives since 2014 and reported some of its key conclusions at a major conference in September 2017. It has developed and costed new economic models to promote antibiotic innovation and sustainable use. A similar programme for diagnostics – dubbed 'DRIVE-DX' – is also now being explored[27].

- Analysis by the Margolis Center for Health Policy at Duke University, USA, of incentives for antimicrobial developers[28]. In August 2017, it recommended combining a market-entry reward with phased payments for products. Payments would be based on an antimicrobial's value to society, which would be reliant on sustainable, appropriate use so as to offer continued infection prevention. This would replace the system of volume-based payments, which leads to overuse.
- The US Food and Drug Administration (FDA) releasing, in August 2017, the final version of its guidance on how to proceed in developing antibiotics for areas of unmet need[29]. In order to streamline development, measures include accepting results from the smallest possible clinical trial programme when a novel drug looks to address an unmet need.

However, industry still needs to increase environmental surveillance and further curb antimicrobial contamination. For example, in Hyderabad, India, an April 2017 study of industrial facilities that supply many drug companies found "excessively high" levels of antibiotic and antifungal drug residue – and bacteria and fungi resistant to those drugs – in nearby water sources[30]. Clearly, more needs to be done.

100

Over 100 companies from more than 20 countries have signed the 2016 Davos Declaration on Combating Antimicrobial Resistance, and together form the AMR Industry Alliance

Research and development

As of March 2017, according to the Pew Charitable Trusts, 41 antibiotics were in development for the US market, from companies located across the world[31]. Fifteen were in phase I clinical trials, 13 in phase II, and 11 in phase III. Two drugs had completed phase III and their new drug applications were under consideration by the FDA.

Since then, there have been many positive news items on antibiotic development. Perhaps the most important is that in June 2017 the FDA approved delafloxacin to treat both Gram-positive and -negative pathogens in skin infections.

Yet less than one in three drugs in the pipeline is from a novel class or has a novel mechanism of action, Pew highlights, and only two of these are potentially active against Gram-negative ESKAPE pathogens. Additionally, while there are around 36 companies with antibiotics in clinical development, only five rank among the top 50 pharmaceutical companies by revenue.

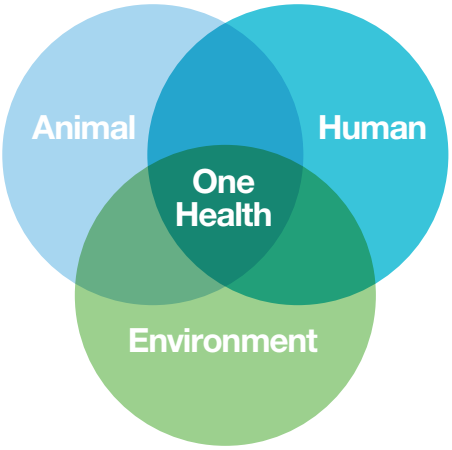
"Schemes that support research into developing new antibiotics and reward the developers even when their products are held in reserve are vital. I am encouraged by the progress made by the G20 and by initiatives such as GARDP and CARB-X, and hope that continued progress will be made in developing new incentive mechanisms and increasing investment in product development."

Jim O'Neill, former Chair of the Review on Antimicrobial Resistance

Incentive activities are therefore seeking to fill the gaps:

- Under German leadership, the G20 has committed to the development of a new Global AMR R&D Hub to improve the alignment and coordination of global AMR R&D and to support increased investment into push and pull incentives for new products.
- All CARB-X's potential new medicines target Gram-negative bacteria. The projects it has funded include several potential new classes of small molecule antibiotics as well as innovative non-traditional products.
- In August 2017, the UK and China announced that they would provide £10m and RMB 60m (~£7m) respectively for joint R&D projects to address AMR[32].
- The Global Antibiotic Research & Development Partnership (GARDP), established in May 2016 as a joint initiative by the WHO and the Drugs for Neglected Diseases *initiative* (DND*i*), is adopting a partnership model for product development. In September 2017, countries including the Netherlands, Switzerland, South Africa, Luxembourg and the UK, along with foundations such as Wellcome, pledged €56.5 million to GARDP.
- In diagnostics for AMR, which is a challenging area because many infections arise from bacteria normally found in our bodies, there are prizes seeking to encourage innovation. These include the £10m Longitude Prize in the UK, and the $20m Antimicrobial Resistance Diagnostic Challenge in the USA, which was established in September 2016. In February 2017, the European Commission awarded a €1m Horizon Prize to Philips and P&M Venge AB for a finger-prick test to identify bacterial infection.

One Health



We often hear about AMR in the context of human health, but the problem is larger. Prophylactic antimicrobial use in livestock allows more animals to be kept in closer quarters, where the spread of disease would inhibit growth. In some countries, antibiotics are used simply to promote more rapid growth of animals raised for food. Maximisation of yield is necessary as the demand for meat grows in line with the world's population.

60,000

tonnes of antimicrobials are used in animals globally per year

Over 60,000 tonnes of antimicrobials are used in animals globally per year, both therapeutically and prophylactically, and many are also used in humans. Only 42 countries have policies in place to limit the use of antimicrobials in livestock. That makes the global livestock industry a major unintentional cultivator of AMR bacteria, and these find their way into human communities.

The One Health approach seeks to unify human and veterinary medicine, agriculture, and food providers against the progression of AMR by reducing agricultural antimicrobial use. Due to the fact that resistance can keep re-emerging, the eradication goal used in diseases like polio works poorly in this area. Therefore, One Health seeks to enable a continued response. Moves by governmental agencies over the past year to support the One Health approach include:

- China outlining, in August 2016, a comprehensive NAP that incorporated many aspects of the One Health approach. It pledges to optimise surveillance of human and food-animal usage of antimicrobials, increase training, and gradually withdraw antimicrobials used by humans from the market for animal growth promoters.
- The UK Department for Environment, Food and Rural Affairs (DEFRA) committing to setting long-term, sector-specific targets for the reduction of antimicrobials in the UK agricultural industry by 2017. A report from DEFRA published in November 2016 shows that in 2015, total UK sales of antibiotics used in livestock decreased by 9 per cent compared to 2014, with sales for use in food-producing animals decreasing by 10 per cent[33].
- The FDA introducing, in January 2017, its Veterinary Feed Directive (VFD), classifying medically important antimicrobials commonly used in animal feeds as VFD drugs. This means that their use in the USA can only be authorised by a licensed veterinarian and cannot be for feed efficiency or growth promotion.
- Maryland becoming, in May 2017, the second US state after California to ban the routine use of antibiotics on farms.

- Vietnam's Ministry for Agriculture and Rural Development announcing, in August 2017, that from the end of 2018 the use of antibiotics in animal feeds will be prohibited and that all antibiotics will be banned from use in livestock by 2020.

250

global food and health leaders are in support of the UNGA's AMR commitments

Moves by industry and non-profit groups include:

- In September 2016, 250 global food and health leaders from both the public and private sectors gathering at the One Health Summit in Washington, DC, in support of the UNGA's AMR commitments. Three core areas were explored: an increase in veterinary oversight, improving AMR monitoring and reporting, and accelerating innovation. Working groups were formed to achieve the targets of the three core areas, and included the involvement of the Gates Foundation, the World Veterinary Association (WVA) and the Association of American Veterinary Medical Colleges (AAVMC). A media statement was released, with 33 companies and health initiatives signing a pledge to work together to combat AMR.
- Also in September 2016, the Natural Resources Defense Council (NRDC), the Center for Science in the Public Interest, Consumers International and other advocacy groups grading the USA's top 25 restaurant chains according to their use of meat raised with antibiotics. Only nine chains passed the assessment, with Panera Bread and Chipotle setting examples for others, receiving an A grade for their strong policies on antibiotic use.
- Several companies pledging to take steps to limit or prevent antibiotic use in the chicken they sell. In February 2017, Tyson Foods, the second-largest poultry producer in the world, said it would stop using any antibiotics in its animals. In August 2017, McDonald's said that it would start eliminating antibiotics defined by the WHO as 'Highest Priority Critically Important' to human medicine from its food chain in 2018. Similarly, in April 2017 KFC said that its chickens will be raised without antibiotics important to human medicine by the end of 2018, as did the parent company of Burger King in June 2017. Taco Bell pledged to do the same in the first quarter of 2017.

Looking ahead

While awareness of AMR is growing in many countries, much more work is needed to address this global health threat. AMR is a challenge that spans an enormous cross-section of modern life around the world. If we are to truly meet the potential of the SDGs, we need to increase our collective efforts on AMR to secure the health and wellbeing of future generations. This global problem needs a global response.

The 2016 UNGA Political Declaration called on member states to accelerate the implementation of their own NAPs and work collaboratively across sectors to advance the GAP on AMR. The UN is providing important leadership through the IACG, which will advance a One Health approach and report back to the UN Secretary-General in 2018 and 2019. Meeting the challenge of AMR will require broad involvement, persistence and innovation – so I hope you will join this effort.

If we come together and commit to this important goal, we can create a better, healthier future for citizens of all countries.

Kathy Calvin
President and CEO, UN Foundation

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