THE EVIDENCE BASE IN ANTIMICROBIAL RESISTANCE TO INFORM DECISION-MAKING – THE NEED FOR EPIDEMIOLOGY AND SURVEILLANCE

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Building global intelligence on superbugs and increasing capacity to gather surveillance data on the rise and rapid spread of these deadly pathogens, is vital if we are to succeed in addressing antimicrobial resistance (AMR).

Resistance to the drugs we have today is rapidly undermining modern medicine. This has been a long-running warning from doctors and scientists, but is now being clearly heard worldwide.

However, to protect progress made against infectious disease and ensure doctors can safely carry out routine and complex medical procedures – such as childbirth, organ transplant and diabetes care – new treatments alone will not be enough.

Understanding the emergence and transmission of drug-resistant infections and having data to clearly determine the effective and appropriate use of these precious medicines, in human and animal health, are critical gaps in the current global response.

In May 2016, the final report of the independent AMR Review – led by Lord Jim O'Neill and funded by Wellcome and the UK government – showed that without effective action the global death toll from drug-resistant infections, already at 700,000 a year, could rise to 10 million within a generation *(1)* . Current data shows AMR is present in every country, but a lack of co-ordinated, comprehensive surveillance needed for effective action.

The World Health Organisation (WHO) has outlined 12 antibiotic-resistant bacteria, the ESKAPE pathogens as research priorities *(2)* - ranking them in three tiers: critical, high and medium. Many strains of these bacteria in many countries worldwide are increasingly untreatable not only with combinations of commonly used antibiotics but also last-resort drugs.

The case of a 70-year-old woman from Nevada dying in September 2016 from systemic inflammatory response syndrome (SIRS) caused by one of the critical ESKAPE pathogens, *Klebsiella pneumoniae*, is now well reported. The woman had been repeatedly hospitalized in India for a hip injury before returning to the United States. Isolates from the patient showed that the strain was resistant to 26 antibiotics. The case was alarming, but not isolated. *K. pneumoniae* is a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, and infections in newborns and intensive-care unit patients. Resistance in the pathogen to the last-resort treatment of carbapenem antibiotics has spread to all regions of the world.

Resistance in *Escherichia coli*, another critical-listed ESKAPE pathogen, to one of the most widely used medicines for the treatment of urinary tract infections, fluoroquinolone antibiotics, is also widespread, with WHO reporting that in many parts of the world this treatment is now ineffective in more than half of patients. And failure of the last-resort medicine for high-priority listed *Neisseria gonorrhoeae*, third generation cephalosporin antibiotics, has been confirmed in at least 10 countries (Australia, Austria, Canada, France, Japan, Norway, Slovenia, South Africa, Sweden and the United Kingdom). These are just a handful of examples of the rise and spread of resistance.

Global recognition and action

Global recognition of the scale and urgency of the problem has, in the past few years, increased. A series of important high level

political commitments have been made, including the 2015 World Health Assembly endorsement of a global action plan, by leaders at the G20 summit and the United Nations General Assembly declaration in September 2016. And with recognition, action is also increasing. Many countries are progressing action plans, to raise awareness, improve infection control and reduce inappropriate antibiotic use – in human and animal health.

Much-needed investment into the early discovery and development of new treatments and diagnostic tools has also started to increase. The latest WHO analysis shows 51 antibiotics in clinical development – and around a third target the 12 priority pathogens *(3)*. Wellcome is among those providing support, including over US$ 150 million for the development partnerships CARB-X *(4)* and GARDP *(5)*. CARB-X, a partnership with the United States government, is now supporting more than 30 product developers in seven countries, all targeting the most serious drug-resistant bacteria.

For lasting, effective change, however, transformation is vital in the way countries track, share and analyse information about the rise and spread of these potentially deadly infections. Only with better information can policy-makers achieve change at national and international levels.

Surveillance and policy

Which pathogens are developing resistance to which drugs and where? Where are patients getting infections from – are they acquiring them from other patients, from healthcare settings, water or food, or the general environment? Which borders are the drug-resistant infections crossing and how quickly? What interventions are effective?

Detailed and up-to-date information, collated and shared in the most effective, co-ordinated way, is needed to determine effective intervention, from direct patient care to national and international policy development. Monitoring the effectiveness of policies is essential.

Such information is fundamental to ensuring patients get the best treatment against the ever-evolving resistance of pathogens. It is vital for national action plans, which ensure appropriate use of antibiotics existing and new, and improve infection prevention and control.

Antibiotics, old and new, must be treated as a precious resource. To minimise the spread of resistance they must not be over or misused. To know which drugs, in which doses, are needed to treat patients effectively, doctors and prescribers need accurate information on how bugs and drugs interact. Without this, they have to rely on best-guess, empirical prescribing. Surveillance and stewardship go hand-in-hand.

Knowledge of how bacteria spread is also critical to improving infection prevention and reducing the overall need for antibiotics, in human and animal health. With better information, policy-makers at the national and international level will have the evidence needed to initiate change. For example, evidence of the spread of *E. coli* resistance from pigs to humans resulted in the recent ban in China of use the powerful antibiotic of last resort, colistin, as a growth promoter in farming.

Global burden in context

The first step to confronting the problem is determining its extent – both the impact in individual countries and in the context of the burden of all mortality. While the severity of AMR is clear, there is currently a poor level of detail on its geographical distribution and prevalence. Without this information, our ability to tackle it is limited.

Work is now underway to map the burden of AMR on human health through a new collaboration between the University of Washington's Institute for Health Metrics and Evaluation (IHME) and the University of Oxford's Big Data Institute (BDI). The IHME-BDI *Global Burden of Disease* AMR study, launched in October 2017, supported by the UK Department of Health Fleming Fund, Wellcome and the Bill & Melinda Gates Foundation. It aims to:

- gather and assemble global data on selected bacteria-antibacterial drug combinations;
- generate globally comparable AMR burden estimates for those "bug-drug" combinations from 1990 to the present for the 195 countries and territories included in The Global Burden of Disease study;
- produce maps of AMR burden that will allow policy-makers and researchers to tailor future studies and interventions to the local level;
- provide free, public access to study results through interactive data visualizations.

Accurate data on the burden and distribution of AMR will provide a baseline and enable researchers, policy-makers, and health officials to study past approaches and replicate successful techniques; better allocate resources – including treatments – to areas of need and improve targeted prescribing; and improve drug development planning.

Global surveillance capacity

Global surveillance efforts are increasing but there are major gaps and differing levels of capacity between countries. The first report from the WHO's Global Antimicrobial Surveillance System (GLASS), showed that 52 countries have enrolled in it so far – with 40 providing information about national surveillance systems and 22 data on levels of antibiotic resistance (6).

Key challenges are highlighted in the recent inventory report of supranational surveillance networks since involving low- and middle-income countries (LMICs), which is where the impact of drug-resistant infections is greatest *(7)*. The study, led by Dr

Elizabeth Ashley, a clinical researcher at the Myanmar-Oxford Clinical Research Unit at the University of Oxford, found that since 2000, 72 supranational networks for AMR surveillance in bacteria, fungi, HIV, TB and malaria have been created that have involved LMICs. Of these, only around half are ongoing. Lack of laboratory resources, training and un-standardized surveillance activities are some of the key barriers.

Industry-generated surveillance

The pharmaceutical industry routinely collects surveillance data that could be hugely valuable to collective global efforts to curb AMR. These industry programmes monitor susceptibility of clinical isolates to marketed treatments and record pre-launch surveillance of new products as part of regulatory approval requirements. External sharing of this data would help inform and define new drug discovery and development strategies, reveal unmet medical needs and allow the modelling of future resistance trends.

In January 2017, more than 100 pharmaceutical companies committed to sharing surveillance data and making it accessible to public health bodies and healthcare professionals, through the "Davos Declaration", now hosted by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) *(8)*.

Public health officials need data on local antibiotic susceptibility to understand and respond to resistance trends. A project supported by Wellcome and led by the Open Data Institute (ODI) is currently underway to understand what data industry holds, develop an open-access platform to host individual studies, and set-up a wider engagement framework with pharmaceutical companies and other interested organizations.

Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC)

In recognition of the critical importance of surveillance and epidemiology and the need to build and co-ordinate global capacity Wellcome has also brought together a new international expert group, called the Surveillance and Epidemiology of Drug-resistant Infections Consortium (SEDRIC) *(9)*.

The SEDRIC board, which met for the first time in January 2018, brings together expertise in infectious disease from across the human and animal health and the environment fields. SEDRIC will build on work by GLASS and others, including the United Kingdom's Fleming Fund, to improve global coordination on tackling AMR, identify critical gaps and barriers, and help countries adopt sustainable best practices and strategies.

It will provide technical expertise and knowledge, but will also look at how technology might be better employed to strengthen existing surveillance networks and activities.

Genomic technology and bacterial sequencing, for example, offer huge potential to help understand the mechanism of resistance and how it spreads. How can this knowledge be better used?

Conclusion

Only through better information can we speed up action and improve public health interventions to get ahead – and stay ahead – of superbugs, and save countless lives. ■

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Wellcome exists to improve health for everyone by helping great ideas to thrive. It is a global charitable foundation, both politically and financially independent that supports scientists and researchers, take on big problems, fuel imaginations and spark debate.

Dr Ghada Zoubiane is the science lead of Wellcome's Drug-resistant Infections priority programme. In her role, she is shaping and delivering Wellcome's AMR strategy, bridging the gap between science and policy and providing the evidence base to inform decision-making.

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References

1. https://amr-review.org/
2. http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/
3. http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/
4. http://www.carb-x.org/
5. https://www.gardp.org/
6. http://www.who.int/glass/en/
7. https://academic.oup.com/jac/advance-article/doi/10.1093/jac/dky026/4921008
8. https://www.ifpma.org/partners-2/declaration-by-the-pharmaceutical-biotechnology-and-diagnostics-industries-on-combating-antimicrobial-resistance-amr/
9. https://wellcome.ac.uk/what-we-do/our-work/surveillance-and-epidemiology-drug-resistant-infections-consortium