Passing Through or Here to Stay: The Global Dimension of Antimicrobial Resistance

Marie Évelyne Danik, BA Hon, JD Class of 2016, Student Fellow of the Global Health Law Clinic, University of Ottawa Faculty of Law
Ioana Pantis, MA, JD Class of 2016, Student Fellow of the Global Health Law Clinic, University of Ottawa Faculty of Law
Rachel Smith, BMSc Hon, JD Class of 2016, Student Fellow of the Global Health Law Clinic, University of Ottawa Faculty of Law
Susan Rogers Van Katwyk, BSc Hon, PhD Candidate, Student Fellow of the Global Health Law Clinic, University of Ottawa Faculty of Law; School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa

Dangerous infectious organisms have followed humans along trade and travel routes for centuries. The Black Death, for example, followed traders' footsteps on the Silk Road from Asia to Europe. In 1918, the Spanish Flu followed the mass movement of troops in World War I. Today, infectious organisms continue to follow humans around the globe, with modern travel making it possible for infections to spread from one continent to another in a matter of hours.

Our current travel partners include antimicrobial resistant organisms, which are increasingly unresponsive to modern treatments. Examples of common resistant pathogens are Methicillin-resistant *Staphylococcus aureus* (MRSA), resistant *Streptococcus pneumoniae* (pneumonia, blood infections), and resistant *Neisseria gonorrhoeae* (gonorrhoea), which the Centers for Disease Control and Prevention recently labelled an 'urgent threat'.[1] There are also pathogens resistant to multiple lines of treatment, such as multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB).[1,2]

The more widely that these organisms spread, the less reliable our treatments for simple infections become. If antibiotics fail, we risk losing many mainstays of modern medicine. For example, we depend on antibiotics for chemotherapy, to treat post-operative patients, and for dialysis for patients with kidney failure.[1] Antibiotic-resistant infections currently cause about 700,000 deaths a year. By 2050, antimicrobial resistance (AMR) could kill 10 million people annually.[2] By comparison, HIV/AIDS caused 2.3 million annual deaths at its peak in 2005.[3]

The Need for a Global Solution

The scale of international human travel – and therefore disease travel – means AMR cannot be solved by single states.[4] One example of antibiotic resistance spread through international travel is the NDM-1 genetic element, which confers resistance to beta-lactams, and was initially found in individuals who received medical care in India. Many countries, including Canada, have found organisms carrying NDM-1 associated with travel from India.[5] Much like climate change, dramatic and collaborative action is needed to resolve the problem. Preventing the looming threat of AMR requires commitment to three goals: (1) conservation of antimicrobials, (2) access to the right antimicrobials for those who need them, and (3) innovation to create new antimicrobials.[6]

Many antimicrobials are used inappropriately in humans. For example, antibiotics are often given out for viral infections that they cannot treat; between 1997 and 2001, 38% of ambulatory care patients in the USA who were diagnosed with influenza were prescribed a course of antibiotics.[7] An article published in January 2016 by University of Toronto medical students addressed this issue in the Canadian context.[8] Health care providers, they say, need to stop administering antibiotics 'just in case' the infection is bacterial, and patients need to stop demanding them. Yet, in many parts of the world, patients can purchase antibiotics over the counter without a prescription or contact with a physician.[9] Countries need to enact regulations to try to limit self-treatment of illnesses with antibiotics.

Similarly, regulations are needed to control antimicrobial use in agriculture, where the drugs are widely used as growth promoters to increase output. Many countries have banned the use of antibiotics for sub-therapeutic purposes, most notably the EU in 2006. In addition, the US has recently moved towards a voluntary re-labelling of antibiotics to reduce their use as growth promoters.[10] However, some last-resort antibiotics, used to treat highly resistant human infections, are still being used extensively in food animals, and the lack of effective surveillance data on the issue further complicates finding solutions.[11]

In addition to restricting inappropriate antimicrobial use, we need to ensure appropriate access to antimicrobials for those who need them. Unfortunately, many low-income people cannot afford the drugs they need to treat their infections appropriately. Currently, a lack of access to drugs means that 5.7 million people die annually from treatable infections.[12] When antimicrobials are too expensive, people often receive no treatment, a treatment with a less effective antibiotic, or take only a partial dose of the antibiotic they were prescribed. The latter cases actually contribute to the spread of AMR by giving bacteria more opportunity to develop resistance. Collective action to ensure that everyone has access to medicines they need at a reasonable price is therefore necessary to prevent more resistant diseases.[12]

Innovation of new antimicrobials is the final key. AMR is a natural phenomenon, so resistant microbes evolve each time we invent a new antimicrobial. Ensuring the continued devel-

Corresponding Author:
Susan Rogers Van Katwyk
Susan.Rogers.Van.Katwyk@uottawa.ca

opment of new antimicrobials can give us more time to develop long-term solutions. However, finding new antimicrobials is scientifically difficult, and much of the necessary infrastructure and expertise to conduct antimicrobial research has declined.[13] Furthermore, complex regulatory requirements for clinical trials of new antimicrobials create a disincentive to get involved in the field.[13] Overcoming these barriers is made all the more difficult by the fact that antimicrobial research and development usually offers poor return on investment for pharmaceutical companies, further reducing the incentive to get involved.[13] Thus, we need a funding mechanism to spur innovation for antimicrobials, vaccines, and tests to help physicians quickly diagnose whether a patient has a resistant strain of disease.[14]

Challenges

Conserving, innovating, and improving access to antimicrobials requires coordinated action from different parties: governments, food producers, pharmaceutical companies, healthcare professionals, and patients. Lining up the diverse interests of these parties is not an easy task, yet the collaboration of these actors is necessary to solve the AMR problem.[15] For example, if a country strictly regulates the use of antimicrobials in health care, but not in agriculture, bacteria will continue to develop resistance and spread.[16]

Similarly, inconsistent regulatory and monitoring systems between countries mean that nations must work together. In our globalized world, people and products are constantly crossing borders.[17] If one country takes action against AMR, but its neighbours and trade partners do not, much of its efforts will be in vain.

This is why a one-health approach is needed: international and cross-sector collaboration on issues of human, animal, and environmental health are necessary to effectively combat AMR.[18] Bacteria can adapt to our defences much faster than we can find new ways to monitor or neutralize them,[19] and we are losing the race. To catch up, countries will need to pool resources and knowledge to start acting in a decisive, concerted way.

The challenges associated with achieving international collaboration are compounded by the difficulty in creating binding international rules. Individual governments may commit to tackling AMR, but will also need the right combination of incentives and deterrents to antibiotic misuse to convince public and private actors to take action.[20]

AMR poses a significant global health risk that will quickly become a global health crisis if left unaddressed. Regardless of the solution, collaboration is key. Canada has taken some initial steps by creating the Action Plan on Antimicrobial Resistance (AMR) and Use in Canada, which commits to improving collaboration between government agencies and developing better surveillance capacity in humans and animals.[21]

But there is still much ground to cover. At the very least, better global data is needed to paint an accurate picture of both our traveling partners and the road ahead. With more comprehensive data, policy-makers will be better able to draw a clear road-map that will lead to decisive, evidence-based policy commitments.

Acknowledgments

The authors would like to thank Steven J. Hoffman and Lathika Sritharan for their support of the Global Health Law Clinic Fellows this year and for their comments on this article.

References

1. CDC. Antibiotic Resistance Threats in the United States, 2013 [Internet]. Atlanta: Centres for Disease Control and Prevention. c2013 [cited 2016 Feb 27]. Available from: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf
2. Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. United Kingdom. c2014 [cited 2016 Feb 27]. Available from: http://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf
3. UNAIDS: 2013 Global Fact Sheet. The Joint United Nations Programma on HIV/AIDS. c2013 [cited 2016 Feb 27]. Available from: http://www.unaids.org/en/resources/campaigns/globalreport2013/factsheet
4. Barlam TF, Gupta K. Antibiotic resistance spreads internationally across borders. J Law Med Ethics. 2015 Aug; 43(S3): 12-16.
5. Wilson ME, Chen LH. NDM-1 and the Role of Travel in Its Dissemination. Curr Infect Dis Rep. 2012; 14: 213-226.
6. Hoffman SJ, Outterson K. What will it take to address the global threat of antibiotic resistance? J Law Med Ethics. 2015 Aug; 43(S3): 6-11.
7. Ciesla G, Leader S, Stoddard J. Antibiotic prescribing rates in the US ambulatory care setting for patients diagnosed with influenza, 1997-2001. Respiratory Medicine. 2004; 98: 1093-1101.
8. Jamal A, Silverberg S, Peterson W. Falling behind: Canada needs a nationwide antimicrobial strategy [Internet]. HealthyDebate.ca. c2016 Jan 13 [cited 2016 Feb 27]. Available from: http://healthydebate.ca/opinions/falling-behind-canada-needs-a-nation-wide-antimicrobial-strategy
9. Gelband H, Miller-Petrie M, Pant S, et al. State of the World's Antibiotics [Internet]. Washington D.C.: Centre for Disease Dynamics, Economics and Policy; c2015 [cited 2015 Oct 30]. Available from: http://cddep.org/publications/state_worlds_antibiotics_2015
10. Review on Antimicrobial Resistance. Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste. c2015 [cited 2016 Feb 27]. Available from: http://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf
11. Landers TF, Cohen B, Wittum TE, Larson EL. A review of antibiotic use in food animals: perspective, policy, and potential. Public Health Rep. 2012; 127(1): 4-22.
12. Daulaire N, Bang A, Tomson G, Cars O. Universal access to effective antibiotics is essential for tackling antibiotic resistance. J Law Med Ethics. 2015 Aug; 43(S3):17-21.
13. IFPMA. Rethinking the way we fight bacteria [Internet]. Geneva: International Federation of Pharmaceutical Manufacturers & Associations. c2015 [cited 2016 Feb 27]. Available from: http://www.ifpma.org/wp-content/uploads/2016/02/IFPMA_Rethinking_the_way_we_fight_bacteria_April2015_FINAL.pdf
14. Balasegaram M, Clift C, Røttingen J. The Global Innovation Model for Antibiotics Needs Reinvention. J Law Med Ethics. 2015 Aug;43(S3):22-26.
15. Årdal C, Outterson K, Hoffman SJ, et al. International cooperation to improve access to access and sustain effectiveness of antimicrobials. The Lancet [Internet]. 2016;387:296 [cited 2016 March 12].
16. Paterson DL, Harris PNA. Colistin resistance: a major breach in our last line of defence. Lancet Infect Dis. 2016 Feb; 16(2): 132-133.
17. WPRO. Antimicrobial Resistance Fact Sheet Number 194 [Internet]. World Health Organization Wester Pacific Region. c2014 [cited 2016 Feb 27]. Available from: http://www.wpro.who.int/mediacentre/releases/2014/AMR_factsheet_FINAL.pdf
18. Podolsky SH, Bud R, Gradmann C, et al. History teaches us that confronting antibiotic resistance requires stronger global collective action. J Law Med Ethics. 2015 Aug; 43(S3): 27-32.
19. Laxminarayan R. Ted Talk: The coming crisis in antibiotics [Internet]. c2014 [cited 2016 Feb 27]. Available from: https://www.ted.com/talks/ramanan_laxminarayan_the_coming_crisis_in_antibiotics?language=en
20. Hoffman SJ, Caleo GM, Daulaire N, et al. Strategies for achieving global collective action on antimicrobial resistance. Bull World Health Organ. 2015; 932:867-876.
21. Government of Canada. Federal Action Plan on Antimicrobial Resistance and Use in Canada: Building on the Federal Framework for Action. 2015 [updated 2015 Mar 31, cited 2016 Apr 15] Available from: http://healthycanadians.gc.ca/publications/drugs-products-medicaments-produits/antibiotic-resistance-antibiotique/action-plan-daction-eng.php?_ga=1.103329223.696880631.1460909881.