Thought Leadership Unit

Antibiotic resistance:
Toward better stewardship of a precious medical resource

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About this paper

At Aetna International, it's our mission to reshape health care across the globe by developing solutions to improve the quality, affordability and accessibility of care. To this end, we take a two-pronged approach: raising awareness of critical health challenges facing the world and promoting effective, value-based care solutions that could help others combat and prevent the worsening of some of the world's most serious health care problems.

Summary

Antibiotic resistance has emerged as one of the world's deadliest health crises.

Antibiotic resistance has emerged as one of the world's deadliest health crises. The spread of antibiotic resistant bacteria is threatening the effectiveness of last-resort treatments for life-threatening infections. Every year, 700,000 deaths (and counting) are attributed to antimicrobial resistance, a category which encompasses antibiotic resistance; that's equivalent to the population of Seattle, Washington or Leeds, West Yorkshire being decimated annually. Without action, the death toll could reach 10 million per annum by 2050.[1],[2],[3],[4]

This paper outlines the scope of the problem and identifies the key contributing factors. Chapter 2 puts forward strategic solutions pursued by the World Health Organization (WHO) and Aetna in partnership with the U.S. Centers for Disease Control (CDC) among others. The paper concludes by demonstrating the efficacy of our multifaceted strategies, including peer-to-peer health care provider comparisons and proactive education and intervention campaigns, and calls for more to be done across the globe.

1 https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

2 https://www.seattletimes.com/seattle-news/data/seattle-once-again-nations-fastest-growing-big-city-population-exceeds-700000/

3 https://thegeographist.wordpress.com/2016/04/07/largest-cities-uk-population/

4 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4232501/pdf/10.1177_2042098614554919.pdf

Introduction

Each year, more than 23,000 Americans are killed and more than two million are sickened by drug-resistant bacteria.

One spring morning in 2004, 18-month-old Simon Sparrow of Chicago woke up feeling ill. By afternoon, his breathing was laboured, his face swollen. By evening, his parents had rushed him to a hospital, where doctors diagnosed septic shock and administered a course of antibiotics. By morning, he was dead.[5]

The direct cause of Simon's death was an infection caused by methicillin-resistant Staphylococcus aureus (better known as MRSA) one of a growing rogues' gallery of so-called superbugs. The indirect and ultimately more significant cause was antibiotic resistance, the result of decades of overuse and misuse (by various industries) of drugs like methicillin, a synthetic version of penicillin that was introduced in 1960.[6]

"It's ironic to me that the same advances in science that led to healthier and longer lives have resulted in the unintended consequence of the creation of bacteria that no longer responded to antibiotics," said Simon's mother, Everly Macario, who, despite having a Ph.D. in public health, hadn't heard of MRSA before her baby's death. "I can't believe I had to go through what so many families experienced 50 years ago: the death of a child caused by a simple bacterial infection."[7]

Unfortunately, the tragedy Macario's family endured isn't unique. Each year, more than 23,000 Americans are killed and more than two million are sickened by drug-resistant bacteria. And the problem is even worse in low- and middle-income countries, where second-line drugs can be prohibitively expensive for many people. If not quickly addressed, antibiotic resistance could lead to a time when routine surgeries are too dangerous to perform and when, as drug-resistance economist Ramanan Laxminarayan has put it, "even a blade of grass is a potentially lethal weapon."[8,9,10,11]

(That stark prediction may seem farfetched, but it's not. Albert Alexander, the first person treated with penicillin, reportedly developed his infection after scratching his cheek on a rose bush.[12])

5 https://www.huffingtonpost.com/entry/antibiotic-resistance_b_859078.html

6 https://harvardmagazine.com/print/44839?page=all

7 http://www.who.int/campaigns/world-antibiotic-awareness-week/personal-stories/en/

8 https://www.cdc.gov/drugresistance/pdf/antibiotic_resistant_fs.pdf

9 https://www.reactgroup.org/uploads/news/The-Lancet-Infectious-Diseases-Commission-on-Antibiotic-Resistance-Nov2013.pdf

10 https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

11 https://www.ted.com/talks/ramanan_laxminarayan_the_coming_crisis_in_antibiotics/

12 https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html

Chapter 1

Without concerted action, the annual death toll could reach 10 million by 2050 …

Scope of the problem

How bad a problem is antibiotic resistance? The UK's Review on Antimicrobial Resistance (AMR), which was sponsored by the UK government and the Wellcome Trust, estimated in 2016 that antimicrobial resistance (a somewhat broader category that also encompasses drug-resistant viruses, fungi and parasites) causes 700,000 deaths each year around the world. Without concerted action, the annual death toll could reach 10 million by 2050 — more than the number of deaths from cancer, cholera, measles and traffic accidents combined. (More than half of these deaths would come from *Escherichia coli* and *Mycobacterium tuberculosis*.)[13]

In a 2015 TED Talk, health journalist Maryn McKenna offered a sobering reminder of life before antibiotics: "Strep throat used to cause heart failure," she said. "Skin infections led to amputations. Giving birth killed, in the cleanest hospitals, almost one woman out of every 100. Pneumonia took three children out of every 10."[14]

And deaths aren't the only issue. As *The Lancet* has reported, "Resistant infections are more expensive to treat and patients infected with resistant strains of bacteria are more likely to require longer hospitalisation and face higher treatment costs than are patients infected with drug-susceptible strains." According to the U.S. Centers for Disease Control, "antibiotic resistance in the United States costs an estimated $20 billion a year in excess health care costs, $35 billion in other societal costs and more than 8 million additional days that people spend in the hospital."[15,16] (This increasing demand for health care services is a key contributor to global medical inflation. For information on our value-based care medical cost containment strategies, read our white paper, **Bending the curve: Addressing rising costs in health care**.)

13 https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

14 https://www.ted.com/talks/maryn_mckenna_what_do_we_do_when_antibiotics_don_t_work_any_more/

15 https://www.reactgroup.org/uploads/news/The-Lancet-Infectious-Diseases-Commission-on-Antibiotic-Resistance-Nov2013.pdf

16 https://www.niaid.nih.gov/research/antimicrobial-resistance-quick-facts

Moreover, when physicians are forced to escalate their response by prescribing riskier antibiotics, side effects can include insomnia, arrhythmia (heart rate irregularity), changes in blood sugar levels, nerve damage and ruptured tendons. Pharmaceutical company Johnson and Johnson has faced thousands of lawsuits over Levaquin (levofloxacin) because it failed to warn patients about the risk of tendon ruptures.[17],[18] (This example points to yet another reason the health care industry needs to develop better wellness, prevention and antimicrobial resistance strategies upstream in the care cycle; focussing on keeping individuals well, happy, productive and viable.)

Of course, those who face long hospital stays or suffer lingering side effects — not to mention those who die as a result of an infection — are unable to contribute to society. The UK's Review on Antimicrobial Resistance puts antibiotic resistance's cumulative impact on global economic output at $1 trillion U.S. between now and 2050.[19] (This is particularly pertinent when you consider that by 2050, the number of people aged 65 or older is expected to reach 1.5 billion — nearly triple the number in 2010.[20])

How antibiotic resistance has developed

To understand antibiotic resistance, we must first understand antibiotics. In 1928, bacteriologist Alexander Fleming famously returned to his London laboratory from holiday and discovered that mould in a petri dish was attacking a colony of *Staphylococcus aureus* bacteria (the same microbes that killed Simon Sparrow). Fleming did little with his accidental discovery of this naturally occurring substance, which he called penicillin, but he did publish his findings in *The British Journal of Experimental Pathology*. A decade later, a group of researchers at Oxford University took up the cause, conducting successful experiments on mice and then treating Oxford policeman Albert Alexander. (He rallied, but then died when supplies of the rare drug ran out.) Research and production shifted to the United States as World War II intensified. With support from the War Production Board, which was interested in treatments for battle wounds, it also sped up drastically. In March 1942, enough doses existed to treat a single patient; in 1945, manufacturers churned out 6.8 *trillion* units of the drug.[21],[22]

17 http://www.center4research.org/antibiotics-riskier-others-know-quinolones/

18 https://www.drugwatch.com/2016/01/26/jj-faces-800-m-levaquin-lawsuit/

19 https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

20 http://www.who.int/ageing/publications/global_health.pdf

21 https://www.pbs.org/newshour/health/the-real-story-behind-the-worlds-first-antibiotic

22 https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html

But penicillin — like all other antibiotics — has an Achilles' heel: bacteria can evolve and fight back. As Fleming noted in his 1945 Nobel Prize acceptance speech, exposing microbes to insufficient doses of penicillin actually allows them to learn resistance and allows naturally resistant microbes to thrive. He even offered a chillingly prescient anecdote about the result of over-the-counter sales (which were allowed in the U.S. until the 1950s and which is still commonplace in many countries):

> "Mr. X. has a sore throat. He buys some penicillin and gives himself not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death? Why Mr. X whose negligent use of penicillin changed the nature of the microbe."[23]

This possibility was more than theory even in penicillin's early years. As *Harvard Magazine* explained in a recent article, "In one English hospital, the proportion of resistant staph infections [those caused by *Staphylococcus* bacteria] quadrupled from 14 percent in 1946 to 59 percent just two years later. By mid-century, the world was in the midst of its first pandemic of antibiotic-resistant infections. As a commercially available drug, penicillin was not yet 10 years old." (It's important to note, as Fleming's anecdote illustrates, that it's the bacteria themselves that become resistant, not the people who use antibiotics.)[24]

Since the discovery of penicillin, scientists have developed dozens of other antibiotics. Today, the World Health Organization (WHO) classifies 29 drugs or drug combinations in its "access" group of first- or second-choice treatments. Seven classes of antibiotics are in the "watch" group, whose use should be limited, while the eight drugs or drug classes in the "reserve" group are considered to be drugs of last resort. While that might seem like plenty of options, in rare cases bacteria have been found that are resistant to every drug available in a given country. The bacterium *Acinetobacter baumannii* — commonly known as "iraqibacter" because it was acquired by many Western soldiers during the Iraq war — has shown resistance to every class of antibiotics.[25],[26],[27]

... in rare cases bacteria have been found that are resistant to every drug available in a given country.

23 https://selectra.co.uk/sites/selectra.co.uk/files/pdf/fleming-lecture.pdf

24 https://harvardmagazine.com/2014/05/superbug

25 http://www.who.int/medicines/publications/essentialmedicines/EML_2017_ExecutiveSummary.pdf?ua=1

26 https://www.theatlantic.com/health/archive/2017/01/a-superbug-resistant-to-26-antibiotics-killed-a-woman-itll-happen-again/513050/

27 https://microbewiki.kenyon.edu/index.php/Acinetobacter_baumannii:_The_Emergence_of_a_Dangerous_Multidrug-Resistant_Pathogen

Some antibiotics, called bactericidal drugs (e.g., penicillin), kill bacteria, preventing further damage to the body; others, called bacteriostatic drugs (e.g., tetracycline), stop bacteria from growing or reproducing, allowing the body's immune system time to fight back. But regardless of how they work, all these drugs inevitably fall victim to antibacterial resistance. Widespread resistance to penicillin was identified just two years after the drug was distributed in 1943. Resistance to vancomycin was noted 16 years after its introduction in 1972. Daptomycin, introduced in 2003, was compromised in a single year.[28],[29]

In effect, the world is in the position of the legendary Dutch boy who plugged holes in a dike with his fingers. Only holes are appearing faster than they can be plugged. And we are running out of fingers.

Overuse of antibiotics has gone on almost since the introduction of penicillin, in part due to heavy promotion by drug companies. In 1945 ...

Major causes of antibiotic resistance

The biological causes of antibiotic resistance cannot be prevented. What we can prevent — or at least mitigate — are the societal causes. Four such causes are paramount: misuse and over-prescription of antibiotics; use of antibiotics in agriculture; lack of research, which has led to an anaemic drug pipeline; and poor hygiene and sanitation.

Misuse and over-prescription

Overuse of antibiotics has gone on almost since the introduction of penicillin, in part due to heavy promotion by drug companies. In 1945, the *Journal of the American Pharmaceutical Association* devoted an entire issue to penicillin; in it, advertiser Abbott Labs promised pharmacists they would "gain both profit and professional prestige by being among the first to distribute this dramatic life-saving drug." By the 1950s the *Journal of the American Medical Association* was also full of advertisements for antibiotics. As one medical history said of Pfizer's messages, "Eye infections, respiratory ailments, skin lesions: Terramycin treated them all. As part of the strategy of positioning the drug as the antibiotic of choice for the maximum number of potential users, the company even produced a cherry-flavoured suspension for children, Pfizer promising to 'Turn Satans into Seraphs.'" [30],[31]

28 https://en.wikipedia.org/wiki/List_of_antibiotics

29 https://www.ted.com/talks/maryn_mckenna_what_do_we_do_when_antibiotics_don_t_work_any_more

30 https://www.nlm.nih.gov/exhibition/fromdnatobeer/exhibition-making-yellow-magic.html

31 Rosen, William. Miracle Cure: The Creation of Antibiotics and the Birth of Modern Medicine. New York: Viking, 2017.

Value-based care

Overuse of antibiotics is a classic case of what happens when providers are reimbursed based on the services they provide rather than on the results they achieve. It also stems from an era where providers simply didn't have the data they needed in order to make informed decisions. Fortunately, we are moving into the age of value-based care and big data. At Aetna International, our goal is to create reimbursement schemes that are based on accountability not activity and to bring to bear the power of analytics, which involves mining the vast amounts of data we collect in order to derive insights and support fact-based decision-making by doctors and other care providers.

Those advertisements and an understandable belief in these "miracle drugs" paid off. Today, according to the Pew Charitable Trusts, 13 percent of outpatient visits in the U.S. result in an antibiotic prescription, and at least 30 percent of those prescriptions — some 47 million per year — are unnecessary (typically because they're given for a viral infection). In India, sales of carbapenems (a class of antibiotics on the WHO's watch list of second-line drugs) increased six-fold between 2005 and 2010, yet still hadn't caught up with neighbouring Pakistan. Among the 35 members countries of the Organisation for Economic Co-operation and Development (OECD), six use at least 25 daily antibiotic doses per 1,000 people. (Chile, by comparison, uses just 9.4 doses, the lowest of the OECD countries.). As OECD's Health at a Glance 2015 report notes, total antibiotic usage varies more than four-fold across member states, while usage of second-line antibiotics varies almost 16-fold — highlighting the desperate need for a concerted global effort to better educate and incentivise health care providers.[32],[33],[34],[35]

A 2014 survey of 1,000 primary care doctors in the UK found that 55 percent felt under pressure, mainly from patients, to prescribe antibiotics, even if they were not sure that they were necessary. 44 percent admitted they had prescribed antibiotics to get a patient to leave the premises. Inappropriate use: viral versus bacterial infections.[36]

Of lesser concern, but still important, is what happens when patients stop taking antibiotics once they begin to feel better. As Alexander Fleming noted, that practice unintentionally gives bacteria a new lease of life. Yet nearly a third of respondents in one recent survey mistakenly believe that they should stop taking an antibiotic once they begin to feel better — similarly highlighting a need for a greater concerted global effort to educate individuals about the use of antibiotics.[37]

Use of antibiotics in agriculture

Despite the growing — often skyrocketing — use of antibiotics among humans, the lion's share of antibiotics actually goes to farm animals. In some countries, up to 80 percent of antibiotics may be used in agriculture, primarily to promote

32 http://www.pewtrusts.org/en/research-and-analysis/reports/2016/05/antibiotic-use-in-outpatient-settings

33 https://timesofindia.indiatimes.com/india/Indians-popping-more-antibiotics-than-ever-Study/articleshow/13128701.cms

34 https://www.weforum.org/agenda/2015/11/which-countries-use-the-most-antibiotics/

35 http://www.oecd-ilibrary.org/docserver/download/8115071e.pdf

36 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4232501/pdf/10.1177_2042098614554919.pdf

37 http://www.who.int/mediacentre/news/releases/2015/antibiotic-resistance/en/

Despite the growing — often skyrocketing — use of antibiotics among humans, the lion's share of antibiotics actually goes to farm animals.

growth, not to treat disease. Thanks to natural selection, every application gives bacteria another chance to develop resistance.[38]

Absolute data on the use of antibiotics in agriculture is hard to come by, but the World Health Organization says animals receive well over half of all antibiotics, which doesn't even account for other agricultural applications (such as on fruit trees to combat fire blight). To better quantify this usage, a global group of scientists in 2015 used statistical analysis to create the first world map of antimicrobial use in agriculture. What they found was alarming: agriculture consumption of antimicrobial drugs was estimated at 63,151 tons in 2010 and is expected to rise by two-thirds by 2030; this is due to both an increase in food production and a shift toward industrialised agriculture and farming in middle-income countries. Moreover, they reported, in Brazil, Russia, India, China and South Africa, "the increase in antimicrobial consumption will be 99 percent, up to seven times the projected population growth in this group of countries."[39],[40],[41]

Antibiotics may promote growth in farm animals, but they also promote the development of drug-resistant bacteria. And those bacteria don't stay on the farm. Instead, they are transmitted to consumers in meat (becoming a health concern when that meat is not handled and cooked properly), they hitch rides in the dust on farmers' shoes and they wash into streams in runoff. (Research has suggested that 75 – 90 percent of antibiotics given to animals pass through their systems un-metabolised.) Study after study has shown a correlation between antibiotic use in agriculture and antibiotic resistance in humans; in fact, most published studies provide evidence-based recommendations limiting use of antibiotics in agriculture. For example, a 2001 multi-country study found that new usage of quinolone in food animals was quickly followed by drug-resistant infections in humans, while a 2004 study in France showed that pig farmers are nearly twice as likely to carry *Staphylococcus aureus* bacteria as non-farmers (44.6 percent vs. 24.1 percent).[42],[43],[44]

Of course, a partial solution to the problem of antibiotic usage in agriculture would be to reduce people's reliance on meat as a source of nutrition, which would have benefits beyond health and wellness. The UK-based Academy of Nutrition and Dietetics advocates that going meat free for one day a week" can improve your health and the environment." How? For one thing, meat has a far larger "water footprint" than fruits, vegetables and grains; with the amount of water used to produce one kilogram of beef (15,500 litres), one

38 http://www.sustainabletable.org/257/antibiotics
39 http://apps.who.int/iris/bitstream/10665/44812/1/9789241503181_eng.pdf
40 https://www.rodalesorganiclife.com/wellbeing/antibiotics-organic-apple-and-pear-trees
41 http://www.pnas.org/content/112/18/5649.full
42 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3194830/
43 https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
44 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3234384/

A new antibiotic costs an estimated $1.7 billion U.S. to develop, and profitability can be questionable, both because new drugs are likely to be held in reserve and because the typical course of treatment is brief ...

could instead produce one kilogram each of bread, cheese, nuts, maize, mangoes *and* rice. Moreover, the livestock sector accounts for 13.5 percent of all human-induced greenhouse gas emissions according to the Food and Agriculture Organization of the United Nations. Moving toward a plant-based diet would thus help in the fight against climate change, reduce water usage and forestall the development of antibiotic resistance.[45],[46],[47]

Lack of research and an anaemic drug pipeline

Given the nature of antibiotic resistance, new drugs are constantly needed, including both new antibiotics and alternative therapies (see our sidebar: An alternative to antibiotics). Unfortunately, research into new antibiotics has slowed considerably. Between 2004 and 2013, just five percent of venture-capital investment in pharmaceutical research was focused on antimicrobial drugs, and that investment declined by 28 percent over that period. One reason for the declining interest may be a lack of places to invest; as of 2013, just four multinational pharmaceutical companies had antibiotics divisions. (By comparison, 21 companies participated in the U.S. War Production Board's World War II-era penicillin program, which, of course, only focussed on a single drug.)[48],[49],[50]

There are understandable reasons for this lack of investment. A new antibiotic costs an estimated $1.7 billion U.S. to develop, and profitability can be questionable, both because new drugs are likely to be held in reserve and because the typical course of treatment is brief — especially compared with a maintenance drug a patient may need to take for decades. Today, drug companies invest their research dollars based on a metric called net present value (NPV), and antibiotics don't score very highly. As the journal *Perspectives in Medicinal Chemistry* has noted, "a characteristic NPV for an injectable antibiotic may be around 100, which is somewhat unattractive compared to a typical cancer drug, around 300, or a neuroscience drug around 720." From a financial perspective then, investing in an antibiotic instead of a cancer drug makes about as much sense as putting money in a savings account instead of in a high-yield mutual fund. Of course, that calculus may change if, as has been projected, the antibiotic resistance death toll begins to outstrip the cancer death toll. [51]

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45 http://www.eatright.org/resource/food/nutrition/vegetarian-and-special-diets/going-meatless

46 http://waterfootprint.org/media/downloads/Hoekstra-2008-WaterfootprintFood.pdf

47 http://www.fao.org/ag/againfo/resources/en/publications/tackling_climate_change/index.htm

48 http://www.euro.who.int/__data/assets/pdf_file/0003/315309/Targeting-innovation-antibiotic-drug-d-and-d-2016.pdf

49 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3707426/

50 https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html

51 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159373/

Also missing is research into tools to rapidly determine not just whether an illness is bacterial or viral in nature but exactly which bacterium or virus is the culprit. Because it takes 36 hours or longer to culture bacteria, physicians sometimes prescribe an antibiotic "just in case" or start a patient on one antibiotic, later switching to a more effective drug. As the UK's Review on Antimicrobial Resistance wryly notes, "This process has remained basically unchanged in decades: most of these tests are lab-based, and would look familiar to a doctor trained in the 1950s, using processes that originated in the 1860s."[52]

The lack of rapid diagnostic tools has surprising side effects, as can be seen in the case of gonorrhoea. Because the *Neisseria gonorrhoeae* bacterium long ago developed resistance to older antibiotics like penicillin and ciprofloxacin, physicians no longer prescribe them, preferring a combination of oral azithromycin and injectable ceftriaxone. (The rule of thumb is that the standard course of treatment must change once 5 percent of bacteria become resistant to a given antibiotic.)[53]

However, many cases of gonorrhoea could actually be treated with the older drugs; data from Public Health England show that ciprofloxacin would work 70 percent of the time and penicillin would work more than 80 percent of the time. What's lacking is a rapid test to determine when the older drugs would be effective. As Neil Woodford, head of Public Health England's Antimicrobial Resistance and Healthcare-associated Infections Reference Unit, has written, "This tailored approach would reduce the pressure that encourages gonococci to develop resistance to any universally-used treatment and would prevent patients being given drugs that will not work. What's more, it will allow abandoned drugs to be used once again where suitable, and will help ensure that new gonorrhoea antibiotics (when we get them) are better conserved."[54]

According to a UN-Water report, 90 percent of all wastewater goes untreated into rivers, lakes or oceans.

Poor hygiene and sanitation

Often overlooked are issues surrounding water and sanitation, which affect millions of people in low- and middle-income countries. As the United Nations reported in 2015, nine percent of the world's people (663 million) still use unimproved drinking water sources, and a third (2.4 billion) still use unimproved sanitation facilities. According to a UN-Water report, 90 percent of all wastewater goes untreated into rivers, lakes or oceans.[55],[56],[57]

52 https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

53 https://amr-review.org/sites/default/files/GCDiagnostictestmodel_WORKINGPAPER.pdf

54 https://longitudeprize.org/blog-post/gonorrhoea-urgency

55 https://longitudeprize.org/blog-post/gonorrhoea-urgency

56 http://mdgs.un.org/unsd/mdg/Resources/Static/Products/Progress2015/English2015.pdf

57 http://apps.who.int/iris/bitstream/10665/204948/1/WHO_FWC_WSH_14.7_eng.pdf?ua=1

The obvious result of dirty water and poor sanitation is that people get sick more often, thereby requiring more antibiotics.

The obvious result of dirty water and poor sanitation is that people get sick more often, thereby requiring more antibiotics. (Untreated water can carry a host of bacteria, including *Campylobacter, E. coli* and *Salmonella*.) In 2008, a review of 1,428 reported outbreaks of waterborne diseases demonstrated the obvious; as the researchers wrote, "At the global scale, water-associated infectious diseases are significantly correlated with socio-environmental factors, impacting all regions which are affected disproportionately by different categories of water-associated infectious diseases."[58,59]

But there's another aspect to this problem, an aspect that doesn't just affect those who drink water from ponds or relieve themselves in open fields. Given the ubiquitous use of antibiotics among both human and animal populations, wastewater — whether from pit latrines, hospitals, farm fields or pharmaceutical plants — is loaded with both antimicrobial agents and drug-resistant bacteria. When that wastewater is released into the environment without proper treatment, drug-resistant bacteria spread and non-resistant bacteria learn resistance.[60]

Yet another aspect to this problem is poor infection control in hospitals and clinics, which is one reason MRSA and other superbugs are more prevalent in health care settings. After *Acinetobacter baumannii* became a problem in the U.S., the Association for Professionals in Infection Control and Epidemiology (APIC) issued a 58-page guide to preventing or halting its spread in health care settings. The guide warns that, unless careful protocols are followed, bacteria can hide in a vast array of places, including floors, bedside tables, supply carts, mattresses, pillows, bed curtains, sinks, bedrails, washbasins, toilets, sinks, doorknobs, call buttons, resuscitation equipment, wheelchairs and even jewellery and artificial fingernails worn by health workers.[61]

Even careful protocols may not be sufficient. In 2012, a team of researchers examined 32 hospital rooms that had been cleaned after patients with a history of drug-resistant *Acinetobacter baumannii* left. Nearly half the rooms tested positive for the bacteria.[62]

58 http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1

59 http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0001483

60 http://apps.who.int/iris/bitstream/10665/204948/1/WHO_FWC_WSH_14.7_eng.pdf?ua=1

61 http://www.apic.org/Resource_/EliminationGuideForm/b8b0b11f-1808-4615-890b-f652d116ba56/File/APIC-AB-Guide.pdf

62 https://apic.org/For-Media/News-Releases/Article?id=fcaf5013-c342-4d5d-b5c2-56ff276ce8d4

Chapter 2

… success relies on integrated, multi-sectorial antibiotic resistance coordination, funding, agreements, accountability and progress monitoring.

What can be done?

Clearly, the antibiotic resistance crisis stems from multiple causes across multiple countries and industries. Fixing it will similarly require a multipronged global effort. In short, we must become better stewards of the antibiotics we have today, work to develop more antibiotics for tomorrow and at the same time address the underlying issues that have led to this situation. No single country and no single industry can succeed on its own. Instead, success relies on integrated, multi-sectorial antibiotic resistance coordination, funding, agreements, accountability and progress monitoring.

What might a plan to move forward look like? The WHO's Global Action Plan on Antimicrobial Resistance offers five objectives:

1. Improve awareness and understanding of antimicrobial resistance through effective communication, education and training
2. Strengthen the knowledge and evidence base through surveillance and research
3. Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures
4. Optimise the use of antimicrobial medicines in human and animal health
5. Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions[63]

Other groups have come up with similar task lists. For example, the 10 key interventions suggested by the UK's Review on Antimicrobial Resistance and the four core actions being taken by the U.S. Centers for Disease Control and Prevention (CDC) largely align with the WHO plan, simply grouping priorities in different ways.[64],[65]

63 http://www.who.int/antimicrobial-resistance/global-action-plan/en/
64 https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
65 https://www.cdc.gov/drugresistance/about.html

An alternative to antibiotics

A decade before Alexander Fleming's accidental discovery of penicillin, two researchers working independently in England and France made similar discoveries. They didn't find penicillin, however; instead, they found viruses that attack bacteria. The French researcher, Felix d'Herelle, called them bacteriophages (literally "bacteria eaters"), but they're better known as phages today.[68],[69]

Better known is a relative term, however. Although d'Herelle and others successfully used phages to treat a range of infections in the 1920s and 1930s, the development of antibiotics in the 1940s consigned phage therapy to the fringes of medicine. In fact, the technique primarily survived behind the Iron Curtain, most notably in Georgia, where antibiotics from the West were often unavailable.[70]

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At Aetna International, we believe the WHO plan offers an important road map, and we are committed to doing our part. While some argue that we have already reached the post-antibiotic era, as the CDC declared in 2013, we believe we need to do everything possible to keep antibiotics viable while we prepare for that eventuality. Fortunately, progress is being made on a number of fronts, as the following examples demonstrate.[66]

Working with "Superprescribers"

One initiative Aetna has undertaken demonstrates the sort of straightforward action that can make a significant difference in the fight against antibiotic resistance while also cutting unnecessary health spending. The U.S.-focussed initiative, which we coordinated closely with the CDC, focussed on acute bronchitis in adults. We chose this condition because it is viral in nature, meaning antibiotics are ineffective against it, and because the National Committee for Quality Assurance (NCQA) in the United States includes it in its Healthcare Effectiveness Data and Information Set (HEDIS), a comprehensive set of quality measures. (The specific measure, "avoidance of antibiotic treatment in adults with acute bronchitis," has an alarmingly low success rate and is perennially difficult to budge.)

Our claims data revealed more than 1,000 "superprescribers" — doctors whose prescribing patterns were far outside the HEDIS standard, as well as about 100 doctors who were attaining success on the standard. Both groups received personal letters from Aetna's chief medical officer, Dr Hal Paz, detailing their positioning relative to their peers and providing information from the CDC on antibiotic resistance. As a result, providers have generally agreed that their prescribing habits could improve and have taken Aetna up on its offer to collaborate and discuss this further. Research has shown that such interventions have a measurable impact on prescribing behaviour. As the authors of one study noted, physicians are sensitive and responsive to accountable justification (where they are prompted to explain why they prescribed an antibiotic) and peer comparison (where they are told how their prescribing behaviour compares to other physicians in their region).[67]

66 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4378521/

67 https://jamanetwork.com/journals/jama/fullarticle/2488307

68 https://theconversation.com/discovered-in-wwi-bacterial-viruses-may-be-our-allies-in-a-post-antibiotic-age-76503

69 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4418462/

70 https://www.nature.com/news/phage-therapy-gets-revitalized-1.15348

Interest in phages is growing as antibiotic resistance reaches crisis proportions. In 2013, for example, researchers funded by the European Union launched a large, multinational clinical trial on the use of phages to treat infections in burn victims. Called Phagoburn, the 45-month study involves 11 clinical partners in France, Belgium and Switzerland.[71]

Anecdotal cases have shown the promise of phage therapy. In the U.S., for example, bacteria-attacking phages saved the life of AIDS researcher Tom Patterson, who was near death due to an untreatable bacterial infection. As Bloomberg News reported, "Within days, Patterson's infection was halted and he woke from his coma. Months later, he returned to work."[72]

A multipronged approach in India

Today, India is among the world's largest consumers of antibiotics for human health. Multiple factors, such as a high burden of disease, poor public health infrastructure, rising incomes and the unregulated sale of cheap antibiotics have amplified the crisis of antimicrobial resistance in the Asian nation.

In response, Indian Health Organisation (IHO), an Aetna company, is taking a three-stage approach. First, we are emphasising antimicrobial stewardship in clinical training, where we talk about everything from conditions for which antibiotics are not needed to situations for which watchful waiting would be appropriate (such as with acute uncomplicated sinusitis). Second, when we audit medical consultations, we are checking antibiotic prescriptions for dosage, duration and rationale for usage. Third, our physicians are identifying incorrect (and correct) antibiotic usage during medical consultations, which gives them the chance to offer patient counselling about appropriate antibiotics use on the spot. (Given that three-quarters of Indians mistakenly think that colds and influenza can be treated with antibiotics, it's reasonable to assume that many are using the drugs inappropriately.)[73]

Other Aetna strategies

At Aetna International, we are adopting value-based care strategies to address rising health care costs, clinical inefficiency and duplication of services to help ensure our customers can access quality care, whether preventative, chronic or acute, and attain the health outcomes they need.

When it comes to antibiotics stewardship, we have an integrated strategy with providers (physicians, health care specialists and hospitals) in our network. We work with our providers — where we directly provide care — and the providers to whom we give our members access. We support efforts of the Joint Commission and other accrediting bodies to make antimicrobial stewardship a true standard in hospitals and outpatient settings alike. We empower our members individually through Care Management interactions, including one-nurse, one-patient case management, preauthorisation, care in the community such as onsite nurses and home health care steerage resulting in long-term care improvements and cost reductions. And we work with members

71 http://www.phagoburn.eu/

72 https://www.bloomberg.com/news/articles/2017-11-27/enlisting-viruses-as-allies-to-fight-superbugs-quicktake-q-a

73 http://www.who.int/mediacentre/news/releases/2015/antibiotic-resistance/en/

Tailoring antibiotic stewardship strategies

As is so often the case, every country is different, which means different strategies are needed to combat antibiotic resistance. What works in the UK or the U.S. won't necessarily work in Uganda or Uruguay.

A 12-country survey conducted by the WHO in 2015 hints at the differences among countries:

- At least 75 percent of respondents from four countries — Egypt, India, Mexico and Sudan — reported taking an antibiotic within the past six months, compared with just 35 percent of those from Barbados.
- Only 56 percent of Russians reported getting a prescription from a doctor or nurse, compared with a survey average of 81 percent.
- Nearly 90 percent of South Africans understand that they should take the full course of an antibiotic, compared with just 47 percent of Chinese.[76],[77]

Clearly, any solution must be tailored to the local situation, whether that means educating pharmacists, as the Syrian Pharmacists' Association is doing, or enlisting an anime character in a public awareness campaign, as Japan's Ministry of Health, Labour and Welfare has done.[78],[79]

and clients alike to build awareness and educate them about appropriate antibiotic usage, especially in those countries that still permit over-the-counter sales of antibiotics. This includes emphasizing the importance of adherence to treatment plans, as failing to continue with the full course of an antibiotic both reduces the treatment's effectiveness and contributes to bacterial resistance.[74]

Such efforts appear to be paying off. Among our expatriate members living in the U.S., for example, we have seen reduced utilisation since 2014; between 2014 and 2016, antibiotics utilisation across our membership population decreased by one-third, dropping from 27 percent in 2014 to 18 percent in 2016, which is a significant result for the early years of the campaign.[75]

74 https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf

75 Aetna International internal data.

76 http://www.who.int/mediacentre/news/releases/2015/antibiotic-resistance/en/

77 http://apps.who.int/iris/bitstream/10665/194460/1/9789241509817_eng.pdf?ua=1

78 http://www.who.int/features/2017/antibiotic-resistance-syria/en/

79 http://www.who.int/features/2017/creative-campaigns-antibiotic/en/

Conclusion

After young Simon Sparrow died of MRSA back in 2004, his mum, Everly Macario, joined with colleagues at the University of Chicago Medical Center to found the MRSA Research Center. She has since become an advocate for the Pew Charitable Trusts' "Supermoms Against Superbugs" campaign, which mobilises parents, doctors, chefs and farmers to "bring a unique perspective and their personal experience to raising awareness of the growing public health and national security threat posed by drug-resistant bacteria."[80]

In a blog post on the CDC website, Macario issued a call to action: "Please join us in this effort. No one individual or group alone, and no single action, can conquer antibiotic resistance ... Think about what you can do today to raise awareness and combat antibiotic resistance — Simon's death will not have been in vain and future generations will thank you."[81],[82]

We at Aetna International are doing our part through proactive education, early intervention, data analysis and an emphasis on value-based care. We pledge to learn from observations of the U.S. health care system and our experience with our expat population in the U.S. and to implement actionable strategies in regions where we have a presence to the benefit of our members, partners and health care providers. We invite our members, customers, providers and everyone else who is affected by this crisis — in other words, everyone on the planet — to join us.

80 http://mrsa-research-center.bsd.uchicago.edu/index.html

81 https://blogs.cdc.gov/safehealthcare/no-man-is-an-island-the-antibiotic-resistance-bell-tolls-for-us-all/

82 http://www.pewtrusts.org/en/research-and-analysis/analysis/2017/04/24/meet-our-supermoms-2017

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About Aetna International

The promise of healthy … anytime, anywhere

Aetna International is committed to helping create a healthier global community. We offer large employers, health care systems and government entities customised technological and health management solutions to help improve health, enhance quality of care and contain costs.

We provide international and national health benefits and services to more than 800,000 people worldwide, and our customers include expatriates, local nationals, the globally mobile and business travellers. We offer comprehensive health care benefits, including medical, dental, vision and emergency medical assistance amongst others, along with preventative and condition management care programs.

Aetna International's parent company, Aetna, is one of the leading health care benefits and services companies in the U.S., serving 46.5 million people with information and resources to help make better informed decisions about their health and wellness.

For more information, see **aetnainternational.com** and **aetna.com**, and discover how we are delivering the promise of healthy … anytime, anywhere.

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