How We Can Stop Antibiotic Resistance

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June 8, 2017

"The world is heading towards a post-antibiotic era in which common infections will once again kill. If current trends continue, sophisticated interventions, like organ transplantation, joint replacements, cancer chemotherapy, and care of pre-term infants, will become more difficult or even too dangerous to undertake. This may even bring the end of modern medicine as we know it."

That's what the Director-General of the World Health Organization said last April when she appeared before the United Nations. Dr Margaret Chan wanted to warn of what many deem to be one of the greatest threats to global health today: the increasingly common problem of infections that do not respond to antibiotic treatment.

It sounds alarmist, but it might actually not be alarmist enough.

The efficacy of the world's antibiotics is quickly decaying – the drugs we're using to treat infections are working less and less. If we continue at this rate without intervention, we may find that there is not a single antibiotic left to treat any type of bacterial infection.

"This would really change life as we know it," says Dr David Weiss, director of the Antibiotic Resistance Center at Emory University. "Consider going to back to an era when a minor accident like a scrape could lead to death." That's what a world of total antibiotic resistance could lead to.

A combination of over-prescribing medications and a cultural dependence on antibiotics has led us to where we are today. (Credit: Getty Images)

But there's good news: we are not likely to continue at this rate. The world is aware of the problem and there are many organisations, governments, and concerned citizens working hard to avoid a worst-case scenario.

The bad news is that the issue is extremely complex and widespread. And thanks to the very nature of bacteria and how they work – and the damage we have already done – the world will never be entirely free from resistance.

What is resistance?

Say you contract a staph infection. In the past that was easily treated with penicillin. But today, it is very possible that your staph infection is actually MRSA – a version resistant to antibiotics (only 10% of current

staph infections *aren't* MRSA). Penicillin is useless against it. In fact, studies show that two in 100 people are carrying around the MRSA bacteria.

Here's how resistance develops: just like people, bacteria have DNA. And just like in humans, that DNA can mutate or change. Then, when inputs from the outside world interact with those mutations, survival of the fittest means only the strongest variations live on.

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So, when humans use antibiotics to kill off bacteria, in some cases, those bacteria spontaneously mutate their genes, which changes their makeup in such a way that the antibiotics cannot kill them. The bacteria that survive those encounters pass these genes on to other bacteria through simple mating ('conjugation') – and those resistant bacteria can spread from one living thing to another.

The tricky part of this is that bacteria can share these genes with each other across bacterial species – so they don't even have to be that genetically similar to pass along resistance. Humans and animals, who are teeming with trillions of different types of bacteria, then pass the resistant bugs along to each other. And, on top of it all, we introduce those resistant species to each other inside our own bodies. So, even if a human or an animal has been exposed to an antibiotic just once in their lives they can contain mutant bacteria that can be easily spread.

Bacteria, it turns out, don't care about political borders or immigration policies – for example, researchers have even found drug-resistant bacteria on the rear-ends of seagulls in Lithuania and Argentina.

The most important part of this is that bacterial resistance is essentially a numbers game: the more humans try to kill bacteria with antibiotics, and the more different antibiotics they use, the more opportunities bacteria have to develop new genes to resist those antibiotics. The less we use, the less bacteria can develop and share resistance.

How big is the problem?

A world of total antibiotic resistance could change life as we know it, making even minor ailments life-threatening.

It's hard to say for sure, but the US Centers for Disease Control and Prevention (CDC) estimates that in the US alone there are about 23,000 people who die every year from antibiotic-resistant infections. For example, they estimate that resistance to antibiotics that treat Clostridium difficile (C. difficile) causes almost 500,000 infections in the US every year, which lead to about 15,000 deaths. (But Amanda Jezek, a spokesperson specialising in policy and government relations at the Infectious Diseases Society of America, a group that represents many of the country's infectious disease doctors and scientists, says the overall number of deaths is a conservative estimate and likely higher.

Meanwhile, a 2015 study published in *Nature* found that global antibiotic consumption went up 30% between 2000 and 2010.

The WHO estimates that with tuberculosis alone there are about 480,000 people worldwide with drug-resistant strains of the disease. In 2014 they estimated that 3.3% of all new cases of TB were resistant to

multiple drugs, and in recurring cases, 20% were resistant. They have also tracked cases of resistance (some very common and some less so) in drugs used to treat E. coli, urinary tract infections, HIV, gonorrhea, malaria, pneumonia, and staph infection (the drug resistant version of which is MRSA).

And according to Public Health England, the "UK government considers the threat of antibiotic resistance as seriously as a flu pandemic and major flooding." If left unchecked, antibiotic resistance could lead to 10 million deaths by 2050 worldwide, costing some £66 trillion.

How did we get here?

Plain and simple, humanity has drastically overused antibiotics.

Not only have doctors spent decades handing out antibiotics to any patient that asked (regardless of whether or not they were needed), some countries still consider antibiotics to be over-the-counter medicines – as easy to purchase as Anadin or Tylenol. According to Dr Marc Sprenger, director of the antimicrobial programme at the WHO, much of Europe is three times more likely to use antibiotics than their fellow European countries Sweden or the Netherlands, where they are used only occasionally. "This has nothing to do with more people getting sick. This is a cultural phenomenon," he says.

On top of that, for many decades agricultural pursuits worldwide have fed huge amounts of antibiotics to livestock and food-producing animals – not only as a means to reduce infection, but also as a method to increase growth. And, while humans do not ingest those antibiotics, they do ingest and handle the bacteria that resides within those animals. So if those animals carried drug-resistant bacteria, you potentially could, as well.

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> – Dr Marc Sprenger (on antibiotic overprescription)

Until recently antibiotics in the US actually listed animal growth as an indication for use on antibiotic labels and a prescription was not required for farmers to obtain them. To illustrate what a problem this is: just last November a strain of E. coli was discovered in Chinese pigs to be resistant to colistin – a last-resort antibiotic that has only been used in the US in the most dire cases of human infection, untreatable by all other antibiotics. In less than six months the CDC detected that strain of E. coli in a patient in Pennsylvania.

So why not just develop new antibiotics that the bacteria can't resist? It has been several decades since a drug company developed and sold a new antibiotic. "You would like to have new antibiotics to treat infections with resistant bacteria, but if you look at the timeline [of new releases] it is empty for almost 30 years," Sprenger says.

That's because the process of developing any new drug is extremely expensive and the potential profit in an antibiotic after that massive investment is relatively low. According to Sprenger, "there are no legal instruments to prohibit the use of a new antibiotic." What that means is if a new antibiotic is released there's no way to stop the world from overusing it. At current usage levels a new antibiotic, he says, would only have about two years on the market before bacterial resistance to it develops.

How do we get ourselves out of this?

First, the entire world needs to get on board. Two years ago this essentially happened when member states of the WHO agreed to accept a Global Action Plan – by then, antibiotic resistance was a problem that had already been on the radar for many decades. The plan lays out extensive solutions and best practices that all countries can take to reduce resistance. "That's historic," says Sprenger. Before then, he says, the only people actively discussing how to reduce resistance were people within medical circles, for the most part. "95% of the worldwide population is now living in a country where they have developed a

national action plan. All these countries have increased activities in education, training, and prevention control."

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> – Dr Katherine Fleming-Dutra

Then, last year, the UN addressed the issue before the General Assembly – only the fourth time in history that a health issue was discussed there. And just this May the G20 leaders signed a declaration on global health that included tackling antibiotic resistance. So it's definitely a grand challenge that world leaders are taking seriously.

Much of the WHO action plan focuses on hospital stewardship and supervision. The CDC is currently working closely with American hospitals to provide guidelines and education for the safe and reasonable prescription of antibiotics. "We have made some progress," says Dr Katherine Fleming-Dutra, an epidemiologist at the CDC. "In the last couple of decades we've seen decreases in prescription to children in the US. We have seen less progress in adults. The rate in adults has been relatively stable."

Once hospitals and physicians get on board with reducing prescriptions the next step is to change regulations around agriculture.

Worldwide consumption of antibiotics has skyrocketed in recent years: one study found that global consumption went up 30% between 2000 and 2010.

Ten years ago the European Union banned antibiotics as growth promoters. And just this January, the US Food and Drug Administration removed growth from the indicated use of antibiotics on drug labelling. According to Dr William Flynn, deputy director for science policy at FDA's Center for Veterinary Medicine, "There was a real recognition that this was something [farmers] needed to take seriously and respond to. We're encouraged by the fact that they were engaging and working with us to find ways to make it work."

But other countries need to follow suit – as evidenced by the recent revelations about antibiotic resistance coming out of China.

One of the most important steps in tackling resistance is tracking it. The CDC have set up a system called the National Antimicrobial Monitoring System (NARMS). "Surveillance for antibiotic resistant bacteria is a big part of our mission," says Dr Jean Patel, deputy director of the office of Antimicrobial Resistance at the CDC. "We do this to measure the burden of infection and also characterise the types of resistance we see. This helps us strategise how best to prevent resistance."

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The CDC funds state health departments around the US (and coordinates with laboratories worldwide) to maintain a network of antibiotic resistant bacteria data and samples. Says Patel: "We can use this to give us national estimates of infection rates to see how bacteria are changing, test new drugs against bacteria, and we also have used the bacteria we collect through this to help with vaccine development." Though, it should be noted, the continued success of the programme could be in jeopardy as US President Donald Trump's proposed budget suggests cutting funds to the CDC by 17% (or $1.2 billion).

Animals also develop antibiotic resistance, which means they could pass their drug-resistant bacteria onto you, too.

But there are also some non-traditional methods being attempted. Emory University in Atlanta, Georgia, has established a unique Antibiotic Resistance Center. One of its main goals is to build diagnostic tests using mutated bacteria collected by the national surveillance system and physicians in their own clinic that can spot resistant bacteria.

"The goal is to have scientists, clinicians, and epidemiologists all working together to address this issue. That's something that hasn't traditionally happened. There has been division between what the scientists and clinicians are doing," says the centre's director David Weiss. "I'm not a doctor. I need to know from the clinicians a lot of what they're seeing on the front lines to help guide our research to be as relevant as possible."

A comprehensive, collaborative approach could work: last year, the National Health Service of England announced that in 2015, antibiotic prescribing reduced by 5.3% compared to 2014. Public Health England says that more responsible prescribing is key: it says that it advised the NHS in 2015 on the development of better practices that aim to slash prescriptions by 10% from 2013 to 2014 levels.

Lastly, there need to be incentives that encourage the development of new antibiotics.

The US National Institute of Health and the Biomedical Advanced Research and Development Authority have set up a biopharmaceutical accelerator called CARB-X. The fund is allotting $48 million to support antibiotic drug discovery projects. "They work with companies in the very early discovery stages to give them funding and technical support to get to the point that they have a product they can do clinical trials with," says IDSA's Jezek. Along those same lines, the IDSA is also currently working to develop legislation that would provide funding for clinical trials so that companies can avoid those hefty costs and stand a chance of making a profit from new antibiotics.

With all of these programmes working together, and similar efforts taking place around the world, there is a lot of hope that humanity will manage to get a handle on the problem. Still, "we can only really slow the development of resistance. We're not going to stop it completely," says Jezek. "Even appropriate use of antibiotics does contribute to resistance."

And that means the challenge will always be immense. As long as there are humans and those humans carry and transmit disease – which they will – the entire world will have to continue fighting for resistance.

http://www.bbc.com/future/story/20170607-how-we-can-stop-antibiotic-resistance