WN *Hot stuff*

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Biocides. Gut microbial ecology

Antibiotics make you fat

Geoffrey Cannon
University of São Paulo, Brazil
Email: wn.the editor@gmail. com

Access April 2013 Michael Pollan, Jeff Leach on gut microbiota here
Access March 2014 New York Times Pagan Kennedy on antibiotics and obesity here
Access December 2014 UK report on global deaths, cost of superbugs by 2050 here
Access June 2015 Update on gut microbiota of Yanomami people here

Personal note

Here I declare an interest and make a confession. One of my own books is *Dieting Makes You Fat (*1983 and in a whole new edition in 2008). Another is *Superbug: Nature's Revenge*, on the overuse and abuse of antibiotics (1998). So I am interested in the topic of this commentary, which is mostly the work of Tim Spector and Martin Blaser.

My confession is that I knew, from my research for *Superbug*, that antibiotics 'promote the growth' of chickens and pigs and also cows. Dosed with antibiotics they get bigger and fatter. Systematic use of antibiotics make lucrative intensive industrial farming possible, by checking infectious diseases otherwise inevitable when creatures are crowded together – and also by producing cheap meat and animal products fast .But I never put 1 and 1 together when writing about the ill-effects of antibiotics on humans. Given the 'unnatural experiment' of factory farming, backed by controlled interventions among laboratory animals plus support from epidemiological observations, the case made that 'antibiotics make you fat' is now pretty conclusive. So what proportion of obesity can be reasonably attributed to exposure to antibiotics, and what can be done? These are the salient questions now

Modern medicine is based on a mistake

The heroes of modern medical science, including Louis Pasteur and (above) Paul Ehrlich, saw bugs as the cause of disease, drugs as the cure. This 'germ theory' identifies antibiotics as 'magic bullets'

Modern medicine is based on a mistake. This has been termed 'the germ theory' or 'the single-cause fallacy', originally proposed by the phenomenally energetic and influential Louis Pasteur. The concept, illustrated by the poster above, is that diseases have one cause, and that the mission of science and medicine is to find the cure and use it. This is also known as 'the magic bullet' theory. The example above was salvarsan, discovered by Paul Ehrlich a century ago, a very toxic but effective treatment for syphilis. This was the beginning of the golden age of antibiotics as cures for microbial infections. Find the bug and the drug, and zap the bug. Job done!

The concept was consolidated last century by the discovery of chemical substances that prevent and successfully treat a series of conditions such as beri-beri, scurvy and goitre, all of which were once prevalent. These chemicals are of course classed as vitamins, minerals and trace elements, and the corresponding conditions as deficiency diseases. This was the beginning of the golden age of nutrition. It also focused the science of nutrition on to the study of nutrients (which is another story). Malnourished children? Give them supplements. Problem fixed!

But the single cause theory, while powerful and effective with infectious and deficiency diseases, was never valid. These diseases also have other types of cause, such as crowding, poverty, industrialisation – and a regular topic of this journal, ultra-processed food products. The theory does not work at all with what are now identified as chronic conditions and diseases such as obesity, diabetes or cancer, which at population level can be successfully addressed only after accepting their social, economic and environmental as well as biological causes. But the germ theory remains the model for medical and allied science and practice. Professionals and public alike, still cling to the notion that there is a 'magic bullet' cure for obesity or cancer and other such conditions. There is and never will be any such thing.

Box 1

Superbugs projected to cause 10 million deaths a year by 2050

Edited from a report by Haroon Siddique in The Guardian of 11 December 2014

The likely impact of antibiotics on obesity is just one of the adverse effects of these potent drugs. A 'low estimate' of the current number of annual global deaths caused by superbugs (bacteria made resistant to drugs by overuse and abuse of drugs) is put at 700,000. But the outlook is far more serious.

Cost: $US 60-100 trillion – or more

Failure to tackle drug-resistant infections will lead to at least 30 million deaths, and will cost the global economy a total of between $US 60 and 100 trillion, from now up to the year 2050, *warns a report* commissioned by UK prime minister David Cameron.

The figures, believed to be the first to quantify the potential impact of superbugs, will be used to make the case to global leaders that urgent action is needed. To put the figures in context, there are currently 8.2 million deaths a year from cancer and annual global gross domestic product stands at $US 70 to 75 trillion.

Former Goldman Sachs chief economist Jim O'Neill, who chaired the report, said superbugs are a more certain threat than climate change in the short term. 'We cannot allow these projections to materialise for any of us, especially our fellow citizens in the BRIC (Brazil, Russia, India, China) and MINT (Mexico, Indonesia, Nigeria, Turkey) world', he said.

The human impact should be enough to prompt major intervention, but the report says the economic figures illustrate that the issue 'transcends health policy'.

A global crisis

No country is immune from the threat. For some nations the outlook is particularly bleak. The world's most populous countries, India and China, face 2 million and 1 million deaths a year respectively by 2050 and one in every four deaths in Nigeria by then is forecast to be attributable to superbugs. Africa as a continent 'will suffer greatly'.

Jim O'Neill said of the $US 60-100 trillion figure, 'As big as that number seems it almost definitely underestimates the economic cost.' This is because the study looked only at a subset of drug-resistant bacteria and public health issues.

It did not examine the social costs, the demand on national healthcare systems, and also secondary health effects. Interventions that have become routine in high-income countries which rely heavily on antibiotics could be severely undermined. Inability to perform Caesarian sections, joint replacements and chemotherapy, that keep people economically active, could together account for another $US 100 trillion between now and 2050, according to the report, although that amount would not be completely lost.

Jim O'Neill said there is hope if international consensus is reached and through advances in diagnostics, stimulating the development of new drugs and alternative therapies such as vaccines. 'With modern technology and the right focus and right guidance, by trying to leverage the world's greatest technology for diagnostics, it would probably make significant difference to the pressure for use of antibiotics,' he said. Sally Davies, chief medical officer for England, said: 'This is a compelling piece of work, which [shows] the true gravity of the threat. [We] simply cannot afford not to take action.'

Counted as cells, about 1 of us is human and about 10 bacterial, all over us but mostly in our guts. At right, one species of gut bacteria. These are co-evolved with us to live with and to protect us

This explains why antibiotics are still seen as 'magic bullets' by physicians and patients. While effective and potentially life-saving, they are no such thing. Also, as suggested by the 'magic bullet' notion, successive generations of professionals and the public have been brought up to believe that antibiotics are wholly beneficial, that in terms of germs, they kill the 'bad guys' and do no harm. (The concept of 'the surgical strike' whereby enemies can be killed while nearby civilians are unharmed, is based on the same notion). This powerfully explains what has become the vast overuse and abuse of antibiotics used on animals and humans.

Weapons of mass destruction

In truth, antibiotics are weapons of mass destruction – of bacteria. This would not matter if all bacteria were harmful or insignificant. But as indicated in the pictures above and in the accounts by Tim Spector and Martin Blaser below, all living creatures including humans of course, are co-evolved with bacteria. Counted as cells, humans are nine-tenths bacteria. These have many necessary and protective functions, including digestion of food and provision of outer immune defences. Bombing our gut bacterial species with broad-spectrum antibiotics is usually reckless.

Antibiotics have a series of ill-effects. First, like all effective drugs, they are toxic – a risk worth taking with serious or persistent bacterial infections, but a risk. Second as indicated, they destroy protective bacteria, and enable invasion of and 'super-infection' by dangerous bacteria. Third, as in effect pesticides used on people, they similarly create strains of bacterial species that can no longer be checked or killed by specific antibiotics. Fourth, a sensational discovery made half a century ago, what is known as 'multi-resistance' transmits from one bacterial species to others, and from one drug to other and even all known drugs. This, with their gross overuse and abuse, explains the general agreement now that drug resistance is as great a menace as climate disruption (see Box 1, above.

The fifth reason is the topic of this report. It is now proved beyond much reasonable doubt that antibiotics in the quantities now typically or commonly used, are an important cause of obesity, particularly in children. Please read on.

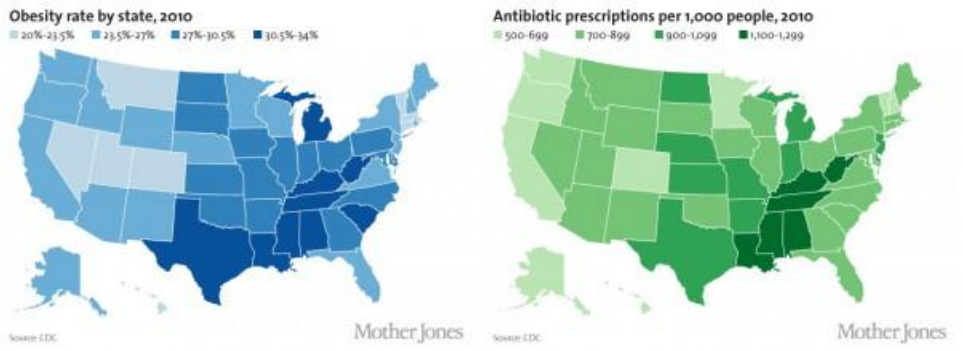
Biocides. Gut microbial ecology. Antibiotics. Obesity

All the evidence points one way

Tim Spector
Department of Genetic Epidemiology, King's College, London
Email: tim.spector@kcl.ac.uk

Editor's note

The text after this note is an edited extract from Tim Spector's *The Diet Myth. The Real Science Behind What We Eat,* published by Weidenfeld and Nicholson in May 2015, with thanks. Together with Rob Knight and other colleagues, Tim Spector has set up the British Gut Project, in collaboration with the American Gut Project. He is interested in encouraging people who join to experiment with their diet. He explains: 'We can't force people to do anything, so what we do is suggest some of the ones that we think are likely to show a change in some people. We piloted some of these recently in the US and the UK, whether it was 'fasting diets', or 'cheese diets', or 'Coca-Cola diets', or 'McDonald's diets'. We're probably going to come up with about ten ideas and we'll try and get people to stick to those, so that way we have a fairly standardised regime, and then the results can be pulled' Contact the British Gut Project at: http://www.britishgut.org/contact.html



Maps of the US state by state compiled by the Centres for Disease Control and Prevention, showing rates of obesity (left) and then rates of antibiotic prescription (right). The correlations were impressive enough to encourage Tim Spector to see if there is any effect on laboratory animals. Yes, there is

Martin Blaser was one of the first to realise the potential long-term dangers of antibiotics and of our misguided attempts to eradicate microbes without thinking of the adverse effects of antibiotics. I first heard him talk in 2009 at a genetics meeting in Long Island, New York, and he convinced me of the reality of those dangers.

He had seen, like many of us, a US government study of the obesity changes over the last 21 years in the US states. In 1989 no state had more than 14 per cent of its population obese. By 2010 no state had less than 20 per cent. The southern US has the highest rates and the west the least. Over a third of US adults are now obese. In 2010 rates of antibiotic use in the same states were published too (see above). The results again showed large differences across the country. Amazingly, the maps for each state overlapped for antibiotic use and for obesity.

Animal and human evidence

We needed direct evidence. We used data from the Avon *Longitudinal Study of Parents and Children*. This follows up 12,000 kids from birth in Bristol, using carefully collected measurements and medical records. Exposure to antibiotics in the first 6 months of life significantly increased – by 22 per cent– the children's amount of fat and their overall risk of obesity over the next three years. This mirrored studies in a Danish birth cohort in which an effect was found between antibiotic use in the first 6 months and subsequent weight at the age of 7

A much larger US study has recently reported the results in 64,000 children. Nearly 70 per cent of kids from Pennsylvania had taken an average of two antibiotic courses before they reached the age of 2. They found that broad-spectrum antibiotics given before that age increased the risk of obesity as a toddler by an average of 11 per cent, with greater risk if the drugs were given early.

These results, although supportive, are not conclusive, and could have been caused by some other factors. So Martin Blaser and his team took this one step further and tested his antibiotic theory in mice. To mimic the effects of antibiotics on babies in the first three years, they used a group of lab mice pups divided into two sets. They gave one set three shots of antibiotics for five days at the equivalent doses that babies are given for throat or ear infections. The antibiotics were followed in both groups by a high-fat diet for five months, at which point they were tested and compared with mice without antibiotics. The results were clear and dramatic. In the antibiotic-treated pups there were significant increases in weight and body-fat levels, and the effects were greatest in the mice that had also been fed high-fat diets.

Everybody uses antibiotics

Most of us born in the last 60 years won't have escaped antibiotics as young children, or high-fat diets at sometime in our lives, and could potentially be suffering the same effects as these mice. We asked our 10,000 adult twins from around the UK if there were any among them who had never taken antibiotics so that we could study them and their microbes. We couldn't find a single one. Even if you escaped antibiotics as a child, you may not have avoided being born by caesarian section. A meta-analysis has shown if you were born by C-section your risk of obesity probably increases by 20 per cent, likely in my mind to be due to microbes.

Box 2
Tom Spector's guts

Tom Spector (above) ate only ultra-processed 'fast food' for ten days. Analysis found that his gut microbial ecology had been devastated, with a massive loss of protective bacteria

Extracted and edited from an account by Tim Spector in May 2015 for The Conversation

When Morgan Spurlock spent a month eating large portions of McDonalds for the purposes of his documentary *Supersize Me,* he gained weight, damaged his liver and claimed to have suffered addictive withdrawal symptoms. This was popularly attributed to the toxic mix in junk foods. But could there be another explanation?

Nobody then had investigated the effect of junk food on westerners from the perspective of the microbiome. My son Tom (above), a university student of genetics, agreed an additional crucial experiment: to track the microbes as they changed from an average western diet to an intensive fast food diet for over a week. The plan was to eat all his meals at the local McDonalds for 10 days. He could eat either a Big Mac or Chicken nuggets, plus fries and Coke. He was allowed beer and crisps in the evening. He would collect poo samples before, during and after his diet and send them to three different labs. Tom started in high spirits and many of his fellow students were jealous of his unlimited junk food budget. As he put it:

> I felt good for three days then slowly went downhill, I became more lethargic, and by a week my friends thought I had gone a strange grey colour. The last few days were a real struggle. I felt really unwell, but definitely had no addictive withdrawal symptoms and when I finally finished I rushed (uncharacteristically) to the shops to get some salad and fruit.

Gut microbial ecology devastated

The results came from Cornell University in the US, and the UK British Gut Project. Tom's community of gut microbes (called a microbiome) had been devastated. Firmicutes were replaced with bacteroidetes as the dominant type, while friendly bifidobacteria that suppress inflammation were halved. Also, after just 10 days Tom had lost an estimated 1,400 species – nearly 40% of his total. The changes persisted, and 2 weeks after the diet his microbes had not recovered. Loss of diversity is a universal signal of ill health in the guts of obese and diabetic people and triggers a range of immunity problems in laboratory mice.

That junk food is bad for you is not news. Knowing that it transforms our gut microbes to such an extent and so quickly is news. Many people eat fast food on a regular basis. Even if they don't get fat, the body's metabolism and immune system are suffering by way of the effects on the microbes. We rely on our bacteria to produce much of our essential nutrients and vitamins, while they rely on us eating plants and fruits to provide them with energy and to produce healthy substances that keep our immune system strong.

Biocides. Gut microbial ecology Antibiotics. Obesity

Modern plagues

Martin Blaser
New York School of Medicine
Email: martin.blaser@med.nyu.edu

Editor's note

The text after this note is edited from Martin Blaser's book *Missing Microbes: How the Overuse of Antibiotics is Fueling Our Modern Plagues,* with thanks. In April 2015 he was selected as one of *Time* magazine's *100 Most Influential People*. The citation by congresswoman and microbiologist Louise Slaughter states:

> As a scientist and author, Martin Blaser is an incredibly important voice on the consequences of our rampant use of antibiotics. Right now, 80 per cent of antibiotics sold in the US are used on mostly healthy animals on factory farms. Over time, this has caused routine bacteria to mutate into untreatable superbugs, putting human lives at risk. Some food companies have responded to public pressure and taken action, but too many in Washington refuse to lift a finger to protect antibiotics, instead bowing to industries that profit from maintaining the status quo. This is why we need people outside the government structure... Martin Blaser's work is a stunning dose of reality in an environment flooded with corporate-agenda-fulfilling pseudoscience.

I never knew two of my father's sisters. In the little town where they were born, early in the last century, they didn't see their second birthdays. They had high fevers, and I am not sure what else. The situation was so dire that my grandfather went to the prayer house and changed his daughters' names to fool the angel of death. He did this for each girl. It did no good. In 1850, one in four American babies died before his or her first birthday. Lethal epidemics swept through crowded cities, as people were packed into dark, dirty rooms with fetid air and no running water. Familiar scourges included cholera, pneumonia, scarlet fever, diphtheria, whooping cough, tuberculosis, and smallpox.

Today, only six in every thousand infants in the United States are expected to die before age 1. Over the past century and a half, the US and many other countries have been getting healthier. Chalk it up to improved sanitation, rat control, clean drinking water, pasteurised milk, childhood vaccinations, modern medical procedures including anesthesia – and of course, nearly seventy years of antibiotics.

Change in patterns and rates of diseases

Yet recently, just within the past few decades, something has gone terribly wrong. In many different ways we appear to be getting sicker. We are suffering from a mysterious array of what I call 'modern plagues': obesity, childhood diabetes, asthma, hay fever, food allergies, esophageal reflux and cancer, celiac disease, Crohn's disease, ulcerative colitis, autism, eczema. In all likelihood you or someone in your family or someone you know is afflicted. Unlike most lethal plagues of the past that struck relatively fast and hard, these are chronic conditions that diminish and degrade their victims' quality of life for decades.

The most visible of these plagues is obesity. In 1990, about 12 per cent of Americans were obese. By 2010, the national average was above 30 per cent. Next time you go to an airport terminal, supermarket, or mall, look around and see for yourself. The obesity epidemic is not just a US problem; it's global. As of 2008 1.5 billion adults were overweight; of these, over 200 million men and nearly 300 million women qualified as obese. Many of these people live in countries that we associate more with famine than with overeating.

The really shocking fact is that this accumulation of body fat has been accelerating not over the course of a few centuries but in a mere three decades. At the same time, the autoimmune form of diabetes that begins in childhood and requires insulin injections (juvenile or type 1 diabetes) has been doubling in incidence about every twenty years across the industrialized world. In Finland, where record keeping is meticulous, the incidence has risen 550 percent since 1950. This increase is not because we are detecting Type 1 diabetes more readily. Before insulin was discovered in the 1920s, the disease was always fatal. Nowadays, with adequate treatment, most children survive. But the disease itself has not changed; something in us has changed. Type 1 diabetes is also striking younger children. Average age of diagnosis used to be about 9. Now it is around 6. Some children are becoming diabetic when they are 3.

The recent rise in asthma, a chronic inflammation of the airways, is similarly alarming. In the US one in twelve people (about 25 million or 8 per cent) had asthma in 2009, compared with one in fourteen a decade earlier. A total of 10 per cent of American children suffer wheezing, breathlessness, chest tightness, and coughing. Black children have it worst: 1 in 6 has the disease. Their rate increased by 50 percent from 2001 through 2009. The rates in all ethnic groups have been rising.

Asthma is often triggered by something in the environment such as tobacco smoke, mold, air pollution, cockroach leavings, colds, and flu. Once an attack begins, asthmatics gasp for air and, without quick medication, are rushed to emergency rooms. Even with the best care, they can die, as did the son of a physician colleague of mine. No economic or social class has been spared.

Food allergies are everywhere. A generation ago, peanut allergies were extremely rare. Now, if you stroll through any pre-school, you will see walls plastered with 'nut-free zone' bulletins. More and more children suffer immune responses to proteins in foods, not just in nuts but in milk, eggs, soy, fish, fruits – you name it, someone is

allergic to it. Coeliac disease, an allergy to gluten, the main protein in wheat flour, is rampant. A total of 10 per cent of children suffer from hay fever. In the US eczema, a chronic skin inflammation, affects more than 15 per cent of children and 2 per cent of adults. In industrialized nations, the number of kids with eczema has tripled in the past thirty years.

These disorders suggest that our children are experiencing levels of immune dysfunction never seen before, as well as conditions such as autism, a much discussed and debated modern plague. In adults the incidence of inflammatory bowel disease, including Crohn's and ulcerative colitis, is rising, wherever we look.

When I was a medical student, esophageal reflux, which causes heartburn, was uncommon. But the ailment has exploded in these past forty years, and the cancer it leads to, adenocarcinoma of the esophagus, is the most rapidly increasing cancer in the US and everywhere else it has been tracked.

Is there a master cause?

Why are all of these maladies rapidly rising at the same time across the industrialised world, and in other parts of the world as they become more Westernised? Can it be a mere coincidence? If there are ten of these modern plagues, are there ten separate causes? That seems unlikely.

Or could there be one underlying cause fueling all these parallel increases? But what cause could encompass asthma, obesity, esophageal reflux, juvenile diabetes, and allergies to specific foods, among all of the others? Consuming too much dietary energy could explain obesity but not asthma; many of the children who suffer from asthma are slim. Air pollution could explain asthma but not food allergies.

Many theories have been proposed to explain each disorder: lack of sleep makes you fat; vaccines lead to autism; genetically engineered wheat strains are toxic to the human gut; and so on.

The most popular explanation for the rise in childhood illness is the so-called hygiene hypothesis. The idea is that modern plagues are happening because we have made our world too clean. The result is that our children's immune systems have become quiescent and are therefore prone to false alarms and friendly fire. A lot of parents these days try to strengthen their kids' immune systems by exposing them to pets, farm animals, and barnyards, or by allowing them to eat dirt. To me, such exposures are largely irrelevant to our health. The microbes present in dirt have evolved for soil, not for us. The microbes in our pets and farm animals also are not deeply rooted in our human evolution. The hygiene hypothesis has been misinterpreted.

Gut microbial ecology

Rather we need to look closely at the microorganisms that make a living in and on our bodies, massive assemblages of competing and cooperating microbes known collectively as the microbiome. In ecology, *biome* refers to the sets of plants and animals in a community such as a jungle, forest, or coral reef. An enormous diversity

of species, large and small, interact to form complex webs of mutual support. When a keystone species disappears or goes extinct, the ecology suffers. It can even collapse.

Each of us hosts a similarly diverse ecology of microbes that has coevolved with our species over millennia. They thrive in the mouth, gut, nasal passages, ear canal, and on the skin. In women, they coat the vagina. The microbes that constitute your microbiome are generally acquired early in life. By the age of 3, the populations within children resemble those of adults. Together, they play a critical role in your immunity as well as your ability to combat disease. It is your microbiome that keeps you healthy. And parts of it are disappearing.

The reasons for this disaster are all around you, including overuse of antibiotics in humans and animals, Caesarian sections, and the widespread use of sanitizers and antiseptics, to name just a few. While antibiotic resistance is a huge problem – old killers like tuberculosis are increasingly resistant and making a comeback – there now seem to be separate ones. These afflict people with scourges of pathogenic bacteria such as *Clostridium difficile* in the digestive tract, resistant to multiple antibiotics, a potential danger in hospital, and methicillin-resistant *Staphylococcus aureus* (MRSA), which can be acquired anywhere. The selective pressure of antibiotic use is clearly increasing their presence.

But as terrible as these resistant pathogens are, the loss of diversity within our microbiome is far more pernicious. Its loss changes development itself, affecting our metabolism, immunity, and cognition.

The 'antibiotic winter'

I have called this process the 'disappearing microbiota'. For a number of reasons, we are losing our ancient microbes. The loss of microbial diversity on and within our bodies is exacting a terrible price. I predict it will be worse in the future. Just as the internal combustion engine, the splitting of the atom, and pesticides all have had unanticipated effects, so too does the abuse of antibiotics and other medical or quasi-medical practices such as sanitizer use.

An even worse scenario is headed our way if we don't change our behavior. It is one so bleak, like a blizzard roaring over a frozen landscape, that I call it 'antibiotic winter.' I don't want the babies of the future to end up like my poor aunts. That is why I am sounding an alarm.

In 2000 I moved to New York University and set up a laboratory. These days my lab is bustling. We are currently working on more than twenty projects, looking at how antibiotics affect resident microbes and their hosts, in both mice and humans. In a typical animal experiment, we give mice antibiotics in their drinking water and compare them with mice that do not get the medication. We start very early in life, sometimes just before birth, and then we let the mice grow, studying how fat they become, how their livers are working, how immunity is developing in their gut, how their bones are growing, and what happens to their hormones and to their brains.

Antibiotics drive obesity

To us, the work is exciting, because in each of those areas we can see changes induced by early-life exposure to antibiotics. We have realized that early life is a key window of vulnerability. Young children have critical periods for their growth, and our experiments are showing that the loss of friendly gut bacteria at this early stage of development is driving obesity, at least in mice. We are just beginning studies on social development and celiac disease. We have many ideas for how we can apply our findings from mouse studies to humans.

Ultimately, we seek to reverse the damage seen in people around the world, including establishing strategies for restoring the missing microbes. A key step in all of our approaches is to reduce the overuse of antibiotics in our children, starting now.

Acknowledgements and status

This first *WN* report on antibiotics and human health is largely based on the work of Martin Blaser and Tim Spector, as published in the specialist literature and electronic media, and in Martin Blaser's boos *Missing Microbes. How the Overuse of Antibiotics is Fuelling our Modern Plagues* (Picador, 2014) and Tim Spector's book *The Diet Myth. The Real Science Behind What We Eat* (Weidenfeld and Nicolson, 2015). Thanks to them and their publishers.

Geoffrey Cannon writes: My own initial research, published as *Superbug: Nature's Revenge* (Virgin, 1995) owes much to the writings and guidance of and interviews with Graham Dukes, Stanley Falkow, Richard Lacey, Stuart Levy, Tore Midtvedt, Richard Novick, and Thomas O'Brien, most of whom I was able to meet as a Winston Churchill Travelling Fellow. Renewed thanks to them, and to the Winston Churchill Memorial Trust. This report does not derive from my work as a member of *The Food System* team at the University of São Paulo

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