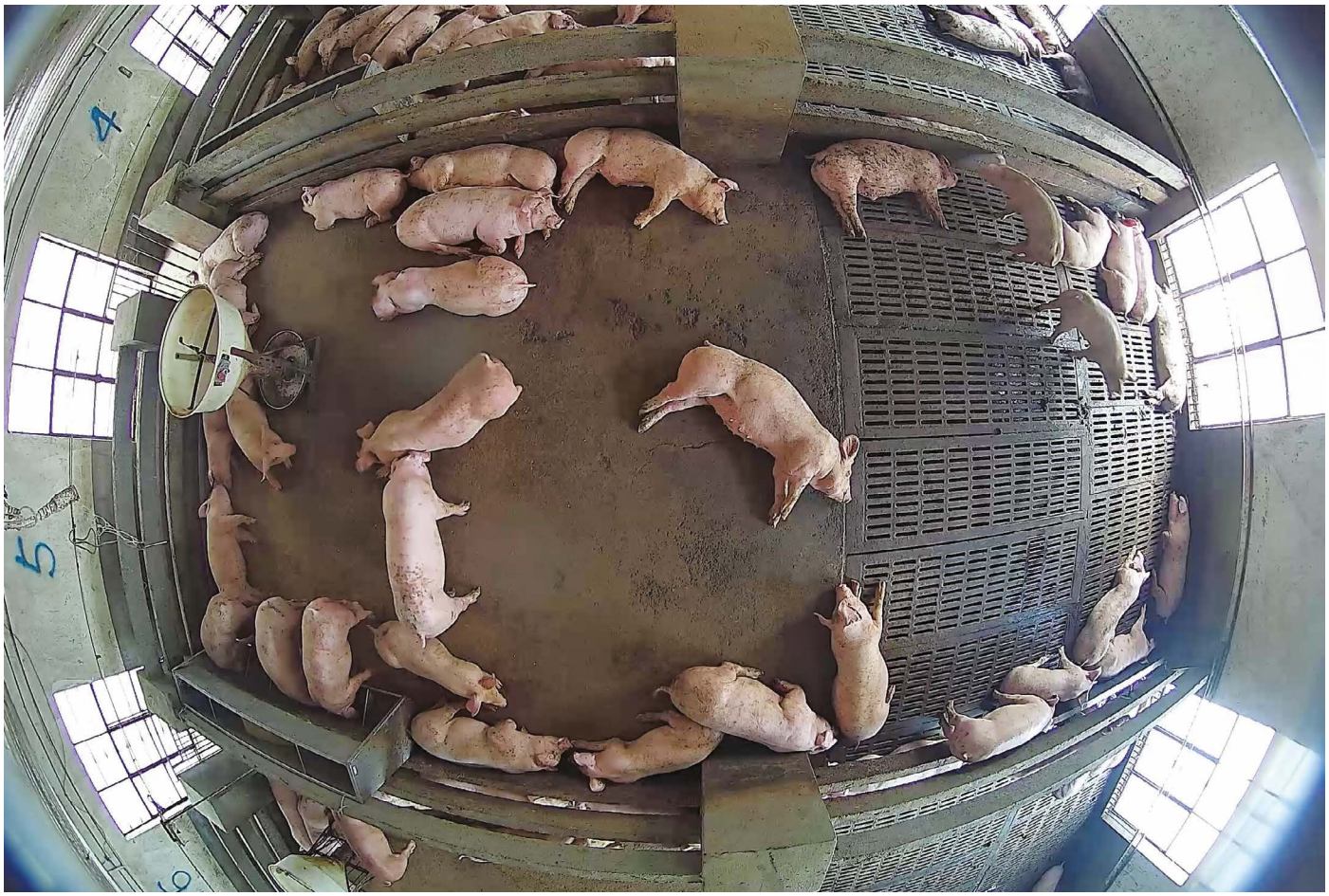

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Pigs at some farms in China are monitored using surveillance cameras to help keep them healthy.

How China is getting its farmers to kick their antibiotics habit

Worries about antimicrobial resistance and disease outbreaks have pushed farms to decrease drug use and improve hygiene. **By Kevin Schoenmakers**

In August 2019, the Chinese government did something it had never done before. Tucked away at the back of a monthly bulletin on veterinary issues, the country's ministry of agriculture and rural affairs published official figures for the volume of antibiotics being used by the country's livestock farms. It was the first time the information had been made public.

A previous assessment by researchers at the Chinese Academy of Sciences calculated that, in 2013, China consumed nearly half the world's antibiotics — 162,000 tonnes, 52% of which was administered to animals[1]. Such widespread use of antibiotics is a cause for concern.

Regardless of whether they originate in a hospital or on a farm, bacteria and other microorganisms that have developed resistance to antimicrobial drugs can end up in people and compromise the ability of physicians to treat common infectious diseases.

The overuse of antibiotics in the agricultural sector has helped to make China one of the world's biggest antimicrobial-resistance hotspots. The nation is estimated to have the second largest number of cases of multidrug resistant tuberculosis in the world. The effects of antimicrobial resistance on Chinese public health are not well studied, says Xiao Yonghong, an infectious-disease researcher at Zhejiang University in Hangzhou, but "China's resistance situation is relatively severe".

Last year's ministerial bulletin, however, brought good news. It said that consumption of antibiotics by China's agricultural sector had fallen by 57% between 2014 and 2018, to less than 30,000 tonnes. According to the report, the quantity of antibiotics used per

tonne of animal produce was now on a par with that in some European countries. China, it seems, is catching up the world's leaders in antibiotics control. Thomas Van Boeckel, an epidemiologist at the Swiss Federal Institute of Technology in Zurich (ETH Zurich), whose work includes tracking the world's antibiotic consumption, notes that the figures suggest an unprecedented decline. Previously, the most successful country was the Netherlands, which decreased its usage by 56% in five years (between 2007 and 2012); China did it in four.

The reduction in antibiotic use by farmers is the result of years of tightening regulation, as well as fresh approaches to infection control that were adopted in response to costly outbreaks of disease in livestock. However, China is not yet home and dry. Unlike reports from the European Union, van Boeckel says, the Chinese bulletin lacks detail and an explanation of its methodology. And even with such a large drop, the sheer size of China's agriculture industry means that the country's total antibiotic use in animals is still several times higher than that of the world's next largest consumer, Brazil.

Despite the progress that China has made, Jeroen Dewulf, a veterinary epidemiologist at Ghent University in Belgium, says, "the story of antibiotics reduction in China will be written over the next ten years".

Trigger for change

According to Wang Yang, a microbiologist at China Agricultural University's College of Veterinary Medicine in Beijing, a breakthrough discovery in 2015 has been key to the reduction of antibiotic use[2].

During a routine monitoring project of the bacteria found in farm animals, researchers, including Wang, noticed increased reports of resistance to an antibiotic called colistin, which is used by farmers to prevent and treat illnesses, and to promote growth.

Physicians began using colistin to treat people in the 1950s. It was one of the first antibiotics effective against a type of bacteria known as Gram-negative, which can cause serious infections, such as pneumonia. But it was replaced in the 1970s, owing to side-effects involving the nervous system and kidneys.

Chinese farmers began using colistin in the 1980s, Wang says, and it soon became popular. In 2015, the country produced 2,736 tonnes of colistin for domestic agricultural use.

Scientists knew that colistin was vulnerable to resistance through chromosomal mutations in the bacteria, but also that the mechanism was imperfect and could not be transferred to other bacteria. "The resistance levels we used to see were always very low," Wang says. The increase in reports of resistant bacteria suggested there was a new mechanism at play.

In 2012, Wang and his colleagues began a 36-million-yuan (US$5-million) project to study the development, spread and control of antimicrobial resistance in animals. And tracking colistin resistance was a top priority. At a farm near Shanghai where the team took samples, workers told the researchers that they used colistin to treat diarrhoea, but that, even with up to twice the usual dose, it was losing effectiveness.

The team, initially mainly made up of researchers from Wang's university and from South China Agricultural University in Guangzhou, was later joined by scientists from the United Kingdom. And ultimately, it discovered a gene that the researchers called *mcr-1*. The gene not only conferred more effective resistance in bacteria, but was also carried by a plasmid — a ring-like strand of DNA that is easily passed between bacteria — raising the possibility that it could spread to bacteria that are already resistant to other antibiotics.

When the team reported its discovery, alarm bells rang around the world. Despite its side effects, colistin had been reintroduced for use in hospitals just over a decade earlier, because so many antibiotics had lost their potency. Further research revealed that *mcr-1* already had a global presence[3].

"The story of antibiotics reduction in China will be written over the next ten years."

To control the spread of resistance, in 2016, China announced a ban on the use of colistin as a growth promoter. Other countries, including Brazil, Japan and India, have since followed suit. The same year, China published a national action plan for dealing with antimicrobial resistance. And on 1 July this year, a ban on the use of growth promoters in animal feed went into effect.

The potential gains are significant. According to the ministerial bulletin, 53% of antibiotics used by farmers in 2018 were used for growth promotion.

When Europe implemented a similar ban, in 2006, the number and size of animals produced temporarily dipped. China's farmers are likely to experience something similar, says Dai Xiaofeng, director-general of the Feed Research Institute at the Chinese Academy of Agricultural Sciences in Beijing. "If you've relied heavily on antimicrobial growth promoters for so long and then suddenly cut them off, this will inevitably have an effect," he says. He suspects the drop will be around a few percentage points, with the worst affected regions seeing a 6% fall in the amount of meat produced.

Dewulf calls the ban "a very important and very necessary first step". Improved feed that is more easily digestible and has a better balance of nutritional elements had already limited the added value of growth promoters, he says. Research in the 1980s found that antibiotics could help pigs to grow around 15% faster, but more recent research shows their effectiveness has dropped to an increase of a few per cent[4].

Anyou Biotechnology Group, a large animal feed producer and farm operator in Taicang, China, welcomes the new policies. The company has always been forward-thinking, says Liu Chunxue, an animal nutritionist at Anyou's research institute, but the impending ban on antibiotics spurred it to develop additives that promote growth without the risk of increasing antimicrobial resistance.

"The last two, three years, the government began to push for healthy feed without antibiotics, so these years we've focused on developing all kinds of additives," says Liu. These include enzymes, fatty acids, essential oils and herbal extracts. After decades of refinements, Liu says, "The food we give to pigs is healthier than the food people eat."

Infection control

The threat of government regulation isn't the only thing that has spurred meat producers such as Anyou to make changes.

In 2018, a disease outbreak in the country's pig herds further sped up the decline in the agricultural use of antibiotics. African swine fever (ASF), a viral disease affecting domestic and wild pigs, resulted in the death of 180 million domestic pigs, or 40% of the country's total stock. "ASF has changed how China's entire pig industry operates," says Hung Ping, founder and president of Anyou.

To contain the virus, his company improved its approach to hygiene. To protect the animals from pathogens, contact with the outside world is now more closely controlled: vehicles arriving at its farms first pass through a disinfection tunnel and then a drying hut; workers spend months on-site without leaving the premises; and newly bought sows are quarantined for four weeks before entering the stalls.

Hsiao Kuo-Shun is the general manager of the company's pig-farming division, which runs around 30 farms throughout China that are working to return to their combined pre-ASF output of about 1 million pigs per year. Before he can enter his company's pig stalls, he says, he has to quarantine for three days.

But better biosecurity does more than just keep out ASF, says Hsiao. "When your pig farm has fewer diseases, you can use less antibiotics," he explains. By mid-2020, the company's farms had reduced the amount of antibiotics used for treatment and prevention per animal by more than one-quarter compared with 2019, according to company figures.

Without quarantining, the only way Hsiao can take a peek at the pig stalls is through the network of cameras installed above every pen. These, too, help Anyou to keep its animals healthy. The cameras are connected to an artificial-intelligence system that analyses whether pigs are clustered too close together, which would indicate that they are cold; whether they are moving around enough; and what their average weight is. Other sensors measure variables such as air quality and temperature, and alert workers when these fall outside optimal ranges. Anyou is also currently testing a smart earring that could be worn by pigs to allow the system to monitor individual animals. Healthier conditions result in lower disease rates, says Hung. "Just like humans, when pigs are stressed [by poor conditions] they get sick easily."

FEATURE CHINA/BARCROFT MEDIA VIA GETTY

A farm worker disinfects a pig pen in China to protect against disease.

Long road ahead

Based on Europe's experience, Dewulf predicts that there will be a temporary shift in which farmers who use antibiotics for growth promotion now give them under the guise of infection prevention. In some European countries, this increase in prevention use lasted just two to three years, he says.

Further reductions will need to come from limiting preventive use, which will be made possible by improved biosecurity and feed quality, he says. The EU has adopted legislation to restrict the preventive use of antibiotics, which will go into effect in 2022.

Dewulf also cautions that cutting down on antibiotics is easier at larger, well-managed farms such as Anyou. Smaller outfits are a bigger problem. Although industrialized livestock farming is often characterized as being "the source of all misery", he says, it generally uses fewer antibiotics and are better at controlling conditions. Blaming small farms feels "a little counter-intuitive", he says.

In 2017, large farms, producing more than 500 pigs a year, accounted for just under half of the market — the current number is likely to be higher. According to China's agriculture ministry, there are around 25 million smaller farms, and some are concerned that these farms might be breaking the rules. A survey of farmers from mostly small- and medium-sized chicken farms in Ningxia, China, found that three-quarters of respondents still used antibiotics that the government had banned[5]. Despite regulations to the contrary, the majority of farmers surveyed had bought antibiotics without prescriptions, and had not kept records of their usage.

Data doubts

Another area in which China still needs to make progress, says Van Boeckel, is data transparency. Among the countries his team has studied, China is one of a few that lacks a publicly available system for reporting antibiotic resistance in animals, making it hard to evaluate the country's progress.

> **"The last two, three years, the government began to push for healthy feed without antibiotics."**

Earlier this year, Wang and his colleagues reported that China's colistin ban had resulted in substantial reductions in levels of resistance[6]. Van Boeckel says those results are encouraging, but laments the fact that the data they used aren't available for other researchers to verify. Using the same methodology but with publicly available data, Van Boeckel says, "we did not see a reduction of the same magnitude".

The data on resistance in animals came from China's Institute of Veterinary Drug Control. Gathering the necessary data sets to evaluate the colistin ban's effects involved working with multiple scientists. It's the reason the paper has six lead authors, Wang says. Van Boeckel would like to see China, as the world's biggest consumer of antibiotics, take a leading role by systematically monitoring antimicrobial resistance and making the data publicly available, as is the case in the EU and the United States. "China adopting best practices for surveillance of antimicrobial resistance could serve as an example for other middle-income countries with fast-growing livestock sectors," he says.

According to the data used in the analysis by Wang and his colleagues, the ban on colistin has been successful. But he cautions that vigilance must be maintained. Other gene variants might replace *mcr-1*. And people with MCR-1-positive *Escherichia coli* bacteria have been found in greater numbers in some provinces than others. "When it comes to controlling antimicrobial resistance," Wang says. "There's a lot of work and a long road ahead."

Kevin Schoenmakers is a journalist based in Shanghai, China.

1. Zhang, Q.-Q. *et al. Environ. Sci. Technol.* **49**, 6772–6782 (2015).
2. Liu, Y.-Y. *et al. Lancet Infect. Dis.* **16**, 161–168 (2016).
3. Wang, R. *et al. Nature Commun.* **9**, 1179 (2018).
4. Laxminarayan, R., Van Boeckel, T. & Teillant, A. *The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector* (OECD, 2015).
5. Xi, J. *et al. Antimicrob. Res. Infect. Cont.* **9**, 10 (2020).
6. Wang, Y. *et al. Lancet Infect. Dis.* https://doi.org/10.1016/S1473-3099(20)30149-3 9 (2020).