Antimicrobial Usage and Resistance in China and the Netherlands

a perspective from the animal husbandry and aquaculture domain

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December 2023

Table of Contents

PART I - Prologue

PART II - Action plan, usage and resistance

PART III – Approach in the animal domain in China

PART IV Next steps

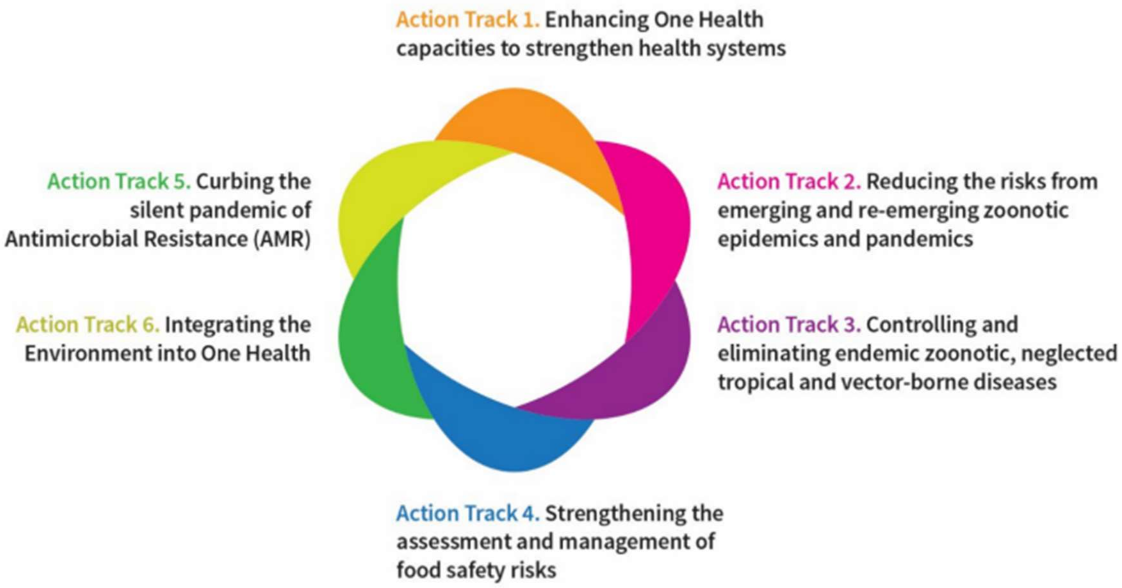
PART I – Prologue

1. Setting the scene

1.1. One Health

The health of humans, animals, plants, and the wider environment are closely linked and interdependent. To describe this interdependence, the term 'One Health' was coined in 2003, soon after the emergence of SARS broke out (Huang et al, 2022). 'One Health' is of relevance in preventing, predicting, detecting, and responding to global health threats and to prevent future pandemics. It requires collaboration across sectors and disciplines to protect global health and address global health challenges (WHO, 2023a).

Since the emerge of the term 'One Health', many papers related to the subject have been produced and many organisations are working (together) on it. Based on research papers, the Centers for Disease Control and Prevention in the United States of America (CDC) express four priority topics of One Health: food safety, vector-borne infections, zoonotic diseases and antimicrobial resistance. The One Health Joint Plan of Action (2022–2026) of the Quadripartite Organizations – the four global leading organizations FAO, UNEP, WOAH and WHO – extends this to six thematic pillars. It provides a framework of interdependent action tracks to remove barriers to enable progress on One Health.



1.2. Emerging burden of antimicrobial resistance

To prevent and treat infections and diseases, *antimicrobials* – including antibiotics, antivirals, antifungals and antiparasitics – are administered in humans, animals and plants. Resistance to antimicrobials occurs when bacteria, viruses, fungi and parasites evolve in such a way to withstand the action of drugs, making them apparently ineffective and infections harder to treat. It increases the risk of disease spread, severe illness and death (WHO, 2023b). It signifies that resistance is a property of a microbe and that (micro) organisms emerge as resistant, not humans, animals or crops. Antimicrobial Resistance (AMR) can be easily transferred between and within different ecosystems and populations. Resistant zoonotic bacteria can for instance be transferred through manure to the soil. Contaminated environments can therefore serve as reservoirs of antibiotic-resistant bacteria (ARB) and antibiotic-resistant genes (ARGs), and from there infect plants, vegetables, fruits and waterways. The chance of human exposure to resistant pathogens will subsequently increase through direct and indirect contact with it. (Velazquez-Meza et al, 2022) (Liu et al, 2023). AMR is the one among global health problems that best illustrates the 'One Health' approach needing collaboration among the human, the animal and the environmental domains (Velazquez-Meza et al, 2022).

AMR occurs naturally over time, usually through genetic changes. But there are several drivers that accelerate antimicrobial resistance, regardless of whether it is in the human, animal or plant domain of One-Health: the absolute use of antimicrobials, which has strongly increased in the last few decades; patients not following the therapy instructions properly, leading to misuse and overuse of antimicrobials; limited development of new drugs to replace those rendered ineffective by rising drug resistance; poor infection and disease prevention and control; lack of access to clean water, sanitation and hygiene; poor access to quality, affordable medicines and vaccines, and thus use of improper drugs; lack of awareness and knowledge; and lack of enforcement of legislation (WHO, 2023a; WHO, 2023b).

Continued increases in AMR have led to fewer treatment options for patients, and an associated increase in morbidity and mortality. According to the project Global Research on Antimicrobial Resistance (GRAM, 2023), more than 1.2 million people died in 2019 as a direct result of an antibiotic-resistant bacterial infection. With inclusion of the 1.2 million, an estimated 4.95 million human deaths were associated with bacterial AMR in 2019 (FAO, UNEP, WHO, and WOAH, 2022). The analysis of 204 countries and territories reveals that resistance is now a leading cause of death worldwide, above of HIV/AIDS or malaria.

1.3. National Action Plans to beat AMR

As AMR is urgent and complex, the World Health Organisation adopted in May 2015 a Global Action Plan (GAP) on AMR, prioritizing the threat of AMR for the very core of modern medicine and the sustainability of an effective, global public health response to the enduring risk from infectious diseases. The Plan called upon member states to develop National Action Plans (NAPs) to address AMR. A 2021 survey from the WHO showed that 86% of responding countries had developed multisectoral NAPs, but only 20% were actively monitoring implementation of those plans (Ding and Hu, 2022).

1.4. The Netherlands' One Health-approach addressing AMR

2015-2019

The Netherlands' National Action Plan (NAP) was issued in 2015 covering up to 2019. The plan propagated a One Health-approach with specific measures for all relevant domains, including human health care, the veterinary sector, the food chain, the environment and international involvement.

In February 2021, the Minister of Health provided an update on the progress made. The measures of the NAP produced a substantial amount of relevant output with tangible results, which likely have contributed to limiting AMR in the Netherlands. Internationally, the resistance rates in the Netherlands are low compared to those in e.g. other European countries. e.g. MRSA 1.9% and ESBL 3.4%. This is partly because, in the Netherlands, you cannot obtain antimicrobials without a general practitioner's or a veterinarian's prescription. As a result, the use of antimicrobials in the

Netherlands in the human health domain is relatively limited (RIVM, 2023) and lowest of all EU countries (VWS, 2021): 7.61 DDD/1,000 inhabitant days in outpatients (NethMap-2022, 2022). But even in a low-incidence country like the Netherlands, cost effective good practices are available to reduce AMR further down, all under the condition of good governance and surveillance systems. Chapter 4 will mention some examples of best practices from the humane domain to lower the risk of acquiring and further spreading (resistant) infections and improving appropriate use of antibiotics.

Monitoring the use of antibiotics in animals is important because it relates to the resistance problem at the source. Targeted programs to reduce the use of veterinary antimicrobials were successful: the sale of antimicrobial veterinary medicinal products in the animal production domain has substantially reduced since 2009 (-70.8%) from around 500 tons in 2009 to 145 tons in 2021 (SDa, 2022). Importantly, almost no critically important antibiotics for human medicine were used. Chapter 5 will elaborate in more detail on measures applied achieving the usage reduction.

2019 onwards

Because "tackling antibiotic resistance is an ongoing endeavour" it was in 2019 already decided to continue the running program and policy to beat AMR (VWS, 2021).

- Promoting the correct prescription and use of antibiotics to stabilise and, where still possible, reduce their use in the human and animal husbandry domain.
- Inhibiting the development of resistance, by investing in research and development of new antibiotics, antifungal agents or alternatives;
- Preventing the spread of Multidrug-Resistant Organisms (MDROs) like MRSA and ESBL;
- Decrease the number of healthcare-associated infections caused by MDRO and decrease in outbreaks in healthcare institutions, through adequate surveillance and good infection prevention.
- Intensify international cooperation.

1.5.The Dutch need for international cooperation

Beating AMR in a country with low AMR levels like The Netherlands, the threat of AMR mainly comes from abroad. Antibiotic-resistant bacteria do not respect national borders, and reducing the import of resistance is essential for the Netherlands. Particular attention in the Netherlands' 'One-Health approach' is paid to international cooperation. Memoranda of Understanding (MoU) were concluded with several important countries in the world: China, Indonesia, Russia, India and the Caribbean nations.

Looking at China, the consumption of antibiotics in the human domain is not extremely high and estimated at 10% of the world consumption (Browne et al, 2021) and at 8-10 DID (Wushouer et al, 2017). In the animal domain consumption was high, but in a downward trend (from 69,292 tons in 2014 to 32,776 tons in 2020) (MOA, 2018-2020). But resistance levels, especially for MRSA and ERSP, are high (29.4% and 96.4% respectively) (CARSS, 2021).

Seen in light of above usage and resistance status, questions arise as what is China's current approach in the fight against AMR? How is the One Health approach incorporated in China's Action Plan and policies? And is there renewed collaboration potential between the Netherlands and China to progress the fight against AMR?

1.6. Report outline

The next parts of the report shed light on AMR in China with a detailed view from the Animal husbandry and Aquaculture domain. Healthy and sustainable agrifood systems are a dominant part of the One Health vision for a better future. Livestock and fish food systems require targeted attention and integrated policies given the multiple effects that the growing demand for protein has on the animal production sector and associated systems (FAO, UNEP, WHO, and WOAH, 2022).

Part 2 covers China's national action plan curbing AMR, and the current antimicrobial usage and antimicrobial resistance in the human and animal domain in China in comparison with the Netherlands and – where relevant – globally.

Given the share of livestock and aqua systems in AMR, **part 3** will set out the approach of the Chinese Ministry of Agriculture to reduce the use in the animal domain.

Taking all information into consideration, the report will in **part 4** discuss in a SWOT the Chinese approach and conclude on potential roadmap for cooperation between Netherlands and China in beating AMR.

PART II – Action plan, usage and resistance

2. National Action Plan curbing AMR in China

Highlights:

- *China's most recent NAP (2020-2025) contains more tangible indicators and assigns more specific task and responsibilities to specific ministries compared to the former NAP (2016-2020). But clear AMR impact objectives are still lacking.*
- *The NAP breaths a "One Health" approach without clearly mentioning it nor an explicit order to do so. The National Health Commission, though, is assigned to establish a liaison mechanism to coordinate between departments (disciplines) involved.*
- *International cooperation is focussed on the problems and challenges faced by global microbial resistance and by providing "Chinese solutions" and "Chinese experience" to curb AMR.*

In 2016, in response to the Global Action Plan on AMR issued by the WHO, 14 ministries and commissions of the Chinese government jointly issued a NAP for combating AMR (2016–2020)[1], which adopted comprehensive management measures at the national level and strengthened regulation in all aspects of drug research and development, production, distribution, application and environmental protection. It was however limited in targets and responsibilities, according to their own conclusion. China had achieved some positive results, but the situation on AMR was nevertheless qualified as 'grim'. Some resistance problems were still intensifying, and there were differences in the level of AMR prevention and control between regions and institutions. To accelerate the curbing of drug resistance, a new NAP was presented by China's National Health Commission in October 2022, covering the period 2022 to 2025 (NHC, 2022). Though containing more tangible indicators and appointing specific ministries responsible for specific tasks, it is still lacking impact objectives i.e. quantitive goals on usage and on resistance of antimicrobials.

2.1.Main tangible indicators

Society

- 80% of rural and urban residents are aware and have knowledge on microbial resistance, infection prevention, and the correct application of antimicrobial drugs.
- 60% of rural and urban residents use antimicrobials in the correct way.

Schools

- 100% of primary and secondary school students have been educated on microbial resistance, infection prevention, and the rational application of antimicrobial drugs.

Veterinary medicine

- 100% of the licensed veterinary personnel in large-scale farms have been trained on the rational application of veterinary antimicrobials.
- 80% of the trained licensed veterinary personnel in large-scale farms apply the knowledge correctly.
- 80% of veterinary drug enterprises sell veterinary antimicrobials on veterinary prescriptions (only).

Human medicine

[1] The NAP is originally named "关于印发遏制细菌耐药国家行动计划（2016-2020 年）". In English it is referred as "National Action Plan Curbing Bacterial Resistance (2016-2020)", or "National Action Plan to Contain Antimicrobial Resistance (2016-2020)".

- 100% of the pharmaceutical retail enterprises sell antimicrobial drugs by prescription (only)
- 75% of the antimicrobial outpatient and inpatient prescription in medical institutions above the second level is appropriate..

Research and Development

- 1-3 new antimicrobial drugs have been developed and marketed
- 5-10 new microbial diagnostic equipment and reagents have been developed.

In relation to the indicators, tasks have been defined. Seven are domestically oriented; One is internationally oriented. They will be described in the next paragraphs.

2.2.Seven domestic tasks

1. Prevent and reduce the incidence of infection to slow the emergence of resistant organisms and spread of resistant infections

- Strengthen infection prevention and control in medical institutions
- Strengthen water, sanitation and hygiene
- Strengthen the prevention and control of environmental pollution of antimicrobials through improved and standardised treatment of sewage and waste water
- Strengthen vaccination against infectious diseases

Specific Animal Husbandry and Aquaculture tasks:

- Strengthen hygiene management on farming and slaughtering locations
- Standardize the treatment of aquaculture and food production wastewater
- Carry out a pilot for monitoring of antimicrobials in aquatic environments
- Optimise vaccination against diseases, enhance the resistance of animals to preventable infectious diseases, and reduce the need for antimicrobials by reducing infectious diseases

2. Strengthen public health education and raise the level of awareness of drug resistance

- Increase the intensity of education for urban and rural residents on awareness of the problem of microbial resistance and improve the knowledge level of infection prevention and rational application of antimicrobials.
- Widely carry out science popularization publicity for primary and secondary school students
- Hold in November of each year, the Antimicrobial Awareness Week, simultaneously with the World Health Organization.

3. Strengthen training and improve professionals' prevention and control capabilities

- Cultivate professional talent teams such as infection prevention and control, infectious diseases, pharmacy, microbiology, veterinary medicine.
- Strengthen the training of medical personnel on the rational application of antimicrobials and the prevention and control of drug resistance

Specific Animal Husbandry and Aquaculture tasks:

- Open courses on microbial resistance, infection prevention and control, and rational application of antimicrobial drugs in veterinary colleges and universities
- Improve the education of aquaculture and veterinary practitioners
- Increase the training of veterinarians and breeding practitioners in the prevention and control of animal diseases and the rational application of antimicrobials

4. Strengthen industry supervision and rationally apply antimicrobials

- Improve the implementation of national rules and regulations at medical institutions on the management of antimicrobials.

- Strictly implement the sale of antimicrobial prescription drugs by pharmaceutical retail enterprises on prescription, and increase the supervision of drug distribution channels.
- Deepen the reform of medical insurance payment methods and give them role in promoting rational drug use.

Specific Animal Husbandry and Aquaculture tasks:

- Guide the safe use of veterinary antimicrobials
- Increase the supervision and management of animal hospitals, animal clinics, and farms
- Promote the green development of the aquaculture industry by decreasing the use of veterinary antimicrobials, and increasing the use of safe, efficient and low-residue veterinary traditional Chinese medicine or other alternative products.
- Strictly implement the withdrawal plan of antibacterial feed additives for growth promotion.
- Promote the sale and use of veterinary antimicrobials on the basis of veterinary prescriptions
- Continue veterinary drug residue monitoring to maintain food safety and public health safety

5. Improve the monitoring and evaluation system for AM susceptibility and resistance in order to provide a basis for scientific decision-making

- Improve the monitoring networks for the clinical application of antimicrobial drugs, bacterial drug resistance surveillance networks, mycosis surveillance networks, and infection surveillance networks
- Establish and improve monitoring, assessment, and early warning systems for microbial resistance risks.

Specific Animal Husbandry and Aquaculture tasks:

- Obtain veterinary antimicrobial drug application data and animal-derived microbial resistance data
- Establish a national microbial resistance reference laboratory and biological specimen bank
- Establish a technical standard system for drug resistance research and monitoring
- Periodically investigate and assess microbial drug resistance biosecurity risks
- Establish an early warning system systems for microbial resistance risks.

6. Strengthen the supply guarantee of related drugs and devices

- Accelerate the launch of urgently needed clinical drugs and medical device products

7. Strengthen scientific and technological research and development for the prevention and control of antimicrobial resistance

- Intensify R&D for new antimicrobial drugs, diagnostic tools, vaccines, and antimicrobial drug substitutes. Pay special attention to the development of antimicrobial drugs suitable for special groups such as pregnant women, children, and the elderly. Include the development of alternative antimicrobial drugs such as Chinese medicines.
- Support research on the molecular epidemiology, resistance mechanism and transmission mechanism of microbial resistance
- Carry out research on the prevention and control of environmental pollution of antimicrobials and its impact

2.3.One international task

8. Extensively carry out international exchanges and cooperation for AMR prevention, surveillance, and control.

- Strengthen exchanges and cooperation with relevant international organizations and countries around the world around the problems and challenges faced by global microbial resistance.
- Actively provide "Chinese solutions" and "Chinese experience" for global microbial resistance prevention and control.

- Promote bilateral and multilateral scientific and technological cooperation with other countries in the formulation of prevention and control strategies and technical standards, monitoring and evaluation, research and development, technology promotion, personnel training, and thematic seminars.
- Promote the international drug resistance surveillance cooperation under the frameworks of the "Belt and Road" and "Healthy Silk Road".

2.4. Is it a “One Health” National Action Plan?

The plan breaths a “One Health” approach without clearly mentioning it. It is obvious to the authors of the plan that communication and exchanges between the several knowledge domains is necessary. To safeguard this, organisational leadership needs to be strengthened (according to their own observations). The National Health Commission, as leader of the NAP implementation, needs to establish a liaison mechanism to improve the coordination between all departments involved. Furthermore, the plan mentions the establishment of a National Advisory Expert Committee on Curbing Microbial Resistance containing experts in different fields and across disciplines.

3. One health landscape in China

Highlights:

- *A very dispersed landscape of Ministries, Administrations, Bureaus and Commissions is involved in the National Action Plan (2022-2025) with risk of slow progress.*
- *China ranks third in the top three countries in terms of the number of publications on One-Health, but they are mostly domestically oriented. China does not have many warm international ties in research, except with the UK. Research cooperation with the Netherlands is currently at a low lever, possibly thwarted by the pandemic.*
- *In 2020 a "One-Health" research center in Chongming, Shanghai was the established. It is a cooperation between Shanghai Jiao Tong University and the University of Edinburgh.*

3.1. China's official domestic stakeholders

Government departments

In China, there is no independent government agency on One Health. This becomes evident when looking at the National Action Plan (2022-2025) and the Ministries, Administrations, Bureaus and Commissions involved:

- National Health Commission (NHC) (liaison mechanism)
- Ministry of Education
- Ministry of Science and Technology (MoST)
- Ministry of Industry and Information Technology
- Ministry of Finance
- Ministry of Ecology and Environment
- Ministry of Agriculture and Rural Affairs (MARA)
- State Administration of Radio, Film and Television
- National Health Insurance Administration
- State Administration of Traditional Chinese Medicine
- National Disease Control Administration
- State Food and Drug Administration
- Health Bureau of the Logistics Support
- Department of the Central Military Commission

Chinese universities and institutes

In 2014, several Chinese universities organised in Guangzhou city an International Symposium on One Health Research. Despite the symposium name, various department and disciplines were isolated and had little collaboration. Two years later, two ground-breaking publications on the colistin resistance gene MCR-1 in *E. coli* published by Liu et al (2016) and Wang et al (2017), showed though the effective cooperation between the Human domain and the Veterinary domain in One Health:

- College of Veterinary Medicine, China Agricultural University, Beijing
- Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou
- Second affiliated Hospital, Zhejiang University, Hangzhou
- National Risk Assessment Laboratory for Antimicrobial Resistant of Microorganisms in Animals. South China Agricultural University, Guangzhou

The crowning achievement, however, was the establishment of a "One-Health" research center in Chongming, Shanghai on May 8th, 2020 (SJTU, 2020). It is a cooperation between Shanghai Jiao Tong University and the University of Edinburgh. It will setup up practice and training bases in Shanghai and Hainan province (Lecheng International Medical Tourism Pilot Zone, Bo'ao), boosting research for risk alerts related to zoonosis, microbial drug resistance and food safety through a human-animal-environment database. Core mission is "Enjoy one world, Create one health".

Subsequently, the journal, Science in One Health has been founded on September 29th, 2022 by the One Health Center (Science in One Health, 2022). It is an Elsevier publication and is an official journal of the Chinese Preventive Medicine Association (CPMA). Prof. Dr. Xiao-Nong Zhou is director of the One Health Center, and editor in chief of the journal.

3.2.China's international (research) partners

To explore global research trends, hotspots and future cooperation directions of One Health, *Liyuan Miao et al* (2022) analysed a total of 12,815 publications (of which 9,036 scientific articles; 3,059 reviews; 597 books; and 123 editorials) in the time frame of 2003 to 2021. They found that China ranks third in terms of the number of publications (n = 1,223 total publications / 1,077 scientific articles) after the United Kingdom (n=1,429 total publications / 1,422 scientific articles) and the United States of America (n=3,588 total publications / 3,581 scientific articles) (figure 1).

Figure 1: Top 10 national collaborative networks for One Health, 2003–2021. (number of publications, and link strength increasing van light to dark blue)

China has compared to the UK and the USA significantly limited cooperation with other countries despite its high number of publications, ranking eighth in the total link strength (figure 1). Zooming in, China's international research partners are predominantly in the UK (*Liyuan Miao et al, 2022)*.

Research cooperation with the UK

In March 2018, the Chinese Ministry of Science and Technology and the UK Department of Health and Social Care opened a call for new collaborative programs between China and the UK to develop solutions that address the issue of infections resistant to antibiotics both in humans and in animals (GOV.UK, 2018). In total, 14 projects on the development of new or improved products or services against AMR, including vaccines, antibiotics and alternative solutions (including traditional Chinese medicine), animal feed and diagnostic technologies were selected and have run for three years.

In 2019 the UK Newton Fund and the National Natural Science Foundation of China (NSFC) made funds available to support new interdisciplinary China-UK AMR partnership programmes on strategies to reduce the burden of antibiotic resistance in China (STAR) (NIHR, 2019).

The close ties between the UK and China are reassured in a new funding opportunity published on 14 April 2023 for China-UK One Health research for epidemic preparedness and AMR, which is co-financed by the Ministry of Science and Technology (MoST).

Research cooperation with the US

The collaboration between the US and China on AMR is (publicly) less intensive than between the UK and China. An example is though the US-based Antibacterial Resistance Leadership Group (ARLG), a group of leading experts working together on clinical research that will impact the prevention, diagnosis, and treatment of infections caused by antibiotic-resistant bacteria (www.arlg.org). ARLG has established a multidrug-resistant organism (MDRO) network of sites in the US, China and other countries with high rates of MDRO organisms. The goal of this MDRO network is to conduct collaborative clinical research focused on AMR that is relevant to patient care in both China and the United States (Van Duin *et al*, 2018).

Research cooperation with The Netherlands

The Netherlands has its own center on One Health: The Netherlands Centre for One Health (NCOH). It aims for an integrated One Health approach to tackle the global risk of infectious diseases. Their cooperation focus is mostly domestic, to bring together Dutch academic research institutes active in various complementary fields of One Health. Second, NCOH works together within the European One Health EJP collaboration programme. Through their One Health Platform NCOH also facilitates data exchange between researchers and research groups and share expertise with co-workers around the world (NCOH, 2023). No specific cooperation models between NCOH and China are evident in the public information sources.

Through governmental, public and / or private Dutch organisations, cooperation between the Netherlands and China takes place already for over two centuries. In 2005 the Netherlands and China signed a MoU boasting the mutual collaboration in the public health domain, in which Dutch RIVM and China's CDC experts exchanged knowledge (RIVM, 2012). Antimicrobial resistance was one of the fields of cooperation. RIVM has longstanding experience with the setting up of large-scale surveillance networks in AMR and is the founding institution of the European Antimicrobial Resistance Surveillance System (EARSS). The activities in the MoU have led to an improved network in China for AMR surveillance, with some 280 hospitals (data 2011) using the software to report antibiotic resistance data.

Due to the success, the action plan was extended in June 2011 with new topics and expanded with other parties and stakeholders. Focus was still on the base principles of exchanging experience and expertise on the technical aspects of setting up and maintaining a national AMR surveillance system. It was concluded in 2016 (RIVM, 2016) that future projects should focus on the One Health principal. It should lead to the creation of a sustainable structure in a Chinese region with the systematic collection of multisector data, such as AMR prevalence and spread and antibiotic use in humans, animals and the environment, leading to information-guided action to reduce the prevalence of AMR. In 2017, the RIVM Centre for Infectious Disease wrote in their strategy that during the period 2016-2021, existing bilateral cooperative agreements in the domain of AMR with China, would be developed further (RIVM, 2017). It is very likely that at least the Covid-19 pandemic has thwarted this.

4. Antimicrobial USAGE and RESISTANCE from the human domain perspective

Highlights:

- *Public data on human antimicrobial use in China are not easily available. Research data on use are approximate and not recent (2010-2015: about 8 to 10 DID), but the data indicate use below the global median (2018: 14.1 DID, Brown et al, 2021; 2022: 16.6, WHO, 2022). Use is however (far) above Dutch human use of antibiotics (2021: 7.6 DID, outpatients).*
- *China has a comprehensive resistance surveillance system in the human domain, enabling data exchange with other countries.*
- *The prevalence of certain antimicrobial resistant isolates is relatively high in China: MRSA (29.4%), ERSP (96.4%), CTX/CRO-R ECO (50%) and CTX/CRO-R KPN (29.8%), with the latter increasing year-on-year.*
- *The Netherlands has an extensive resistance monitoring system, detailing in data from general practitioners, hospital outpatients, hospital inpatients and intensive car units, providing more targeted options for combating AMR.*

4.1.Antimicrobial USAGE (human domain)

China

The China Medical Economic Information (CMEI) system is one of the largest government-approved information consultation and service platforms, which was designed to collect and analyze hospital medication usage under the administration of the China Pharmacy Association (CPA). The database covers more than 1,000 city-level public hospitals across mainland China. The sales of participating hospitals accounts for approximately 40% of total drug sales at city level public hospitals in China (Wushouer et al, 2017). However, no reliable and comparable human antibiotic use data at a population level nationwide are available. Insights are depending on research published like a study on trends and patterns of antibiotic consumption in Shanghai municipality (Lin et al, 2016). Or on a study to estimate population-based antibiotic consumption at national level in China (Wushouer et al, 2017).

The research of Wushuoer et el (2017) extracted monthly surveillance data on antibiotic sales from the CMEI system from January 2011 to December 2015, converted them to into DDD per 1,000 inhabitants (in the specific hospital area) per day (DID). The research indicates an increase in antibiotic use from about 8 to 10 DDD/1,000 inhabitant days (DID). The most frequently used antibiotic class in China (in 2015) were cephalosporins which accounted for 28.6% of total consumption, followed by beta-lactam-beta-lactamase inhibitor combinations with 20.0%, macrolides with 17.4%, and fluoroquinolones with 10.5%.

Netherlands[2]

In the Netherlands RIVM investigates the use of antibiotics within and outside healthcare facilities. The data are published annually in NethMap (Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands).

[2] Information in this section is retrieved from NethMAP-2022, June 2022.

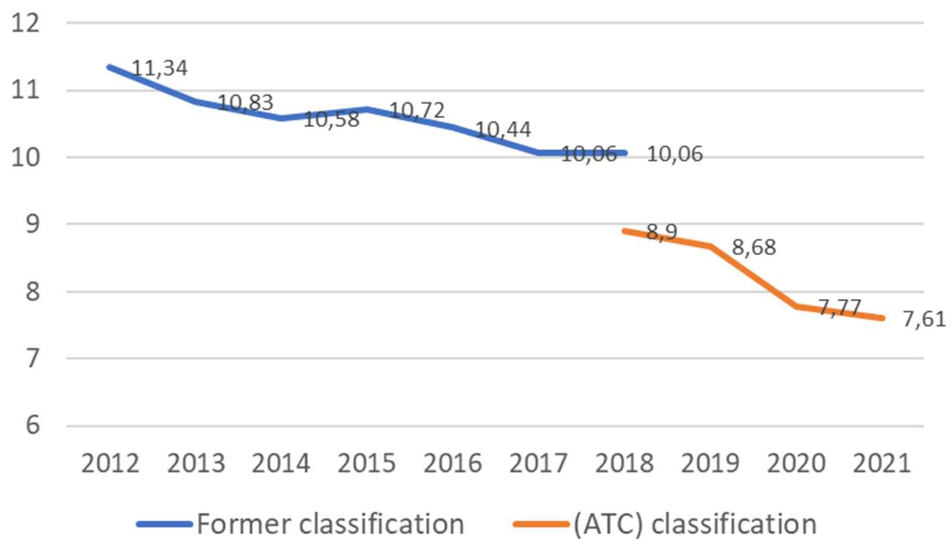


Figure 2: 2012-2021 use of antibiotics for systemic use in outpatients in the Netherlands (DDD/1,000 inhabitant-days)

Outpatients

Data on outpatient antibiotic use are based on dispensing data from Dutch community pharmacies. Covid-19 had a major impact on antibiotic use in the past years, but despite this, total outpatient use of systemic antibiotics is still on decline to the current level of 7.61 DDD/1,000 inhabitant days (DID) (figure 2), mainly due to a decrease in the use of tetracyclines and macrolides.

As two third of the antibiotics in outpatients are prescribed by a general practitionar, they play an important role in reducing the use of antimicrobials. Below are two examples of best practices by GPs in the Netherlands to improve appropriate use or lower use of antibiotics (Oberje et al, 2016) (Stadhouders et al, 2020):

Rapid diagnostic tests for lower respiratory tract infections. Acute bronchitis is the most common lower respiratory tract infection. Even though evidence suggests that acute bronchitis benefits little or not at all from antimicrobials, GPs prescribe them to 80% of the patients. On the one hand due to diagnostic uncertainty by the GP and on the other hand due to perceived patient pressure, patient satisfaction, and patient expectations to get (antibiotic) treatment. Point-of-care testing (POC) to distinguish between acute bronchitis and pneumonia supports the GP for better decisions and appropriateness when antibiotics advised.	*Interactive booklet to inform parents on childhood fever*. In line with the POC example, information material has been developed to 'educate' parents with information for childhood fever. In many cases this fever has viral origins, rendering antibiotics ineffective. The booklet provides amongst others a self-assessment tool to provide parents with guidance on how to act on their child's fever. It reassures parents and reduces time for GPs to explain why antibiotics might not be an effective treatment option. For every 100 patients (parents) who were provided with a booklet, roughly 3 cases of antibiotics were being prevented.

Hospitals

Data on the use of antibiotics in Dutch hospitals is collected by means of a questionnaire distributed to all Dutch hospital pharmacies. As might be expected, due to Covid-19 the use of antibiotics in 2020 increased in hospitals to 85.79 DDD/100 patient-days or to 333.1 when expressed in DDD/100 admissions. An increase was especially seen in Flucloxacillin, second- and third-generation Cephalosporins, and Macrolides (especially azithromycin and vancomycin). The only group of antibiotics that showed a further decrease in use are the aminoglycosides. Hospitals with highest use in antibiotics are the large teaching hospitals.

Long term care facilities

The average antibiotic use in long-term care facilities remained stable with 50.4 DDD/1,000 residents/day, though there is a huge variation in total use across different organisations. The use of tetracyclines, betalactamase resistant penicillins, combination of penicillins, lincosamides and nitrofurantoin decreased; the use of penicillins with extended spectrum, macrolides and fluoroquinolones increased.

Global

Browne et al (2021) estimated a total global antibiotic consumption of 40.1 billion DDD in 2018 (95% uncertainty interval 37.2–43.7). South Asia, comprising India, Pakistan, Nepal, Bangladesh, and Bhutan, with a population of 1·8 billion, consumed over a quarter of all antibiotics in 2018 (25.2%). Whereas China, with a population of 1.4 billion, consumed 10%. (figure 3)

Antibiotic consumption expressed into the WHO rate of DDD per 1000 population shows an average of 14.1 (95% uncertainty interval 13.2–15.6). Rates were estimated highest in North Africa and Middle East (23.6 DDD per 1000 per day), closely followed by North America (23.4 DDD per 1000 per day). The lowest rate in Central sub-Saharan Africa (8.2 DDD per 1000 per day).

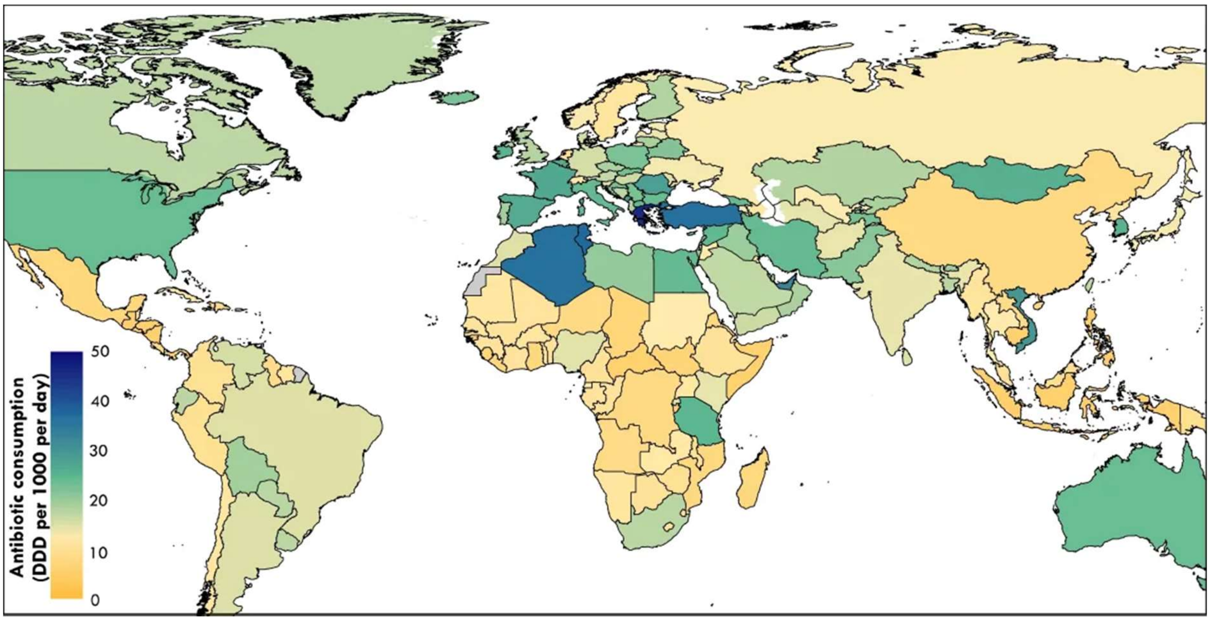


Figure 3: Total antibiotic consumption rates for 2018, in DDD per 1000 population per day (Brown et al, 2021)

The GLASS report of the WHO – based on data of 2020 comprising 26 CTAs – shows a median value of the consumption of antibacterials of 16.6 DDD per 1000 inhabitants per day (range, 12.3-31.2) (WHO, 2022). Both China and the Netherlands are not included in these data.

4.2.Antimicrobial RESISTANCE (human domain)

China[3]

In 2005 the (then) Ministry of Health (nowadays National Health Commission, NHC) notified on the establishment of the China Antimicrobial Resistance Surveillance System (CARSS) and the Center for Antibacterial Surveillance. CARSS was launched in 2005 for hospital antimicrobial resistance surveillance, and until recently, over 1,400 centers in 31 provincial-level administrative divisions throughout China have participated. This system is currently the most comprehensive and macroscopic notifiable disease surveillance system in China (Qianlin Li et al, 2022; Hui Wang, 2022).

Next to this there is the China Antimicrobial Surveillance Network (CHINET). Where CARSS data show the different bacterial resistance rates among different provinces and autonomous regions for each specific bacterium, CHINET data mainly represent the bacterial resistance profiles of teaching hospitals and show the changing trends of bacterial resistance in China (Hu et al, 2018).

Each year CARSS releases a national resistance surveillance report. The surveillance comprises around a dozen organisms resistant to certain medications. In January 2023, the report covering information up to the year 2021 was published (table 1) (figure 4 and 5).

Table 1: China National resistance surveillance report, CARSS, 2021.

Abbreviation	**Full name**	**Average detection rate 2021**	**Trend past 10 years**
MRSA	methicillin-resistant Staphylococcus aureus	29.4%,	Down
MRCNS	methicillin-resistant coagulase-negative staphylococcus		
PRSP	penicillin-resistant Streptococcus pneumoniae	1.2%	Down
ERSP	erythromycin-resistant Streptococcus pneumoniae	96.4%	
VREA	vancomycin-resistant Enterococcus faecalis	0.2%	
VREM	vancomycin-resistant Enterococcus faecus (Faecium?)	1.2%	Down
CTX/CRO-R ECO	cefotaxime or ceftriaxone (third-generation cephalosporins) resistant Escherichia coli	50%	Down
CTX/CRO-R KPN	cefotaxime or ceftriaxone (third-generation cephalosporins) resistant Klebsiella pneumoniae	29.8%	Down
QNR-ECO	quinolone-resistant Escherichia coli	50.6%	
CR-ECO	carbapenem-resistant Escherichia coli	1.6%	Stable
CR-KPN	carbapenem-resistant klebsiella pneumoniae	11.3%	Up
CR-PAE	carbapenem-resistant Pseudomonas aeruginosa	17.7%	Down
CR-ABA	carbapenem-resistant Acinetobacter baumannii	54.3%	Down

[3] The information in this section has been retrieved from http://carss.cn/Report/Details?aId=862

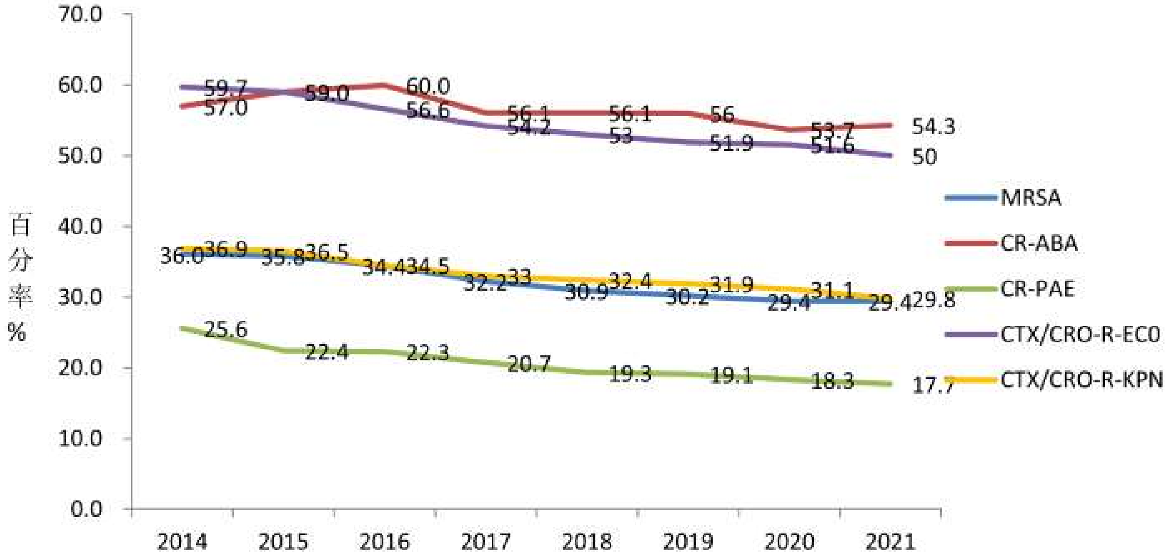


Figure 4: China National resistance surveillance report, CARSS.

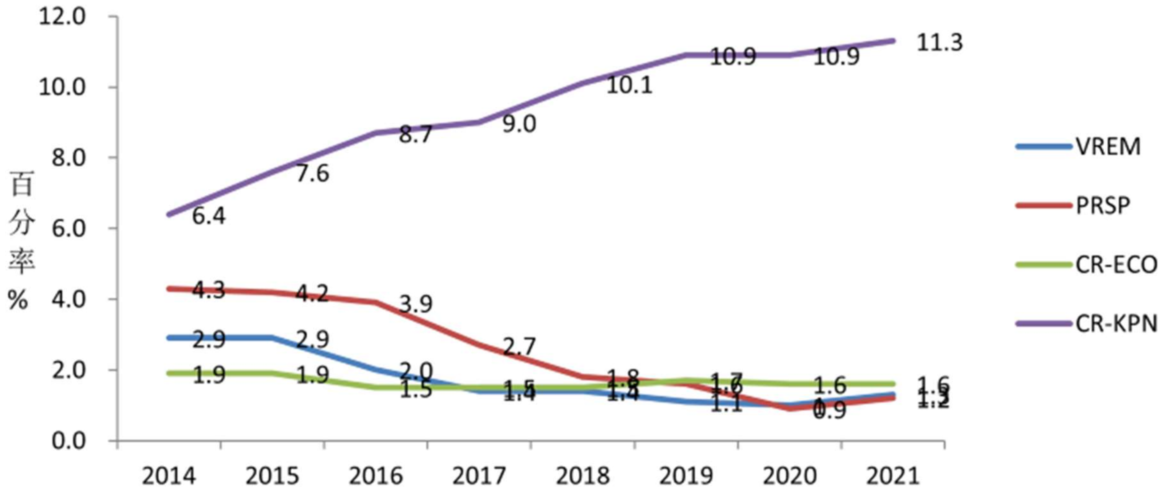


Figure 5: China National resistance surveillance report, CARSS.

Netherlands[4]

In the Netherlands, the Infectious disease Surveillance Information System on Antibiotic Resistance (ISIS-AR) monitors antimicrobial resistance for a wide range of pathogens in the three different settings: at general practitioners (GP), in hospitals (including and excluding Intensive Care Units (ICU)), and in long-term care facilities. Data of 2021 are shown in below table 1. Long term data from 2001 to 2021 of a few selected resistant antimicrobials are shown in Annex 1 (ECDC, 2023).

[4] Information in this section is retrieved from NethMAP-2022, June 2022.

Table 2: Prevalence of antimicrobial resistant pathogens, 2021 (NethMAP-2022, 2022)

Abbreviation	**Full name**	**Prevalence 2021**	**Trend since 2017**
MRSA	methicillin-resistant Staphylococcus aureus	1.9%	Stable
PRSP	penicillin-resistant *Streptococcus pneumoniae*	Hospital 7%	Stable
ERSP	erythromycin-resistant *Streptococcus pneumoniae*	GP 13% Hospital 10%	Up Stable
VRE_{fm}	vancomycin-resistant *Enterococci*	0.2%	Down
CTX/CRO-R ECO	cefotaxime or ceftriaxone (third-generation cephalosporins) resistant *Escherichia coli*	GP 2-3% Outpatient 5% Inpatient 6% UCI 11%	Stable Stable Stable Stable
CTX/CRO-R KPN	cefotaxime or ceftriaxone (third-generation cephalosporins) resistant *Klebsiella pneumoniae*	GP 3% Outpatient 7% Inpatient 8% UCI 16%	Stable Down Stable Stable
QNR-ECO	quinolone-resistant *Escherichia coli*	GP 5-9% Outpatient 4-9% Inpatient 4-7% ICU 6-9%	Stable Stable Stable Stable
CR-ECO	carbapenem-resistant *Escherichia coli*	ICU 0%	Stable
CR-KPN	carbapenem-resistant *Klebsiella pneumoniae*	ICU 1%	Stable
CR-PAE	carbapenem-resistant *Pseudomonas aeruginosa*	GP 9% Outpatient 2% Inpatient 2% ICU 2%	Stable Stable Stable Stable
ESBL-E	extended spectrum beta-lactamase producing *Escherichia coli*	3.4%	Up **
ESBL-E	extended spectrum beta-lactamase producing *Klebsiella pneumoniae*.	4.8%	Up **

0 or - = Resistance absent or not calculated
* In age > 12 years old
** Down in GPs and hospitals except intensive care units. Up in intensive care units.

Two examples of best practices in the Netherlands from the humane domain to lower the risk of acquiring and further spreading (resistant) infections, and lowering hospital stay (Oberje et al, 2016) (Stadhouders et al, 2020):

Pre-hospital-admission MRSA screening. For healthcare institutions, it is important to know whether a patient may have MRSA. At the outpatient clinic or if a patient needs to be admitted to the hospital, questions are asked to the patient related to risk factors (e.g. working or living on a livestock farm or farm with veal calves, pigs, or broilers). In a research project in five hospitals, surgery patients were further screened by a rapid PCRA followed by simple nasal ointment treatment. This practice resulted in a 60% reduction in surgical infections of *S. aureus,* and a 2-day reduction in hospital stay of the patient.	*Multidisciplinary teams to facilitate outpatient parenteral anti-microbial therapy (OPAT).* In-hospital intravenous admission of antibiotics increases chances of (resistant) infection transmissions. Reducing in-hospital length-of-stay through OPAT lowers the chances of development and spreading of resistance. Research showed that if OPAT is not initiated and monitored by the treating physician only but also supported by a multidisciplinary team of an infectious disease specialist, a pharmacist, and a specialised nurse, additional patients received OPAT instead of inpatient care, more patients were switched to the less costly options of orals, and hospital stay of the patients reduced.

Europe

In 1998, the European Antimicrobial Resistance Surveillance System (EARSS) was implemented and coordinated by the Dutch National Institute for Public Heath and the Environment (RIVM). EARSS was a network of national AMR surveillance networks in Europe. EARSS addressed the need for AMR data to raise awareness of the AMR problem and for informed decision-making among stakeholders and policymakers. In 2010 this surveillance network and its coordination was transferred to the European Centre for Disease Prevention and Control (ECDC), together with all the other disease-specific surveillance networks, and continues now as the European Antimicrobial Resistance Surveillance Network (EARS-Net, 2023). EARS-Net performs surveillance of antimicrobial susceptibility of eight bacterial pathogens commonly causing infections in humans:

- Escherichia coli
- Klebsiella pneumoniae
- Pseudomonas aeruginosa
- Acinetobacter species
- Streptococcus pneumoniae
- Staphylococcus aureus
- Enterococcus faecalis
- Enterococcus faecium

The atlas of EARS-Net provides data per country, but not an average for Europe, as data for some isolates differ enormously between countries. For instance, MRSA is below 5% in north-western European countries but as high as 40% or more in South-Eastern countries (if data are already available).

Global

In October 2015, WHO launched the Global Antimicrobial Resistance Surveillance System (GLASS, 2023), the first global collaborative effort to standardise antimicrobial resistance surveillance. GLASS supports the strategic objective of WHO's Global Action Plan on antimicrobial resistance to strengthen the evidence base. The Netherlands is enrolled in GLASS for antimicrobial resistance (AMR) surveillance, not for antimicrobial consumption (AMC) data. China is not enrolled in the system (figure 6).

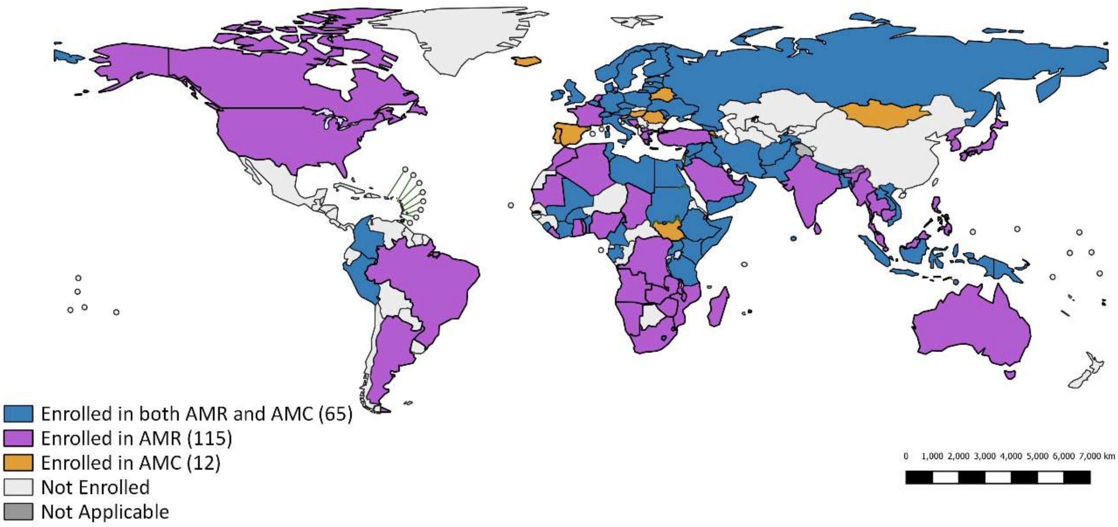


Figure 6: GLASS enrolment map, December 2022 (127 countries enrolled)

5. Antimicrobial USAGE and RESISTANCE from the animal and aquaculture domain perspective

Highlights:

- *China has a comprehensive veterinary antimicrobial usage monitoring system. Results are reported yearly by MARA, however reporting limits mainly to total use in the sector and no data on use per species or use per animal.*
- *After several years of decline in veterinary antibiotic use in in China, the use has increased since 2018 again, even before the feed ban had taken effect (which caused in the Netherlands a temporarily higher use).*
- *In 2018-2020 some critically important antimicrobials were (still) used in animal and aquaculture production, though as the least in their antimicrobial class. Colistin is forbidden to use since 2017.*
- *Netherlands provides very detailed antimicrobial usage in the animal sectors expressed in Defined-Daily Dosage Animal (DDDA).*
- *Usage has declined with 70% in the Netherlands compared to the reference year 2009, due to a targeted approach with benchmark data per farm.*
- *China has a "Veterinary Drug Resistance Monitoring Database System", but data are hard to find in public reports.*
- *Netherlands is strong in resistance monitoring and applies a more comprehensive schedule than China does (e.g. MRSA on farms and farmers).*

5.1. Antimicrobial USAGE (animal and aquaculture domain)

China

A study of Zhang et al (2015) estimated that China consumed roughly 162,000 tons of antibiotics in 2013, of which 52% were used in agriculture (i.e. over 84,000 tons). Slightly more approximate data for the animal husbandry sectors are available since 2014. The Ministry of Agriculture and Rural Affairs publishes since that year the “State of Veterinary Medicine”, showing the production, import and export of veterinary drugs (MOA, 2018-2020). It assumes that the net value of these three components is the actual use in the agricultural and aquatic sectors. Lacking any other data sources, these reports are the nearest estimates and provide a good insight in the developments of antimicrobial usage in the animal and aquatic domain over years.

For some years the usage of antimicrobials showed a downward trend from 69,292 tonnes in 2014 to 30,903 tons in 2018. However, since 2019 the total amount is slowly increasing again, absolute and per ton food produced.

In 2019 the usage increased by 3.8% to 30,904 tons and in 2020 by 6.1% to 32,776 tons (Figure 7). According to the estimates of Mulchandani et al (2023), the global antimicrobial usage was 99,502 tonnes per active ingredient, making China – with around one third of global use – by far the biggest consumer in the world. There are a few limitations to the research of Mulchandani: the 95% confidence interval ranges from 68,535 to 193,052; and, 6 of the 10 largest meat producers in the world have no public government data available, affecting the accuracy of the estimates made by the research.

Per ton produce MARA indicates that since 2014, the use of veterinary antimicrobials per ton of animal products in China has shown an overall downward trend but also rebounded in 2019 to 160 grams and in 2020 to 165 grams (Figure 8). MARA states that compared to data of use in the EU in 2017, they performed better than some EU countries (e.g. Spain, Italy).

Most of the veterinary antimicrobials are produced in China. Only small amounts are imported (varying from 0.7% to 5.7% of the total usage).

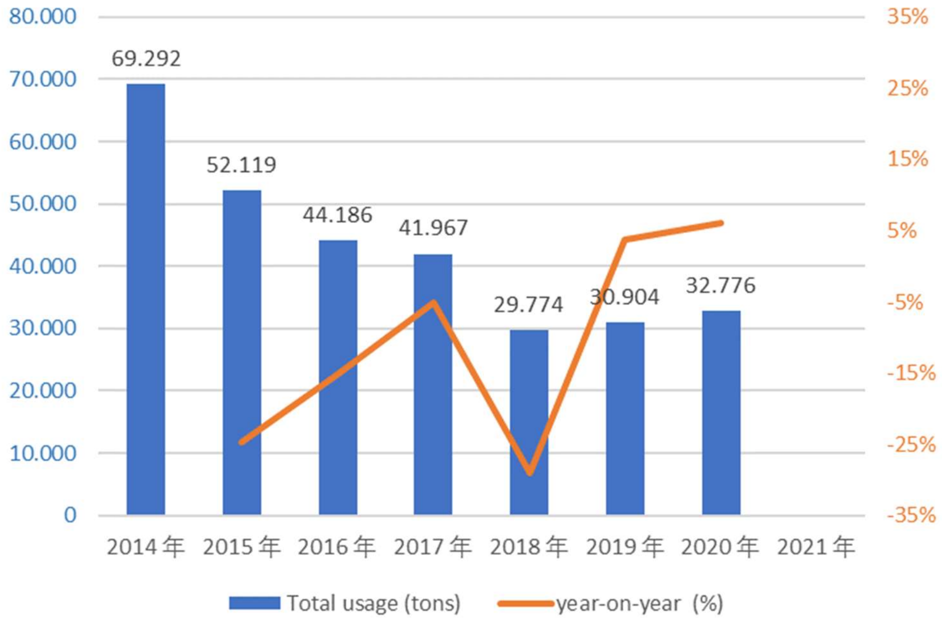


Figure 7: Total veterinary antimicrobial usage in the Chinese livestock industry.

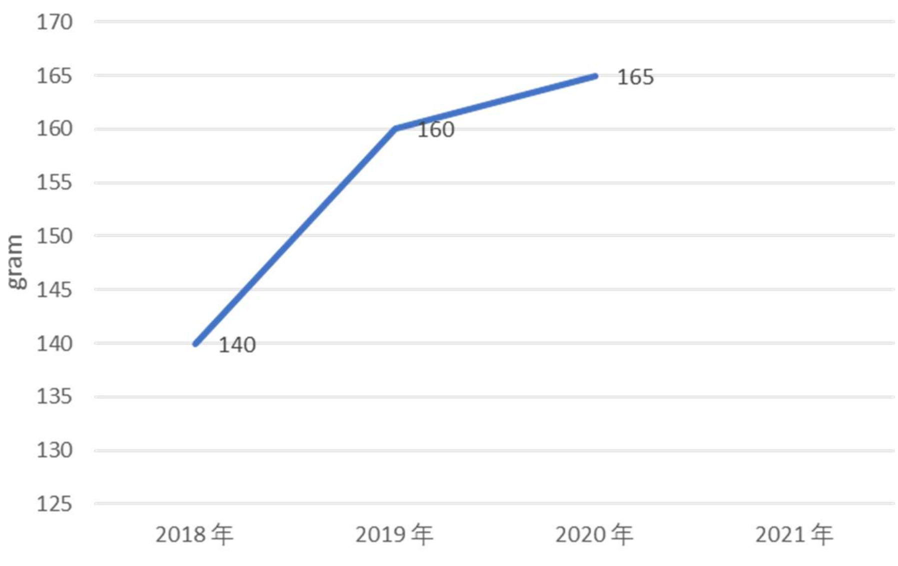


Figure 8: Veterinary antimicrobial usage per ton produce in the Chinese livestock industry.

With the prospect of the ban of antimicrobials in animal feed from 1 January 2021 onwards (*siliao jin kang ling*), changes in the use can already be observed in 2020. Less antimicrobials are used in feed and for growth promotion (Figure 9 and Figure 10). As was to be expected, the usage of antimicrobials to treat diseased animals has increased. However, we see that the route of administration via water has increased at the expense of feed. It cannot with certainty be concluded that antibiotics for growth promotion have decreased, or whether it has been substituted by water application.

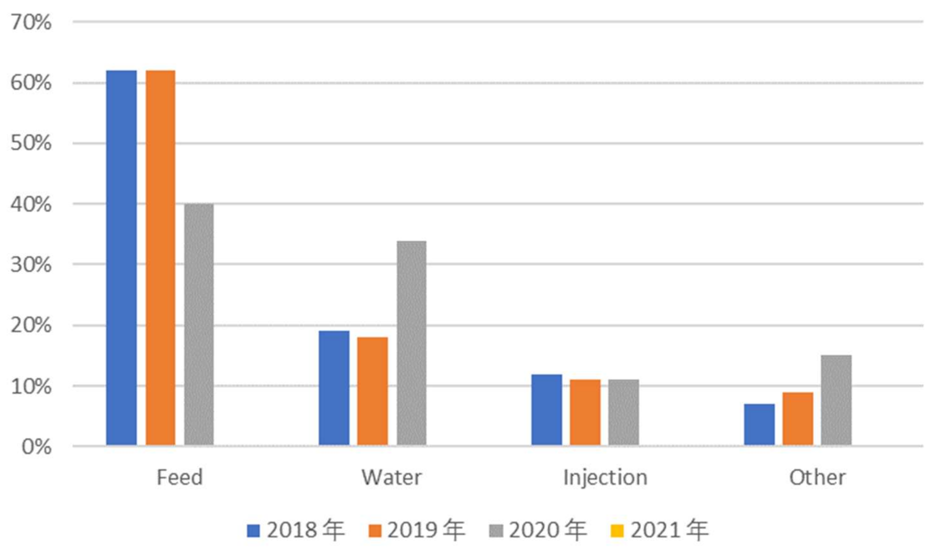


Figure 9: Application route of veterinary antimicrobials in the Chinese livestock industry

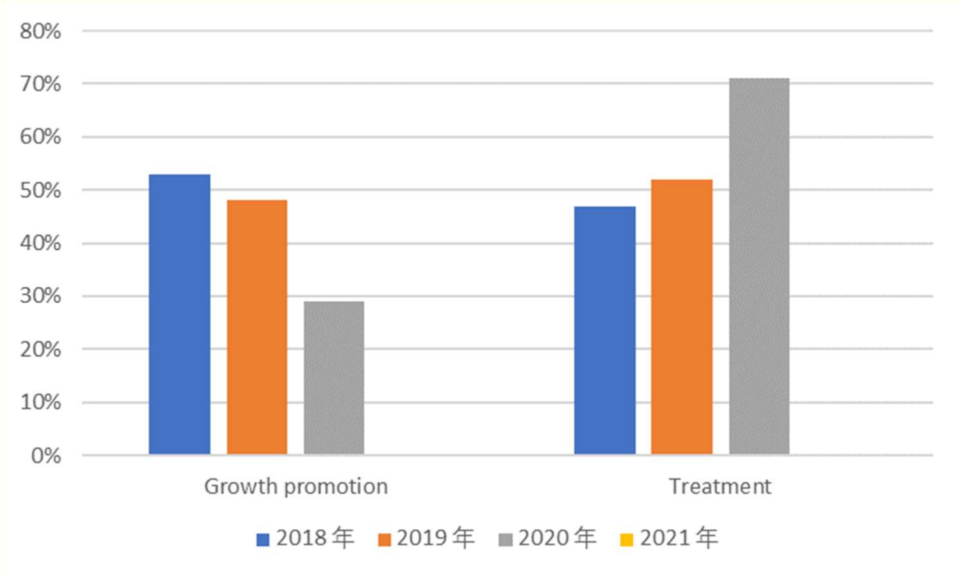


Figure 10: Purpose of administering veterinary antimicrobials in the Chinese livestock industry

According to the classification of veterinary antimicrobials, the largest use of antimicrobials fall in the following classes (according to the categorisation of veterinary antimicrobial agents for food-producing animals, OIE, 2018):

- Tetracyclines (2020: 30.52%)
- Penicillins (mostly β-lactamase and inhibitors) (2020: 12.55%)
- Macrolides: Macrolides are for instance used to treat Mycoplasma infections in pigs and poultry, haemorrhagic digestive disease in pigs (Lawsonia intracellularis) and liver abscesses (Fusobacterium necrophorum) in cattle.
- Polypeptides: Colistin is a cyclic polypeptide, which is forbidden to use in animal husbandry in China since 2017.
- Sulphonamides (2020: 13.08%)

Year on year, Tetracyclines rank first in use. The relative amount of tetracyclines is decreasing though from 45.9% in 2018 to 30.5% in 2020, bringing the other four in favour for use.

A research of Fang et al (2021) in Yunnan under smallholders (less than 30 pigs) and large-scale farmers (over 30 pigs), covering the period 2014-2015, shows a likewise ranking: Penicillins, Tetracyclines, Cephalosporins, Quinolones and Sulphonamides. Research of Xu et al (2020) on chicken farms in Ningxia province, with farms housing at least 500 birds, shows also the high use of (Amino) Penicillins, Tetracyclines, and Cephalosporins.

China; use of Critically Important Antimicrobials (CIA)

In the "State of Veterinary Medicine" of 2018, 2019 and 2020 it can be read that in those years antimicrobials were used in animal and aquaculture production in China which are on the WHO list of Critically Important Antimicrobials for human medicine: streptomycin (2019), rifaximin (2019, 2020), and amoxicillin (2018, 2019). It cannot be concluded that these are the only ones. The reports do not give much more details than the class of antimicrobials. They sporadically mention examples of antimicrobials used the most or the least in a certain class. These three were used the least in their class.

There are no antimicrobials mentioned in those reports which are on the Annex of Regulation (EU) 2022/1255 designating antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EU, 2022). But the same remark needs to be made: The reports do not provide enough details.

Netherlands

The Veterinary Medicines Institute (SDa, Diergeneesmiddelenautoriteit) publishes yearly the monitoring results of antimicrobial resistance and antibiotic usage in animals in the Netherlands (MARAN, 2022). The report is based on total sales data originating from the federation of the Dutch veterinary pharmaceutical industry. It is estimated to cover 98% of all sales in the Netherlands. Approximate 85% of sales in 2021 were exclusively to the major livestock farming sectors (pigs, poultry, veal calves, dairy and other cattle, meat rabbits). According to the report, 3.4% of the sold medicines is exclusively authorized for companion animals.

The results of 2021 show that in total 145 tonnes of antimicrobial veterinary medicinal products were sold, which was a decrease of 5.8% compared to 2020. The report makes an important remark on how to interpret the data per sector in animal husbandry: "Veal calves and pigs used almost 80% of the total mass of all antibiotics sold for therapy. Animals treated in these two sectors are large and therefore need more antibiotics per administration than small animals like broiler chickens. This illustrates that sales data provide limited information about exposure of animals at risk." Therefore, the antimicrobial use is based on annual prescription data and expressed in Defined-Daily Dosage Animal (DDDA).

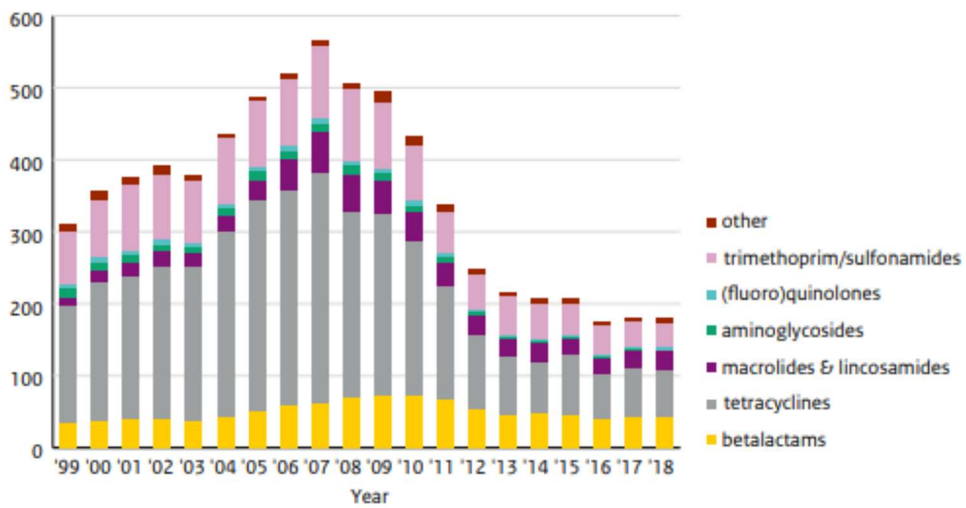


Figure 11: Antimicrobial Veterinary Medicinal Product sales in tons (STAF, 2020)

The most sold antimicrobials were Tetracyclines, Penicillins and Macrolides (figure 11). Sales of Polymyxins (colistin) reduced 77% since 2011.The Dutch target for colistin use since 2020 is 0 DDDA. Rabbits, turkeys and veal calves are the highest consumers of antimicrobials in the Netherlands (figure 12).

In retrospective, the 2006 ban on the addition of antibiotics to feed as growth promoters had the unintended side effect of increasing the curative usage (as we see now too in China). The total amount of antibiotics administered increased rather than decreased. Subsequently, in 2009, a reduction plan was developed in the Netherlands to reduce the total usage on livestock farms. Benchmarks have been drawn up based on the DDDA. This allows a farmer to make a comparison with other farms. If a farmer exceeds a certain DDDA limit, sanctions are imposed and a plan to reduce usage is mandatory. In 2020 an additional concept was added: Livestock farms with persistently high usage levels (exceeding the action threshold for two consecutive years). It is agreed to combine forces to further reduce the amounts of antibiotics used at these farms. After all, these farms are at higher risk for development of antibiotic resistance and could subsequently contribute to the spread of resistant bacteria. The total package of policies proved to be successful. More than ten years of antibiotic reduction policies in the Netherlands has resulted in more than 70% reduction of sales of antibiotics.

The reduction of antibiotics is however not equally distributed over the different species in livestock. The broiler sector achieved the largest percentage decline. The veal sector the smallest. The decrease in dairy and other cattle seems to be low in percentage terms, but this sector has traditionally already had low use.

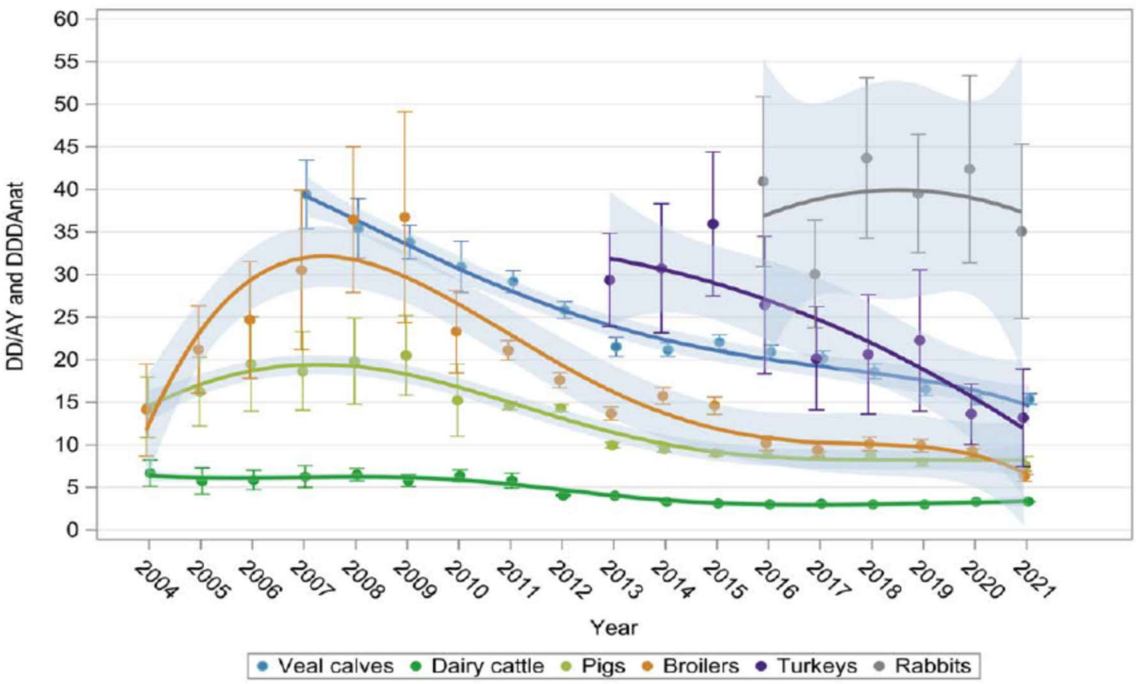


Figure 12: Number of DDDA per animal-year of antimicrobial veterinary medicinal products per animal sector

Netherlands; benchmarking of veterinarians

In 2014 the Netherlands' livestock sectors introduced a benchmark enabling monitoring and assessment of veterinarians' prescription patterns: VBI. It represents the number of days per year the average animal within an animal population for which a particular veterinarian was responsible, was given antibiotics. Action threshold values are defined, and antibiotic prescription patterns are reviewed. When exceeding thresholds, a veterinarian will have to take appropriate action to reduce the amounts of antibiotics used at livestock farms. VBI makes it explicitly clear that the veterinarian also has a role in reduction of antimicrobial use and AMR and makes it a more joint responsibility of the farmer and the veterinarian.

5.2.Antimicrobial RESISTANCE (animal and aquaculture domain)

China

Every year MARA formulates a plan to monitor antimicrobials, its residues and animal-derived bacterial resistance for the agricultural sector and for the aquacultural sector.

Aquaculture

There are two plans: 2023 National Aquatic Products Veterinary Drug Residue Monitoring Plan and the 2023 National Aquatic Animal Disease Surveillance Plan (MARA, 2023a). For aquaculture bacterial drug resistance is not surveyed.

Animal Husbandry

The monitoring in the animal husbandry sector is more intensive. There are three plans (MARA, 2023b):

- 2023 Veterinary Drug Quality Supervision and Sampling and Risk Monitoring Plan
- 2023 Livestock and Poultry Products Veterinary Drug Residue Monitoring Plan
- 2023 Animal-derived Bacterial Drug Resistance Monitoring Plan

All plans contain a table with the number of samples per province and in total (veterinary drug residue plan, total 3,900 samples; veterinary drug quality supervision plan, total 6,870 samples; bacterial drug resistance plan, total 8,700 strains). The resistance plan stipulates in detail the bacteria strains (E. coli, Enterococcus, Staphylococcus aureus, Campylobacter, Clostridium, Salmonella, Haemophilus parasuis) to be taken at animal level of which some of the Enterococcus need to be dog and cat based.

The monitoring plans need to be implemented at provincial level. Provinces act differently on it: assigning their own departments with the tasks and responsibilities (Shanghai municipal People’s Government, 2021), delegating it to local authorities (Zhejiang province, 2022), or opening a tender process enquiring bids for monitoring and sampling (Jilin Province, 2022).

Data need to be entered into China's veterinary drug database "Veterinary Drug Resistance Monitoring Database System" at China Veterinary Drug Information Network (www.ivdc.org.cn). Yearly a summary meeting on the results is held in Beijing, but it was hard to find any quantitively data on the monitoring results, besides notifications of the meeting discussing the information (CIVDC, 2023).

Zhang et al (2017) focused in a research paper on antimicrobial resistance among Escherichia coli from chicken and swine in China, in the period 2008–2015. The findings of the study include: (1) multi-drug resistance was highly prevalent in E. coli; (2) E. coli isolates showed high resistant rate (>80%) to several old drugs, including ampicillin, tetracycline and sulfisoxazole; and (3) increasing resistance to colistin, florfenicol and ceftiofur was observed.

Netherlands

An extensive part of the MARAN report (MARAN, 2022) sheds it light on antimicrobial resistance percentages of the food-borne pathogens Salmonella, Campylobacter spp., and E. coli spp., and for the organisms which are resistant to critically important antimicrobials (such as MRSA).

Salmonella

Isolates were obtained from human patients, food-producing animals, food products of animal origin and other food products as potential sources of infection for humans via the food chain, and animal feed as potential source of infection for food-producing animals.

Table 3: Antimicrobial resistance of Salmonella from livestock, meat and humans; Netherlands.

		2020	2021
Salmonella	sulfamethoxazole	30%	26%
	tetracycline	27%	25%
	ampicillin	25%	22%
	nalidixic acid	16%	16%
	Ciprofloxacin (Fluoroquinolones)	16%	16%
	trimethoprim	12%	12%
	carbapenem antibiotic meropenem	0	0

Campylobacter jejuni and C. coli

Regarding Campylobacter, resistance of isolates from broilers, poultry meat, veal calves, and pigs for ciprofloxacine and tetracycline remain high in both C. jejuni and C. coli. For tetracycline even very high resistance levels were measured for C. jejuni (91.0%) and C. coli (95.6%) from veal calves. Since 2021 caecal samples of veal calves and fattening pigs are included in the AMR monitoring program.

Isolates from human patients with campylobacteriosis show a continuously increasing trend of resistance for ciprofloxacin and tetracycline resistance until 2019. In 2020, however, resistance levels for all measured antibiotics dropped, which dropped even further in 2021. the COVID-19 lockdown might have played a role here.

E. coli

E. coli isolates were obtained from caecal samples from broilers, pigs, veal calves at slaughter and faecal samples of dairy cows at farms. Resistance levels varied substantially between the different animal species: resistance in pigs and veal calves stabilised; resistance in broilers decreased; resistance in dairy cows remained low; and, resistance in raw meat and vegetable samples are very low.

But overall, the highest resistance levels were detected for ampicillin, tetracycline, sulfamethoxazole and trimethoprim. These drug classes are the most frequently used classes in veterinary medicine in The Netherlands. In addition, high levels of resistance were also observed for fluoroquinolones in broilers and for chloramphenicol in white veal calves. Resistance for colistin was completely absent.

MRSA

For MRSA surveillance in livestock, each year one animal sector is monitored. For the year 2021 dairy cows and persons working and/or living on these farms were sampled. For 2020, pig and persons on pig farms. For 2019 and 2018 broilers and persons working on broiler farms (table 4).

Table 4: Number of MRSA found on Dutch farms and in persons working/living on these farms from 2018-2021

Year	Animal	MRSA positive farms (n)	Total farms tested (n)	Prevalence (%)	MRSA positive humans (n)	Total humans tested (n)	Prevalence (%)
2018/2019	Broilers	*0*	*195*	*0.0*	*4*	*133*	*3.0*
2020	Pigs	*133*	*149*	*89.3*	-	-	-
2020/2021	Dairy cows	*11*	*181*	*6.2*	*1*	*107*	*0.9*

On retail meat, the highest prevalence of MRSA was found on turkey meat, followed by lamb, chicken and veal.

As expected for MRSA, nearly all isolates tested resistant against (benzyl)penicillin and cefoxitin. High levels of resistance were also observed for tetracycline (up to 100% in chicken meat and in samples from veal calf caeca). Also, high levels of resistance to trimethoprim were seen for dairy, pig, poultry, veal calves (61.3% - 95.5%), and to fusidic acid (48.6%) in sheep/goats.

PART III – Approach in the animal domain

6. Approach of Chinese Ministry of Agriculture and Rural Affairs

Highlights:

- *MARA takes a (firm) approach to the veterinary drug use dossier and is willing to expose their data, opening possibilities to cooperate with foreign countries. However, the focus is still on reduction of drug use, not on reduction of resistance yet.*
- *In the vast country China is, many levels of departments, bureaus and stations are involved in implementation and enforcement, risking fragmentation of responsibilities and ultimately blind spots in the control of antimicrobial usage and residues.*
- *The system for veterinary prescription drugs and over-the-counter drugs is far from foolproof, especially in rural areas at smallholders.*
- *China is making use of its unique traditional medicine knowledge and focussing in veterinary medicine too on TCM as alternatives for antimicrobials. A subsidy system will be implemented for development of alternative products.*
- *Reduction of veterinary drugs is not (yet) in the hearts and minds of the agricultural sector, let alone the concept of AMR. They comply with legislation, but no more than that.*
- *Though still a long way to go in AMR for the sector, the feed sector thinks they have contributed in implementing the "feed ban" and the search for alternatives for pharmaceutical feed additives.*

6.1.MARA Action Plan

In line with the NAP, the Chinese Ministry of Agriculture and Rural Affairs (MARA) formulated in 2017 the "National Action Plan to Curb Bacterial Drug Resistance of Animal Origin (2017-2020)". In practice, the focus in this plan was on reducing the use of veterinary antimicrobials, which was badly needed given a high usage at that moment of time, although it was declining. A pilot program te reduce the use of veterinary antimicrobials was started in 2018. The pilot was in 2021 elevated to a "National Action Plan for the Reduction of the Use of Veterinary Antimicrobials (2021-2025)" and actively refers to curb antimicrobial resistance of animal origin.

6.2.Objectives to reduce usage

NAP curbing Bacterial Resistance of Animal Origin (2017-2020)	**NAP Reduction of the Use of Veterinary Antimicrobials (2021-2025)**
The proportion of provinces selling veterinary antibacterial drugs on veterinary prescription has reached 50%	More than 50% of largescale farms fully implement the veterinary prescription drug system
Human-animal antimicrobials or antimicrobials prone to cross-resistance are phased out as animal growth promoters.	
More than 100 safe, efficient and low-residue new veterinary drug products have been developed and promoted	
More than 100 high-risk veterinary drug products have been eliminated	

Veterinary antimicrobial residue monitoring remains above 97%.	Veterinary drug residues supervision and sampling remains stable at more than 98%. More than 50% of the large-scale farms comply by the end of 2025 fully with the veterinary drug withdrawal period not to exceed maximum residues levels.
Improve the level of scientific drug use in the farming link	Effectively improve the safe, standardized and scientific use of veterinary antimicrobials More than 50% of largescale farms have by the end of 2025 have strictly implemented the management system for the safe use of veterinary drugs. More than 50% of largescale farms have by the end of 2025 standardized scientific drug use.
Train new vocational farmers, front-line veterinarians and aquaculture practitioners	
	Promote reducing the use of veterinary antimicrobials. The use of veterinary antimicrobials per ton of animal produce should maintain a downward trend.
	Breeding companies (and programs) should explore and implement resistance reduction
Form a monitoring network for veterinary antimicrobial drugs and bacterial drug resistance covering the whole country	

6.3. Systems to reduce usage

To achieve the objectives of the NAP, systems should be in place for e.g. supervision of the production plus sales of veterinary antimicrobials and the application of them in feed; tracing the use of antimicrobials, their residues in animal products and the development of animal-derived bacterial drug resistance; promotion of veterinary Traditional Chinese Medicines (TCM) and safe plus low-residue alternative products; training of veterinary practitioners and technicians; and, motivation of producers to reduce the use of veterinary antimicrobials.

Production and sales

The production and sales of veterinary antimicrobials should strictly implement and comply with the GMP for Veterinary Drugs as revised in 2020. In 2022 MARA carried out a clean-up operation on the implementation of the new version of the GMP. The activities of veterinary drug manufacturers who failed to pass the inspection and acceptance of the new GMP were stopped, their ability to apply for a QR code for the veterinary drug traceability system were turned off, and their veterinary drug production licenses were cancelled. With the clean-up, a total of 946 manufacturers stayed in business, while around 40% of the manufacturers were eliminated, bringing a reshuffle to the veterinary drug industry (BOABC, 2022).

Application in feed

In the early 2000s MARA's predecessor published the specifications for the use of veterinary drugs and additives in feed. Back then, the mode was still "allowed, if". Twenty years later this changed. In 2021 MARA published a comprehensive update of the feed and feed additive catalogue. Only feed raw materials and nutritional and general feed additives listed in the catalogue can be used in animal feed products. New materials or additives not in the list must be approved by MARA first before they can be used in animal feeds, though chances are low. But the bombshell under the feed industry was announcement No. 194 published in July 2019, also known as the "feed ban". It stated that from January 2020, production of feed with pharmaceutical feed additives (i.e growth promotors) would not be allowed anymore, and from July 2020 this feed would not be allowed to give to food-producing animals anymore. But when animals are sick, certain prescription drugs are allowed to mix in/over feed. The feed products containing pharmaceutical feed additives must comply with the provisions of the Feed Labeling standard. Announcement No. 176 of 5th August 2022 went a step further, prohibiting certain drug varieties not only in animal feed, but also in animal drinking water (MARA, 2022).

Of all measures related to AMR in animal husbandry and aquaculture, the "feed ban" had the biggest impact. The feed industry is thus essential in convincing the sector of the usefulness and necessity of the ban and finding solutions. In the previous years this topic got therefore wide interest in the events of feed related associations and their members. The Beijing Feed Industry Association has conducted several activities (BFIA, 2019-2020), but assumes now that the concept of reducing antimicrobial resistance has been accepted by everyone and not much follow-up is needed. Talking to several feed companies[5], the feedback is that they indeed have developed excellent solutions. However, the biggest difficulty is not the problem of antibiotic substitutes. It only accounts for 10%. The other 90% relates to a complex of elements in feed and water management, health management and farm management. It is like the foundation of a building, and only when the foundation is firmly laid and an integrated feed-farm-health solution can be provided, the feed ban can be truly realized, and the impact of the feed ban on the industry can be minimized.[6]

The concept of AMR is unfortunately not really alive among the industry. No special measures are taken to go a step further on reducing drug usage and resistance.

Development of alternatives including TCM

In the search for alternatives, MARA will promote the establishment and implementation of a subsidy system for alternative products for veterinary antimicrobials, such as Veterinary TCMs.

Tracing of the use antimicrobials

In 2018 MARA announced that in the period 2018-2021 pilots would be launched to monitor and reduce the use of antimicrobials on farm. No less than 100 large-scale farms would be organized every year to carry out pilot work on the reduction of veterinary antimicrobials. Farms that met the evaluation standards of the pilot were allowed to use the logo "farms with veterinary antimicrobials use reduction standard". As expected, a variety of organisations were involved in the organisation and implementation: MARA for the coordination; The provincial veterinary administrative department for organizing the registration, preliminary examination, recommendation, supervision and effectiveness evaluation of the farms participating in the pilot; China Institute of Veterinary Drug Inspection for organizing and formulating the evaluation methods and standards; and, China Animal Husbandry Association, together with the China Dairy Association, the China Veterinary Association and the China Veterinary Drug Association, for organizing the formal review of the application materials.

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[5] Anonymous conversations.

[6] Personal communication, Trouw Nutrition

Recently, January 2023, a pilot project in pigs started in Guizhou Province. They will use the national veterinary drug traceability system to accurately count the use of antimicrobials. Provinces, cities, districts or counties who carry out pilots successfully, will be rewarded, as the result of the pilot is included in the evaluation and the assessment of the food safety review by the State Council and used as an indicator in the national farm produce quality and safety.

When farmers sell their livestock and poultry, the transport should accompany the drug records and they shall be checked by the relevant departments for compliance on absence of forbidden substances and respecting withdrawal periods.

6.4. Guidelines to reduce use of veterinary antimicrobials

In the Annex of the "National Action Plan for the Reduction of the Use of Veterinary Antimicrobials (2021-2025)" MARA provides practical guidelines for the sector to reduce the use of veterinary antimicrobials. Most guidelines have as basis to comprehensively prevent the risk of transmission of animal diseases by e.g.:

- Selection of high quality – robust – breed varieties, with high health status
- Provide sufficient and balanced nutrition based on scientific feed formulas
- Established the concept of biosecurity on the farm
- Install disinfection units in breeding farms

Other guidelines refer to the conscience handling of farmers

- Strictly follow regulations on the use of veterinary antimicrobials
- Follow guidelines of licensed veterinarians
- Be cautious about combining antimicrobials
- Reduce preventive group treatment and increase curative individual treatment
- Actively replace drugs to TCM or other alternative product (high efficient plus short withdrawal time drugs should be replaced by low efficiency and ling withdrawal times)

6.5. Regulations to reduce use of antimicrobials

Measures Veterinary prescription drugs and over-the-counter drugs [7]

Veterinary prescription drugs refer to veterinary drugs than can only be purchased and used with a veterinary prescription issued by a veterinarian. Prescription notes are kept in triplicate, the first by the animal treatment institution or licensed veterinarian that prescribes the drug, the second by the veterinary drug operator, and the third by the animal owner or animal farm. Prescription notes should be kept for more than two years.

Veterinary over-the-counter drugs (OTC drugs) can be purchased on one's own and used according to the instructions on the package; a veterinarian is not involved in this process.

To streamline the difference, a lists of veterinary prescription drugs was developed and published by the Ministry of Agriculture and Rural Affairs in 2013 (MARA, 2013a), 2016 (MARA, 2016) and 2019 (MARA, 2019). All other non-prohibited veterinary drugs are OTC.

There is a small loophole regarding veterinary prescription drugs. As said, these drugs can only be bought and sold on the base of a veterinary prescription, except directly to animal (breeding) farms that employ fulltime licensed veterinarians registered according to the administration of

[7] Information in this section has been retrieved from MARA, 2013b. http://www.gov.cn/zhengce/2022-10/12/content_5721384.htm

licensed veterinarians. They will subscribe these drugs themselves to the company they are working in.

Furthermore, despite all regulations, the research of Liu et al (2023) shows that the system is far from foolproof, especially in rural areas. Most commercial farmers purchased veterinary drugs directly from veterinary drug manufacturers and were relying on the veterinarians employed by large drug manufactories to check their animals and offer them instructions on drug use. But smallholders mostly purchased veterinary drugs from local veterinary feed and drug stores without any licensed or official veterinarian. Also, both smallholders themselves and feed and drug store sellers reported that many smallholders routinely use human antibiotics bought from pharmacies for their backyard animals (Fang et al, 2021; Liu et al 2023), despite that MARA’s Regulation on the administration of veterinary drugs prohibits the use of human medicine in animals already since 2004 (MARA, 2013b). Perceived better quality and efficacy are the main reasons.

Rural veterinarians have to comply with other regulations and shall use veterinary drugs in accordance with the "Catalogue of Basic Medicines for Rural Veterinarians".

Biosecurity and hygiene

In 2020 the Biosecurity Law of the People's Republic of China was adopted (NPC, 2022). It contains very general articles and refers to the state's effective prevention and response to threats from dangerous biological factors and related factors, the stable and healthy development of biotechnology, the relative absence of danger or threat to people's lives and health and ecosystems, and the ability to preserve national security and sustainable development in the biological field (article 2). It is not specifically aimed at biosecurity measures to prevent everyday diseases on animal farms.

Biosecurity is an important issue in the Chinese livestock sector though. But more from the concept to prevent the introduction of highly contagious animal diseases, than from the idea to create a healthy environment for the animals where fewer antibiotics are needed.

6.6. Who is in charge at farmers level? [8]

The national responsibility of antimicrobial use control in livestock and fish food systems is shared among the Ministry of Agriculture and Rural Affairs (MARA) and the China Food and Drug Administration (CFDA). CFDA regulates the registration, production, distribution and quality control of antimicrobials; MARA regulates antimicrobial use and residues in animal production.

Each province government has a MARA corresponding Department or Bureau (DARA). Under their supervision, the local Animal Husbandry and Veterinary Bureau (AHVB), Agro-product Safety and Quality Department (ASQD), and Agricultural Law Enforcement Team (ALET) carry out the factual oversight of and guidance to farmers on veterinary drug use and residues. The Animal Husbandry and Veterinary Station (AHVS) is the grassroots level veterinary public service institution under supervision of both the county-level AHVB and the township government.

Antimicrobial usage

Veterinary Stations make direct contact with farmers and are responsible for disease prevention, policy dissemination and agricultural technical extension services. The Chinese Veterinary Medical Association administers Licensed Veterinarians who are responsible for providing veterinary care services to farmers, including prescription of antimicrobials.

According to research of Liu et al (2023), it is hard for Veterinary Stations to reach out to all producers and train them on veterinary drug use. Especially smallholders do not make time to

[8] Information in this paragraph has been retrieved from a qualitative study done by Liu et al, 2023.

attend the trainings, do not have the knowledge to fully understand veterinary information, or even maybe illiterate and cannot read dosage instructions on drug packages. These farmers also indicate that they don't have the financial means to call a Licensed Veterinarian to advise and prescribe drugs. They act according to their own experiences.

Antimicrobial residues

The AHVS usually incorporates several Official Veterinarians, defined by the Chinese Official Veterinarian System as law enforcement officers authorized by the government. They make direct contact with farmers and are responsible for drug residue inspections in farmed animals. The ASQD monitors the testing and checks also for prohibited drugs. As the registered entities in the information platforms for selection of farms are mostly large-scale farms, smallholders are not selected for random testing. ALETs in turn are responsible for investigating and dealing with te/he illegal practices.

ARABs are responsible for the oversight of veterinary drug residues in agricultural produce during slaughtering. The Market Supervision and Regulation Bureaus (MSRB) are responsible for supervision of agricultural products during the distribution stage.

PART IV – Next steps

7. Reflections on the approach to curb AMR

7.1.Strengths and Weaknesses of China's AMR approach

One Health and Multi stakeholder collaboration?

China takes a serious stance on combatting AMR. Their National action Plan (2022-2025) breaths an integral One Health approach. It focuses on cooperation between different stakeholders (e.g. government, private sector). It includes horizontal collaboration between different sectors (e.g. health, agriculture, environment, education). There is funding, and it has monitoring mechanisms to track antibiotic use and resistance. China checks many of the boxes needed to reduce AMR (WHO, 2018b), but this multisectoral collaboration is sometimes facing obstacles in practice.

An obstacle for an effective One Health approach in China may be the substantial number of ministries, bureaus and administrations - from the government stakeholder alone - involved in implementing the national action plan. It is therefore probably necessary that ministries each formulate their own sectoral plan to contribute to the central NAP. The Chinese Ministry of Agriculture and Rural Affairs (MARA), in the awareness of agriculture's crucial role in AMR, defined a sectoral NAP for the reduction of the use of veterinary antimicrobials (2021-2025). The central NAP provides no further insight in eventually integrating these sector plans at the national level.

AMR and antimicrobial usage targets?

There are ample data available on veterinary antimicrobial usage. Also, on resistance rates in the human domain. But resistance in some bacteria in China are relatively high (MRSA) and even absolutely high (ERSP). In the first instance, this is a danger to China's medical care itself. Hence a need for an integrated One Health approach in China to reduce resistance. Nonetheless no targets for reduction of either usage or resistance were found in the national action plan and the plan of MARA. The MARA plan focusses on measures for appropriate prescription and use, hoping to reduce the use and the likelihood that AMR will decline. National and sectoral goals for antimicrobial usage and resistance would not be out of place, and would allow for interferences to actively achieve trend reversals.

7.2.Opportunities and Threats of China's AMR approach for the Netherlands

Limited awareness in practice, high attention in research

In the vast country China is, it is difficult to fully reach, advise and monitor all target groups on antibiotic use. For instance, small holders in the animal domain are a risk group in combatting AMR and even more so because (i) many veterinarians cannot pay them the extra attention they need, and (ii) they apparently can get quite easily unlimited antimicrobials at human pharmacies to use at their animals. But larger scale farmers and companies are also a risk. The problem here, in all likelihood, is not the lack of regulation. This has been tightened up in animal husbandry in China in recent years. Rather, it's a matter of awareness. There is limited sense of danger of excessive antibiotic use and the consequences for resistance. The sector complies with the regulations and moves on. The Chinese sector is not at the forefront and is not very innovative to go a step further than the law. The drive for the reduction of antibiotics, alternatives, and best management practices comes mostly from foreign groups and companies in the Chinese market. Without explicit demand from the sector, with a few exceptions, it is not easy for a company to base a market strategy onto this and to profile its knowledge and technology in this area.

It is remarkable, however, that university research is well aware of the emerging problem (see the number of Chinese publications, and the groundbreaking research on the colistin resistance gene MCR-1 in E. coli, leading to a ban on the use of colistin in animal husbandry in China). But research cooperation between China and The Netherlands is not as large as between China and some other countries.

TCM as alternative

Traditional Chinese Medicine (TCM) is thousands of years old and forms a substantial segment in human medicine in China. China has been proud of its TCM in medicine, and the believe of Chinese people in TCM is high. Many prefer traditional Chinese remedies to Western remedies (Xu and Xia, 2019). Though no explicit data were found to support it, it might play a role in the observation that the use of antibiotics in China is not so high as often perceived (8-10 DDD; well below the global 95% uncertainty interval 13.2–15.6 from the research of Brown et al (2021)). China's knowledge of TCM might be an exceptional advantage in combating AMR and in the development of alternatives for the use of veterinary antimicrobials in the animal domain, not only in China but in other countries too.

High prevalence resistant bacteria

MRSA is an important concern in healthcare. MRSA in the Netherlands is fortunately extreme low (below 2%). The threat to MRSA in the Netherlands therefore does not come from inside, but from outside, from countries with a double-digit prevalence like China. Though the trend of MRSA in China in the human domain in the past eight years is downward from 36.0% to 29.4%, without (more) targeted programs, it will be a long process to reach a single digit prevalence, if at all possible. In addition to MRSA, ERSP, CTX/CRO-R ECO, CTX/CRO-R ECO and CR-ABA, are a threat to low resistance levels in the Netherlands too.

7.3. Cooperation potential between Netherlands and China

Antimicrobial resistance increasingly burdens public health and healthcare budgets. The threat of AMR to human health was in the EU estimated to be as high as an annual cost of $1.5 billion PPP per year (OECD, 2018). Fighting against AMR and investing to combat AMR is thus not only saving lives but is also likely to save money. With the Netherlands having low resistance levels, and China having moderate to significant high resistance levels, it will eventually save money for the Netherlands to cooperate with China on AMR.

Roadmap

Far and foremost, (1) China needs to set antimicrobial usage targets at farm level and per veterinary clinic, and subsequently monitor and evaluate targets. Without them, it depends too much on chance whether the use decreases, partly because it seems that there is little initiative in the sector without new regulations. The Netherlands has a well-established system to define antibiotic usage at farm level (in DDDA) and antibiotic prescription per veterinarian (VBI). With usage data in the animal domain in China increasing again, China could benefit from the Dutch monitoring and mentoring system and learn from their experience in setting and reducing step-by-step threshold values. The system may also stimulate awareness in the sector. It is not about which antibiotics are allowed and which not, but about how much antibiotics are acceptable. (Capacity building)

Then, (2) innovations along the lines of China's structure of livestock farming must take place in feed and for management practices to give farmers and licensed veterinarians the tools to know how to use antibiotics safely and responsibly. Purely reducing antibiotics by banning without additional support for replacement measures is irresponsible and can lead to animal-unfriendly situations. The Netherlands can co-develop with China a package of measures. (Best-practice development)

In addition to the management measures mentioned in the former, (3) foreign companies have a broad spectrum of proven technologies that play a role in improving health and reducing antibiotic use at farm level. Model farms can demonstrate to the sector what the effect of these technologies are in the Chinese context. (Demonstrations)

Also, (4) though in particular the livestock sector in China needs to gear up to reduce the use of antimicrobials and prevent (further) resistance of bacteria, the independent approach of the agricultural domain must be elevated and integrated to the One Health approach. Joint analysis and research by the Netherlands and China on two important topics can be a good catalyst for this: reduction of MRSA and TCM as alternative in both the human and animal sectors. (Innovation)

And finally, (5) the Netherlands and China now both have a One Health center. This creates a perfect opportunity to work together from science on One Health and to conduct targeted research to moderate and hopefully reduce AMR in China. (Science collaboration)

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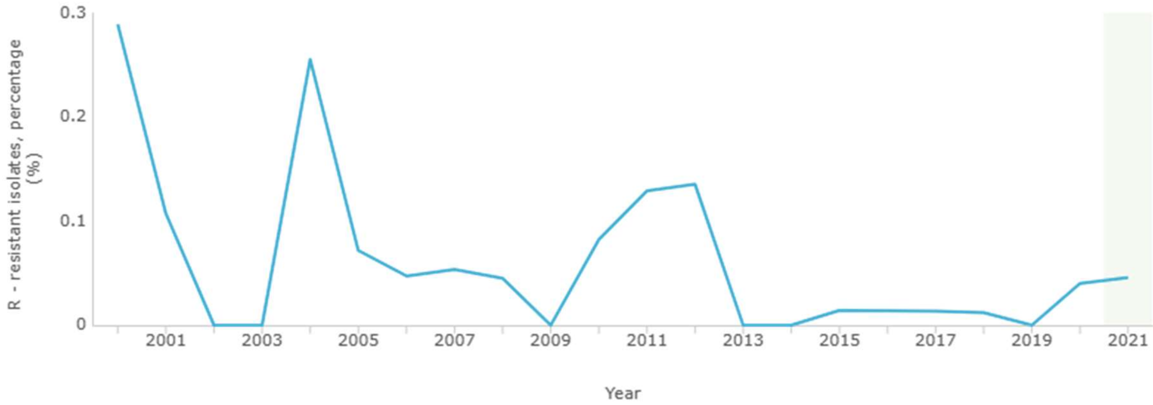
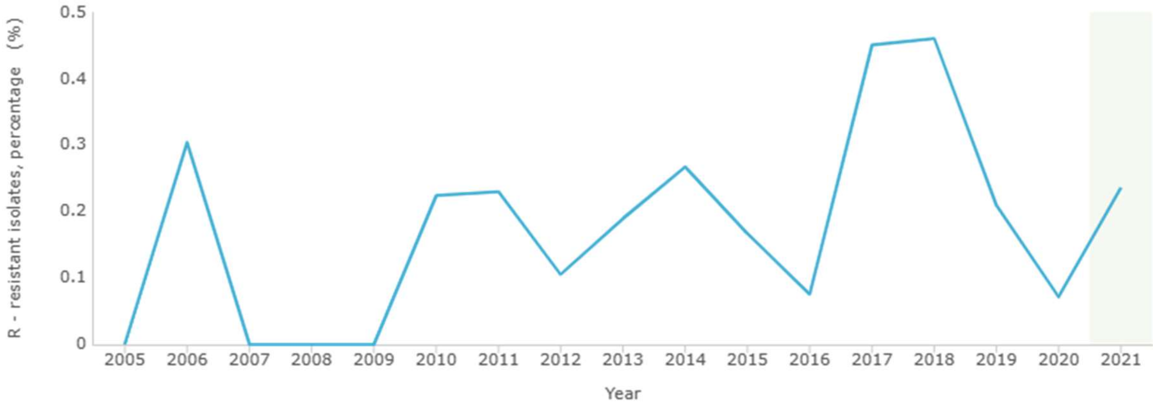
Annex 1: Resistance data for the Netherlands, retrieved from the WHO system, 2001-2021. Source: ECDC, 2023.

CR-ECO

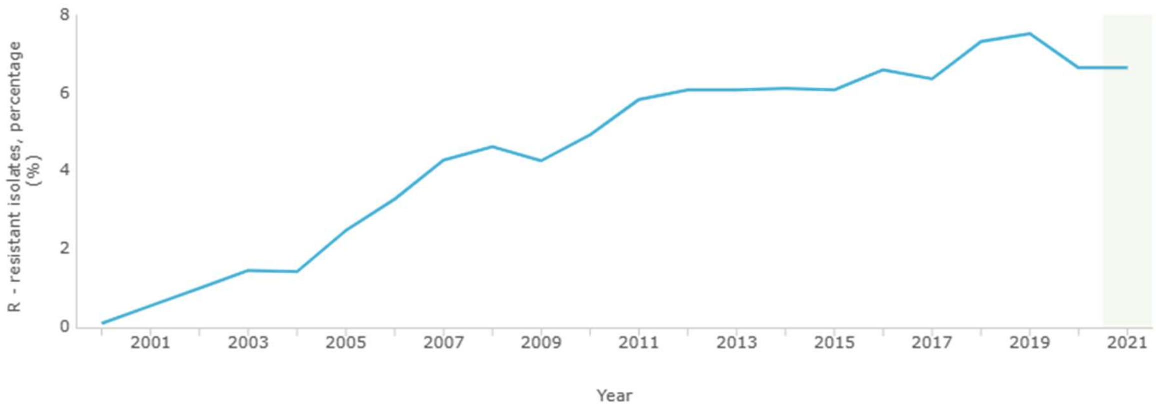


CR-KPN

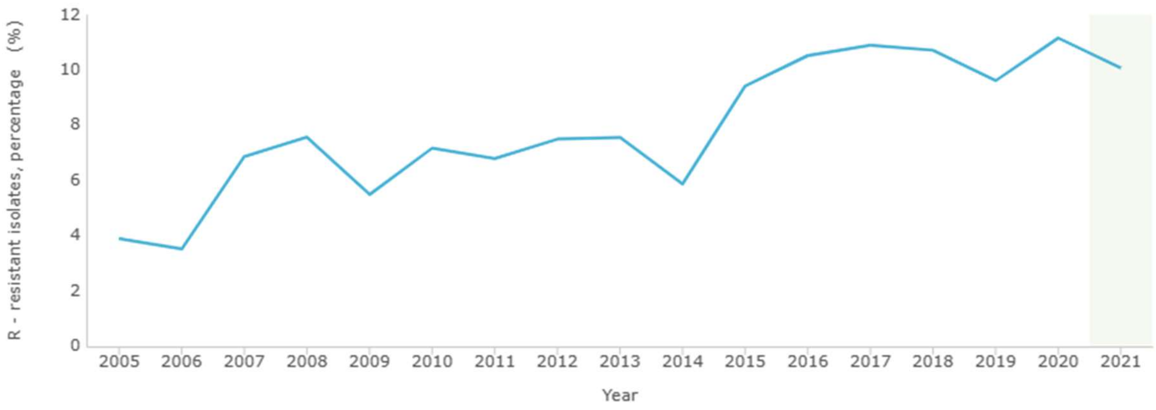


CR-PAE

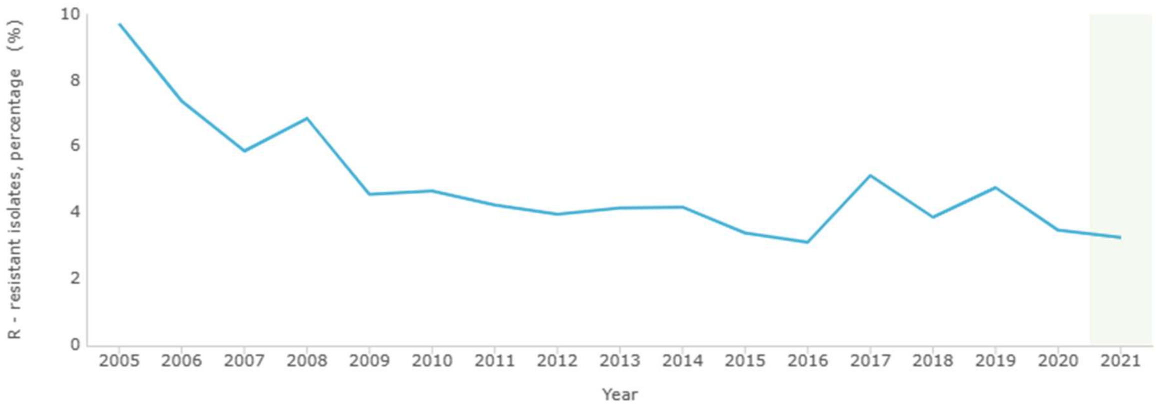
CTX/CRO-R ECO



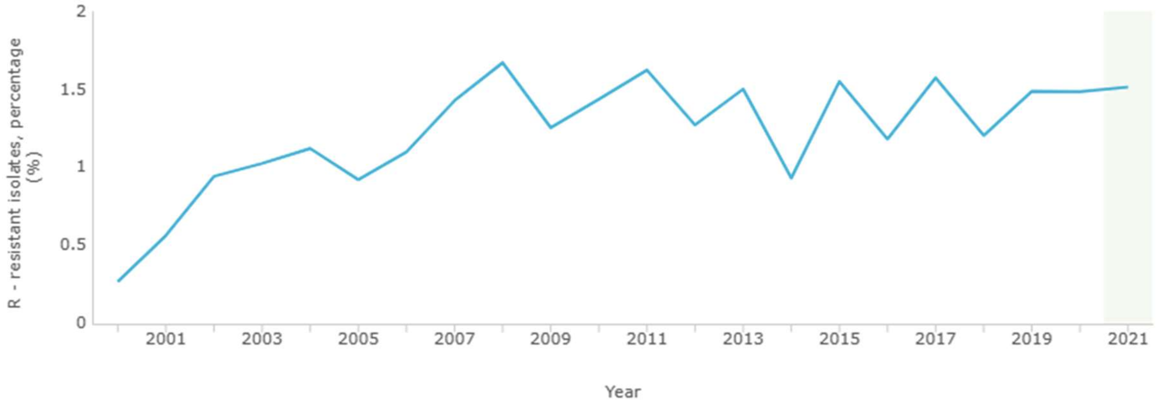
CTX/CRO-R KPN



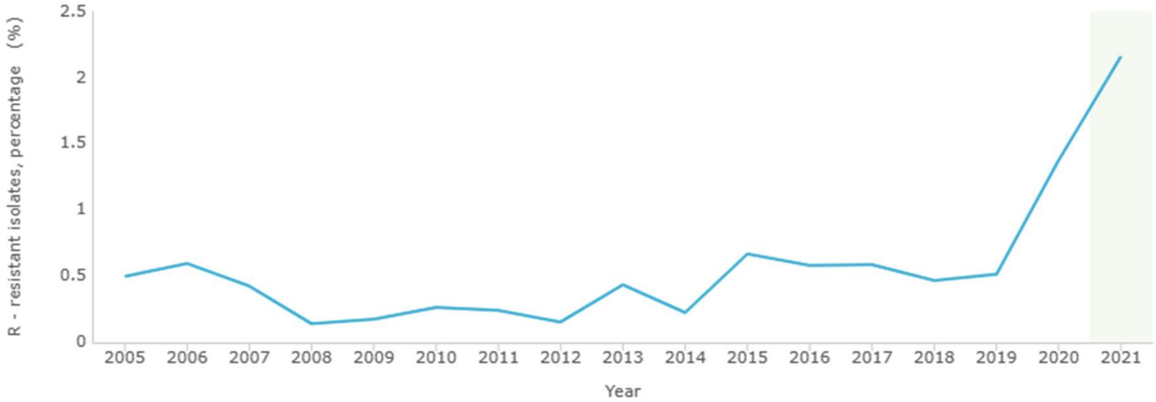
ERSP



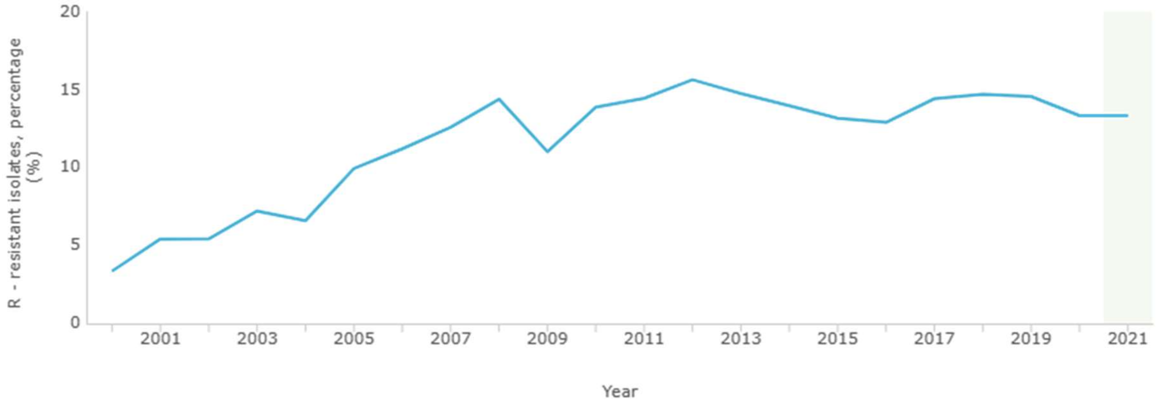
MRSA



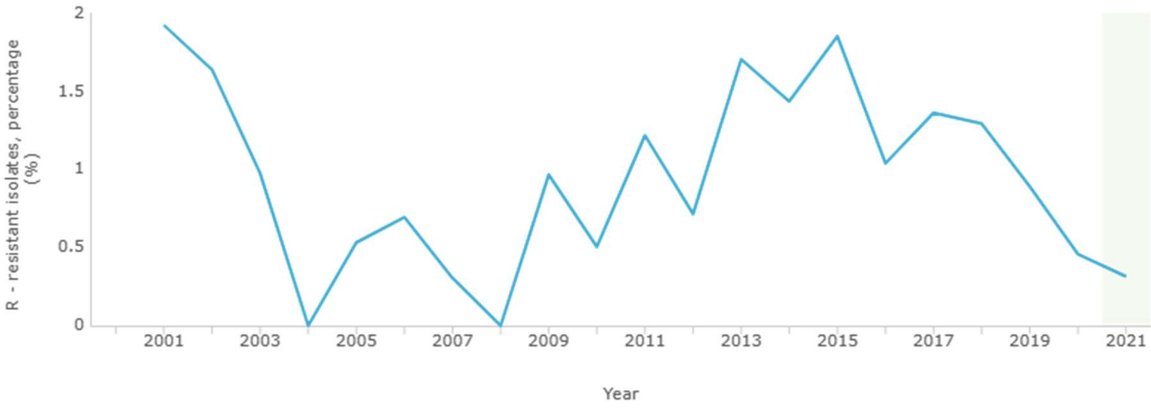
PRSP



QNR-ECO



VREfm


R - resistant isolates, percentage (%)
2
1.5
1
0.5
0
2001
2003
2005
2007
2009
2011
2013
2015
2017
2019
2021
Year

A report commissioned by the department of Science, Technology, and Innovation of the Embassy of the Kingdom of the Netherlands in Beijing