

SCIENCE POLICY RESEARCH UNIT

SPRU Working Paper Series

SWPS 2021-04 (August)

Exploring the Antibiotics Innovation System and R&D policies in China: Mission Oriented Innovation?

Yuhan Bao, Adrian Ely, Michael Hopkins, Xianzhe Li and Yangmu Huang



SPRU Working Paper Series (ISSN 2057-6668)

The SPRU Working Paper Series aims to accelerate the public availability of the research undertaken by SPRU-associated people, and other research that is of considerable interest within SPRU, providing access to early copies of SPRU research.

Editors

Roberto Camerani

Contact

R.Camerani@sussex.ac.uk

Associate Editors

Area

Karoline Rogge
Tim Foxon

Energy Policy

K.Rogge@sussex.ac.uk
T.J.Foxon@sussex.ac.uk

Ben Martin
Ohid Yaqub

Science and Technology Policy

B.Martin@sussex.ac.uk
O.Yaqub@sussex.ac.uk

Andrew Stirling
Rob Byrne

Sustainable Development

A.C.Stirling@sussex.ac.uk
R.P.Byrne@sussex.ac.uk

Carlos Sato
Josh Siepel

Innovation and Project Management

C.E.Y.Sato@sussex.ac.uk
J.Siepel@sussex.ac.uk

Maria Savona
Alberto Marzucchi

Economics of Innovation

M.Savona@sussex.ac.uk
A.Marzucchi@sussex.ac.uk

Guidelines for authors

Papers should be submitted to swps@sussex.ac.uk as a PDF or Word file. The first page should include: title, abstract, keywords, and authors' names and affiliations. The paper will be considered for publication by an Associate Editor, who may ask two referees to provide a light review. We aim to send referee reports within three weeks from submission. Authors may be requested to submit a revised version of the paper with a reply to the referees' comments to swps@sussex.ac.uk. The Editors make the final decision on the inclusion of the paper in the series. When submitting, the authors should indicate if the paper has already undergone peer-review (in other series, journals, or books), in which case the Editors may decide to skip the review process. Once the paper is included in the SWPS, the authors maintain the copyright.

Websites

UoS: www.sussex.ac.uk/spru/research/swps

SSRN: www.ssrn.com/link/SPRU-RES.html

IDEAS: ideas.repec.org/s/sru/ssewps.html

Exploring the Antibiotics Innovation System and R&D policies in China: Mission Oriented Innovation?

Yuhan Bao^{a,b}, Adrian Ely^b, Michael Hopkins^b, Xianzhe Li^c and Yangmu Huang^c

a. School of Public Policy and Management, Tsinghua University, China

b. Science Policy Research Unit, University of Sussex, UK

c. School of Public Health, Peking University, China

Abstract: One possible response to the growing problem of Antimicrobial Resistance (AMR) in pathogenic infections is the development of new types of antibiotics. However, the pharmaceutical companies that have traditionally led such innovation face a lack of incentives at the present time due to high levels of market uncertainty and low expected returns. Mission oriented innovation with coordinated investment and market-shaping policies may offer an approach to accelerating antibiotic innovation. This paper aims to evaluate whether pre-Covid-19 Chinese policies concerning AMR can be seen as constituting a mission-oriented approach and whether these policies have influenced antibiotics innovation in China. It adopts a mixed method approach to deliver several insights. By using historical event analysis based on data collected from interviews, public and commercial databases as well as policy documents, the paper finds that China's recent actions concerning AMR since 2008 comprise many elements of mission-oriented innovation policy. The National Action Plan to Contain AMR has provided a clear mission since 2016 to tackle the problem of AMR and provides the opportunity to coordinate and integrate these policies into a more coherent and evolving mission-oriented innovation approach. Analysis of relevant research grants and publications suggest that these policies (including the 2016 National Action Plan) have drawn the scientific community towards antibiotics research and provided more support to this area. Case studies following the development of new antibiotics are used to illustrate how the established elements of mission oriented innovation policy have or have not contributed to antibiotics innovation in China. Further research is required to more comprehensively analyse R&D investments, and to understand the effects of recent policies, especially after 2016.

Key Words: Antimicrobial Resistance, mission-oriented innovation, National S&T major research project, market shaping policy.

1. Introduction

Against the background of widespread and increasing rates of antimicrobial resistance (AMR) in pathogenic infections, exacerbated by the widespread use of antimicrobials during the Covid-19 pandemic, innovation to deliver new antibiotic medicines is becoming an important issue of global concern. Pharmaceutical companies characterize antibiotic drug R&D as having relatively low financial returns, with the result that few companies are willing to invest in this area, with antibiotic drug development pipelines becoming relatively depleted as a result. Between 2000 to 2016, only 5 novel classes of antibiotics were brought to market globally, significantly less than in the 1980s or 1990s, and none of these were targeted at the deadly and most readily drug resistant gram-negative bacteria (Renwick et al. 2016).

The barriers to antibiotic innovation are diverse. The high risk of product failure and knowledge spill-overs during basic research prevents companies from investing in research in this phase and constrains the discovery of effective lead compounds (Mossialos et al. 2010). The expensive cost and uncertainty of preclinical testing hinders the role of academia and

entrepreneurs respectively, especially against a background of weak connectedness between them (Mossialos et al. 2010). The enormous cost of clinical trials reduces the efforts of SMEs which have been looked to as the primary investors in antibiotics (Renwick, Simpkin, and Mossialos 2016). The differences among the approval processes of different countries increase the cost for approving a new antibiotic in the absence of harmonized approaches (Van Zwanenberg et al. 2011). Furthermore, as they represent a rivalrous and non-renewable common pool resource (Foster and Grundmann 2006; Tarrant et al 2019), markets for antimicrobials are more uncertain (both temporally and in aggregate) because a) spread of resistance may curtail their utility and b) regulations to limit use may constrain adoption by the market. Finally, the limited use, intense market competition and low profit margins for new antibiotics also represent adverse conditions for innovation (Chorzelski et al. 2015).

The above barriers not only reflect the market failures inhibiting antibiotic innovation, but also systems failure and even directionality failures (Weber and Rohrer 2012; Schot and Steinmueller 2018). In response to these failures within the innovation system for new antibiotics, “mission-oriented” (Foray, Mowery, and Nelson 2012; Mazzucato et al. 2018; Mazzucato 2018a) approaches are alluring, with an emphasis on public investment in basic research at first coupled with then a “market-entry reward” at later stages (O'Neill 2018).

China is estimated to be the world's largest consumer of antibiotics (Zhang et al. 2015). Excessive and irrational use of antibiotics leads to the development of AMR, which brings serious threats to Chinese health (Ying et al. 2017). Chinese and UK scholars have highlighted this in the past (Chen and Ely 2011) and over the past decade since 2008, China has gradually paid more attention to this issue and taken action to govern the use of antibiotics (Wang et al. 2016). This paper investigates the additional response of developing new drugs against AMR, which is being viewed with greater importance by the international health community, and focuses on antibiotic innovation in China prior to the arrival of the Covid-19 pandemic.

The innovation system of China has been changing rapidly in recent decades, especially since the reform and opening-up of the 1970s and 1980s (Oldham et al. 1997). Markets and competition have become increasingly valued characteristics of the Chinese innovation system. As a result, antibiotic innovation in China faces similar problems to those in Western markets. In drug development and other strategic areas, the objectives of ‘indigenous innovation’ and ‘technological independence’ have been important elements in subsequent Five Year Plans. The country's innovation system has generated some successes in drug development, such as the anti-malarial drug artemisinin, which has its origins in traditional Chinese medicine and was developed in the 1970s¹ (Guo 2016).

China's contemporary innovation system is regarded as a “whole nation system,” which emphasizes the government's role in mobilizing resources nationwide to achieve pivotal goals and thus steering innovation and development. This notion originated from the description of China's state-run sports system which used the resources to train athletes with high potential to win gold medals at the 2008 Beijing Olympics (Cao 2015). It was subsequently this applied to the understanding of China' innovation system (Zhong 2009), and became an official term in Chinese Government policy (CPC/SC 2012). The apparent similarity between the concept of “whole nation system” and a coordinated national system for “mission-oriented” (discussed later) innovation raises questions about the potential of China's innovation in new antibiotics: does China have the institutions and policies in place to play a significant role in the global

¹ YouYou Tu won the 2015 Nobel prize in physiology and medicine for the discovery of the compound.

battle against AMR?

In considering the above situation, this paper addresses the following questions:

1. Do China's policies to support antibiotics innovation have the characteristics of mission oriented innovation policy? If so, how was this policy framework established?
2. How effective is antibiotic innovation in China?

Section 2 introduces mission oriented innovation policy as a way of coordinating innovation within the context of a national system of innovation, in response to grand challenges. Section 3 describes the mixed methods approach used in this research and data sources used. Section 4 provides a summary of recent history in relation to China's antibiotic innovation, whilst Section 5 describes funding and scientific output (publications). Section 6 describes the origins of China's indigenous innovative antibiotics through a series of case studies. Section 7 provides a discussion of the empirical results and addresses the research questions above, and Section 8 draws conclusions, including identifying the limitations of the study and providing suggestions for further research.

2. Mission Oriented Innovation Policy: Historical and Contemporary Relevance

It has been widely acknowledged that innovation does not only have speed but also direction (Rosenberg 1969; Freeman 1979), raising questions not of "how much?" / "how fast?" but of "which way?" / "who says?" and "why?" (Stirling 2009; Ely et al. 2013). Faced with "social challenges" or "grand challenges" (covering areas including health, clean energies, climate change and so forth - see Hicks 2016; Kuhlmann and Rip 2014), mission-oriented innovation is regarded as a possible response to the questions of direction (Mazzucato 2018b). Mission-oriented innovation is to some extent inspired by the success of the iconic U.S. government-sponsored Manhattan (atomic bomb) or Apollo (moon landing) projects (Foray, Mowery, and Nelson 2012). By integrating diverse resources and people under the guidance of specific goals, these projects achieved remarkable technological feats making them early models of mission-oriented innovation. Yet, the original form of mission-oriented innovation could be said to date back to the late 19th century when "catching up" was the dominant idea for developmental states such as Germany (Kattel and Mazzucato 2018). Thereafter, innovation oriented towards defence and space exploration during the time of World War II and the Cold War progressed in a context in which the market was almost completely dominated by government actors (Mowery 2012).

The newest incarnation of mission-oriented innovation has surpassed the earlier forms both in breadth of mission and complexity of policies, as it is assumed to tackle "grand challenges" (Foray, Mowery, and Nelson 2012). Such contemporary missions are totally different from earlier ones, being multi-dimensional, systemic in nature and involving a range of government and non-governmental actors. This represents one of the key characteristics of present day mission-oriented policies, such as innovation in the energy sector which not only targets energy security but also needs to consider climate change and economic competitiveness (Anadón 2012). Rapid and wide application of technology is seen as part of the solution to tackle such complex social challenges, with the implication that mission-oriented innovation should play an important role in affecting the demand for technologies, their direct use by government, public procurement and regulatory approaches (Foray, Mowery, and Nelson 2012). From the supply side, public investment in basic R&D and in the dissemination of new

technologies is regarded as the most important form of support, but public policy should also catalyze or augment private sector investment.

Mazzucato further developed the framework of mission-oriented innovation policy with sophisticated work on the distribution of public/private risks and rewards and a deeper consideration of the demand side to advocate the formation and *shaping* of new markets (Mazzucato 2016; Mazzucato 2018a; Kattel and Mazzucato 2018). Going beyond policies justified by “market fixing” (i.e. public investment in basic R&D, replacing the private R&D investment that is absent due to market failure), which Mazzucato argued do not provide the directionality demanded, mission-oriented innovation instead aims to create and shape new markets (Mazzucato 2016). The archetypical example of a mission oriented innovation policy organization – NASA - started its work by bringing different talents together to work on cutting-edge science and technology, in turn crowding in business and creating new expectations for the market. Finally, this results in a new, “co-shaped” market for space technologies (Mazzucato 2018b).

In contrast to the older challenges (e.g. moon landing) new challenges are less circumscribed/ more systemic in nature, and much more relevant to social needs. As such, they should be co-defined by various stakeholders (Mazzucato 2018b). The implementation of the mission oriented policy response must involve different sectors and a wide range of actors, in order to drive a systemic change. The process for designing and implementing mission-oriented innovation is necessarily complex but can be seen as incorporating various elements.

First, a well-defined mission agreed by different stakeholders is needed to provide a vision and direction. Such a mission should be widely broadcast and should legitimize follow-up actions by various actors. Second, a portfolio/mix of policy tools are needed - grants, prizes, new forms of procurement and other financial instruments can be included in such a portfolio (Mazzucato 2018a). Third, all the policies across different sectors should be well-coordinated to overcome the coordination failures that have existed in other policy areas (Kattel and Mazzucato 2018).

In this paper, we will take coordinated public research investments and market-shaping policies to stimulate the government, private and third sector experimentation and innovation as the two key elements of mission-oriented innovation. These two basic pillars (coordinated public investment and market shaping) will be investigated through a mix of quantitative and qualitative methods.

3. Methods

This paper adopts a mixed-method approach. In order to answer the questions outlined in section 1, we rely on numerous sources:

- documentary evidence including policy texts relevant to antibiotics from government websites,
- bibliometric data about publications on antibiotics from both Chinese language and English language publication databases,
- quantitative data on investments in R&D from government reports and databases and
- qualitative data collected from elite interviews about policies and research in China.

The first question (Do China’s policies to support antibiotics innovation have the characteristics of mission oriented innovation policy? If so, how was this policy framework established?) is addressed using historical event analysis (Hekkert et al. 2007), drawing on relevant policy texts and analyzing policy changes to develop chronological descriptions and timelines (see Appendix 1). Where possible, we also trace public R&D expenditure using data on grants from the National Science Foundation of China (NSFC) from 2010 to 2019 to analyze the changes in public investment. These data are from <https://www.letpub.com.cn/> (LetPub 2019), a database exhibiting the NSFC grants over the past 10 years. We use “抗生素” (“antibiotics”) as the search string in this data base to identify the NSFC grants on antibiotics, as the search string “抗生素耐药性” (“antimicrobial resistance”) only returns very few grants, providing little information for further analysis. Data from several other funding sources are unfortunately not available for the detailed analysis (see Table 1). Documentary evidence to inform the historical event analysis and quantitative data on R&D spend are supplemented by evidence from elite interviews with scientists and policy researchers, as well as representatives of the China Food and Drugs Administration (CFDA), Ministry of Industry and Information Technology (MIIT), Ministry of Science and Technology (MOST), National Science Foundation of China (NSFC) and National Health Commission (NHC) (interviewees and major talking points are listed in the Appendix 2, although the names and key information about their position are omitted).

Table 1 Major R&D Funding Sources in China and data availability

Major fund for R&D	Period of Operation	Data available?
The National High Technology R&D Program of China (863 Program)	1986-2016	yes
The National Basic Research Program (973 Program)	1997-2016	yes
National Key Technologies R & D Program	2006-2016	no
International Science & Technology Cooperation Program of China	2001-2016	no
Special Fund for Research in the Public Interest (of different ministries)	2006-2016	no
Industrial Technology Research and Development Funds (of different ministries)	?-2016	no
National key R & D plan (integrating the above 6 program)	2016-present	no
National S&T Major Research Project	2001-present	not detailed
Natural Science Foundation of China	1986-present	yes

The second question (how effective is antibiotic innovation in China?) is addressed using English and Mandarin Chinese language searches in databases to support bibliometric analysis in an attempt to understand the patterns of publication in different fields associated with AMR. Where possible, these data will be disaggregated by funding source in order to understand trends in the investment of major R&D funders. Chinese language bibliometric databases are used because many indigenous innovation-related research is not reflected in English language databases. These Chinese language databases are often neglected in international

analyses due to the language barriers, diverse publication formats and even the lack of digitalization (Wagner and Wong 2011). Research articles published in Chinese will be analyzed based on CNKI, the largest database for Chinese journals. We use “抗生素耐药性 (antimicrobial resistance)” as the subject term search string to search in CNKI within the research area of pharmacy, as there are other research areas which also relate to AMR (such as environment, economy and biology). The time period used runs from 1989 to 2019 (until December of 2019).

The analysis of English publications is based on PubMed and Web of Science. Within PubMed, searching by using MESH (Medical Subject Headings) terms provides a more accurate characterisation of each paper’s focus, as these are systematically categorized through an intense indexing process by examiners. We use the MESH term “Anti-Bacterial Agents [D27.505.954.122.085]” to search in PubMed, also only within the research area of pharmacy. We obtain a list of PubMed IDs (PMID - the unique identifier number used in PubMed) of a paper. We then use this PMID to search in Web of Science and to obtain further information on these papers, allowing analysis of publications including authors (e.g. co-authorship from China or UK).

Case studies on established and new antibiotics in China are also used to address the second question, by looking beyond publications towards commercialisation. Documentary evidence and insights from elite interviews will be drawn upon to understand patterns of antibiotic innovation in China and the structures and incentives at play. Four case studies (detailed in Table 2) are used to illustrate the timeframe and dynamics of development of different indigenously-produced antimicrobial compounds, some of which are “new to world”. These new drugs are detailed in the Chinese reports or other media, with information checked against the website of the Chinese Food and Drug Administration (CFDA) to include drugs which were entirely developed by the local companies in China with no foreign investment. The case studies provide a systematic way to analyze the drugs’ innovation, history including the key contributions of R&D, and other aspects of the innovation process.

4. Recent history of innovation policies relating to antibiotics in China – towards mission-oriented innovation policy?

This section traces the development of science, technology and innovation policies in China with the intention of considering the extent to which they can be considered “mission-oriented” (as per the discussion above) towards antibiotic innovation. The section draws on elite interviews and a range of policy documents (outlined in chronological order in Appendix 1, which also illustrates which government bodies were involved in their design and implementation). This allows an assessment of the first element of mission-oriented innovation policy – co-ordination across R&D investments.

4.1 Heritage Elements of Mission-Oriented Innovation Policy Based on National Plans

In our interviews, policy makers always traced China’s innovation policies concerning AMR back to 2006, after the state council initiated the Medium to Long-Term National Plan (MLP) for the Development of Science and Technology (2006-2020) (China State Council 2006). A highly influential document, the MLP identified 16 National Scientific and Technological Major Projects (国家科技重大专项), each of which focused on a relatively broad area of research. Antibiotics were included in two such projects, namely those on “New Drugs Development”

and on “Prevention and Control of Major Infectious Diseases”, which were launched from 2008.

However, the Medium to Long-Term Plan for the Development of Science and Technology was not the first national plan for science and technology in China, nor the first national plan mentioning innovation in antibiotics. The “Long-term Plan for the Development of Science and Technology for 1956–1967” formulated in 1956 (China State Council 1956) set 12 areas for major projects, including nuclear weapons, rocket/missile technology and crystallized bovine insulin (Wang 2016). Other projects were later added to the plan in response to social and political needs, such as the project on satellite technology (which led to the first Chinese satellite Dong Fang Hong I in 1974), and another project on the creation of new drugs to cure malaria (which resulted in the development of the drug Artemisinin mentioned above - see Zhang & Zhang 2019). Interestingly, this 12 year (1956-1967) plan also mentioned the creation of new antibiotics and their application in the agriculture, industrial and food sectors. Its inclusion was due primarily to the lack of capability in the Chinese pharmaceutical/ drugs industry and the threat of many infectious diseases at that time (China State Council 1956). These early innovation policies, which were based on national plans and mobilized resources through administrative measures and commands, were the original form of the “whole nation system,” in the absence of market-based mechanisms.

China’s research policies are still framed in the context of national plans, and adapt to the new situation every few years. Before the emergence of the National Scientific and Technological Major Project for “New Drugs Development” since 2006, the National High-tech R&D Program (“863 Program”) which was initiated in 1986 also set biological and medical research as one of the major focal areas and supported several projects on innovation of new antibiotics (Yixian 2019). In 1989 the State Pharmaceutical Administration started the “National New Drug Fund” (国家新药研究基金) to support new drug discovery at a time when imitation was still the main strategy for China’s drug development. It aimed to transform the copying strategy into the “creation and copying (模仿创新)” strategy (SDA 1989). In 1993 the state council established the national leading group for the coordination of new drug research and development and this leading group initiated a “1035 project” on new drug research and development in China (Chen and Chen 2019). This project set goals for the 9th five-year plan: to develop 10 new drugs with patent protection, support the establishment of five new drug screening centers, five drug safety evaluation centers, and five drug clinical trial and research centers by the end of the 20th century, which represented the desire to establish a modern innovation system for drug development (Chen and Chen 2019). In 2001, the Ministry of Science and Technology started the National Major Science and Technology Project (国家重大科技专项) "Innovative medicine and modernization of traditional Chinese medicine" as part of the 10th five-year plan (MOST 2005). These national research projects were both responses to international competition and national demand, and underpinned the wider national goal to establish a modern innovation system for drug discovery.

Thereafter, the National Science and Technology Major Projects (国家科技重大专项) which started from 2008 can be seen as extensions of the classic mission-oriented S&T major research projects such as “atomic and hydrogen bombs”, “man-made satellites”, “manned space flight”. These historical projects illustrate the ability of China’s national political system to concentrate resources to realize national targets. From the perspective of the Ministry of S&T, the national major projects were seen as the core of China’s development, designed to mobilize resources to serve specific national goals such as development of key products, breakthrough of key technologies and other engineering projects (MOST 2006). Combining

the advantage of the socialist system in concentrating resources with an increasing appreciation for the role of the market mechanism, the National Medium-Long Term Plan (2006-2021) mentioned above chose 16 specific areas which a) responded to market demand generated by economic and social development and b) represented major bottlenecks in further development (MOST 2006). From 2006 to 2018, there were about 150-200 antibiotic R&D related research projects supported by the government's major projects, with a total amount of funding of 400 million Yuan RMB (National Health Commission 2017)(approximately USD 60 million).

There are some important differences between the recent major S&T research projects and the major projects in 1960s. The biggest difference relates to changes in the innovation system. Researchers were all employed by the government in the 1960s and they had permanent positions. The research teams were organized by the government, which could mobilize national resources and researchers to work on critical problems. The biggest reward for researchers was not money but fame and progress within the system (Oldham et al. 1997). On the contrary, present innovation systems are marketized and the major S&T research projects are competitively funded. Intellectual property benefits brought by research have become a new dominant motivation for researchers, so the coordination and mobilization between the state and across different research teams is much more difficult and to some extent unrealistic (Li and Su 2014). A competitive application process for funding characterises the operation of the Major S&T research project around new drug discovery, although the focus and direction of research is decided by the researchers themselves. This means that the outputs of major S&T research projects rely heavily on the individual reputation and performance of researchers, rather than the earlier model of a national coordinated approach towards targets (Li and Su 2014).

However, the MLP and present major projects do appear to echo the classic mission-oriented innovation policy of the Manhattan/ Apollo project forms in other ways. The state still tries to play an important role in providing guidance and concentrating resources within the national innovation system. The combination of market-mechanisms and traditional elements based on national plans can be said to form what is now known as the “new whole nation system” (新举国体制) (National Health Commission 2018).

4.2 The Formation of a Mission around AMR: Domestic and International Influences

The Chinese government's growing concern about AMR is the result of both domestic and international influences. As a matter of fact, China has been aware of the dangers of AMR and has been responding through policy for many years. In 2004-5, the Ministry of Health established a monitoring system of antibiotics clinical application and antibiotic resistance, “China Antimicrobial Resistance Surveillance System” (CARSS) (National Health Commission 2017). It started to provide basic information about the use of antibiotics and the status of resistance across a network of hospitals. The work of CARSS was strengthened in 2012, extending its monitoring range from 149 hospitals in 2011 to 1349 hospitals in 2012.

In 2009, various health system reforms aimed to achieve rational use of drugs by decoupling the income of doctors and their drug prescriptions for patients (He 2019). However, in 2010, dangerous levels of antibiotic abuse caused great concern about AMR, leading to the first concerted national action for controlling AMR. The Ministry of Health initiated a three-year campaign on regulation of antimicrobial drugs in 2011 (Xiao et al 2013; Xiao and Li 2016), responding to the warnings provided by CARSS:

“The turning point for Chinese governance of AMR should be seen as 2010 (not 2016), as a matter of fact. China established the CARSS from 2004, and in 2010 the CARSS revealed that the problem of AMR was serious at that time, so the Ministry of Health took many administrative measures to regulate the use of antibiotics. (statement of Interviewee F, Appendix 2)”

This campaign was purely a domestic response to the problem (Interview records of Interviewee F, Appendix 2). In 2012, the Ministry of Health issued the Administrative Measures for the Clinical Use of Antibacterial Drugs, which restricted the abuse of antibiotics in medical treatment and was also an important output of the three-year campaign (Ministry of Health 2012). From 2010, it is clear that AMR entered into the policy agenda for the Ministry of Health and became a focus for policy makers. Awareness of the problem of AMR also gradually began to permeate wider society.

International influences also accompanied these domestic actions. In 2011, the WHO identified “combatting antimicrobial resistance” as the theme for the World Health Day (Qu, Huang, and Lyu 2019). The Ministry of Health and WHO jointly held the world’s first conference on rational drug use and the opening ceremony for World Health Day (WHO 2011). The representatives from WHO and the Ministry of Health both emphasized the urgency of taking action on AMR (WHO 2011). The minister Mao Xiaowei who was responsible for the above campaign attended that meeting and introduced the actions needed in this area (Interview records of Interviewee F, Appendix 2). However, the international influences were not the major driving force for the restriction of usage of antibiotics:

“China took actions to regulate the use of antibiotics at an early stage, this was not due to international influence but because of the self-awareness of the problem. (statement of Interviewee F, Appendix 2)”

2015 was an important point for Chinese policy concerning AMR. At the 68th World Health Assembly, it adopted the Global Action Plan on Antimicrobial Resistance (Qu, Huang, and Lyu 2019). The Global Action Plan set five strategic objectives including improving awareness, strengthening knowledge, reducing infection, optimizing the use of agents and increasing investment in new medicines, diagnostics tools, vaccines and other interventions (WHO 2015). The Global Action Plan also required each country to make a national action plan to tackle the problem (WHO 2015).

After this, China took two further actions in 2016. One was the establishment of a joint working mechanism for the prevention and control of AMR, which consisted of 12 ministries. According to an interview with a representative of the National Health Commission, two regular meetings are held each year for the joint working mechanism to report on progress (Interview records of Interviewee F, Appendix 2). The National Health Commission, the Ministry of Agriculture and Countryside, the Ministry of Science and Technology are the main players in the mechanism. The other action was the adoption of the “National Action Plan to Contain Antimicrobial Resistance (2016-2020)” by 14 ministries (National Health Commission 2017). It highlighted the importance of AMR in other ministries beyond the Ministry of Health and included actions to restrict the antibiotics use in agriculture, the surveillance of antibiotics in the environment, as well as more publicity to improve awareness. Innovation and industrial polices about antibiotics from different ministries were also for the first time coordinated around tackling AMR (National Health and Family Planning Commission 2016). Therefore, the

Action Plan made AMR a clear target of the whole nation and society, and one of the important policy issues for most ministries.

4.3 The Convergence of Mission-Oriented Innovation Policy Elements

The National Action Plan and joint working mechanism provided the opportunity for China to coordinate the work of different departments and also the opportunity to integrate the elements of mission-oriented innovation policy into one framework. The National Action Plan itself did not increase investment, nor add any new antibiotic innovation policy instruments. However, considering that antibiotics had only been a part of the previous major S&T research project on new drug discovery, the drafting and implementation of the Action Plan formed a clearer mission around antibiotic innovation, and made it possible to coordinate public investment from different areas. According to a government official from outside the Ministry of Health:

“The government released a policy named the National Action Plan to Contain Antimicrobial Resistance some years ago. This National Action Plan contains the concrete requirement for each Ministry - The Ministry of Science and Technology are making and executing relevant policies under the request of this National Action Plan. I think the release of this National Action Plan testifies to the high attention from central government on these issues. (statement of Interviewee C, Appendix 2)”

The National Action Plan also had indirect impacts on later innovation policies. From 2016, many new national research plans or projects, such as the “Outline of the Healthy China 2030 Plan” and “Plan and Guidance for Pharmaceuticals development” in 2016, “The 13th five-year plan for TCM science and technology innovation”, “The 13th five-year plan for Hygiene and Health Science and Technology innovation”, “National Key Technologies R&D Program of ‘modernization of TCM’ and ‘R&D of Key Food safety technology’ (2017-2021) in 2017, clearly included antibiotic innovations.

The 2018 Status Report on Antimicrobial Administration and Antimicrobial Resistance in China clearly stated that research and development on new antibiotics will be enhanced by a targeted and merit-based approach under the new whole nation system (National Health Commission 2018). On this basis, combined with the co-ordinating actions of the 2016 Action Plan and joint working mechanism, we could say that the first pillar of mission-oriented innovation policy (co-ordinated R&D policy) has been fulfilled, as a new mission was clearly added to the “new whole nation system”.

With regards to the other pillar of mission-oriented innovation policy, measures to shape the market are still to some extent lacking, however at least three measures exist. The first regards subsidies from National Basic Medical Insurance scheme towards using new antibiotics. The 2018 Status Report (National Health Commission 2018) mentioned that China will list new innovative drugs on the National Drug Catalogue for Basic Medical Insurance - a useful market-pull incentive for the clinical application of innovation outputs. This policy has been implemented for some antibiotics. For example, Etimicin (approved in 1999) was listed in the China National Reimbursement Drug List (NRDL) in 2009 (Fan and Zhao 2019); Cefathiamidine (approved in 1994) has been listed in several provinces’ RDLs since 2005 and was later added into NRDL (Bioon 2007); Antofloxacin Hydrochloride, an innovative fluoroquinolone antibiotic (found in 1993 and approved in 2009), has been listed on several provinces’ Reimbursement Drug list since then (Dong 2018). Furthermore, as part of the

negotiation process of the NRDL in 2019, many innovative drugs were listed including an innovative antibiotic “Nemonoxacin” which had just been approved in 2016 (Zhejiang-Medicine 2019).

The second market shaping policy is the accelerated process for sales on the market. The China Food and Drug Administration (CFDA) opened a “fast track procedure” for new drugs produced by major projects in 2006, and issued detailed policies for registration and review in 2015. New innovative kinds of antibiotics, or those suited for specific serious disease contexts, can benefit from priority approvals on the basis of these policies (Interview records of Interviewee E, Appendix 2). The third policy is the support provided for the manufacturing and marketing of new antibiotics. The Ministry of Industry and Information have funds to support the commercialization and industrialization of new drugs after their approval. These have not been applied recently, because there are still no antibiotics that have emerged during this period (Interview records of Interviewee D, Appendix 2). However, similar support was used many years ago to support the manufacturing and marketing of Etimicin, an innovative aminoglycoside found in 1980s and approved in 1997 (Fan and Zhao 2019). Specifically, after it had been approved in 1997, Etimicin was included in the national “Torch Plan,” which aimed at promoting the commercialization and industrialization of high-technology products (Fan and Zhao 2019).

Here, it is important to recognize that - due to their common pool resource nature - antibiotics are different from other kinds of products that are usually incentivised by mission oriented innovation policy, such as renewable energy technologies, in which their ever-increasing use is to be welcomed. Rational and therefore limited use of antibiotics is vitally important (more important than the innovation of new antibiotics) in the battle against antimicrobial resistance. In China, the situation has improved considerably since 2011 as discussed above, however intrinsic contradictions exist between the fast-track approvals/reimbursement subsidy through the NRDL and the regulations for rational use. As discussed below, this raises key questions about the ‘market-shaping’ pillar of mission-oriented innovation policy in this case, and the even more severe co-ordination challenges that this brings to national and international policy processes.

What does this tell us with regard to our first question?

1. Do China’s policies to support antibiotics innovation have the characteristics of mission oriented innovation policy? If so, how was this policy framework established?

To summarise, the above review of relevant policies has revealed that the AMR or antibiotic innovation are gradually becoming a clear topic and focus, especially after the establishment of National Action Plan to Contain Antimicrobial Resistance (2016-2020). Elements of both pillars of mission-oriented innovation policy can be identified in China. The National Action Plan brought together diverse policies that existed beforehand, and made AMR a mission for society. Under this framework, the research policies around antibiotics have a clearer direction. The National Action Plan also expands the toolbox beyond co-ordinated R&D to include improved surveillance, rational use in different sectors, publicity and awareness raising. From the perspective of market shaping, the addition of innovative antibiotics to the National Basic Medical Insurance, the improvement of fast track drug examinations and approvals and the support for manufacturing and marketing through downstream policy instruments akin to the historic Torch programme, contribute further to the “mission-oriented” nature of China’s antibiotics innovation policy. We next turn to other data sources to deepen

this answer and to begin to address question 2.

5. Influence of Mission-oriented Innovation Policy on China's Antibiotic Innovation System: Empirical evidence

5.1 The Rising Research Awareness on Antibiotics

Historically, China's policies for supporting antibiotic drug research were not strong enough to have had direct impacts on the research process. This did not specify detailed targets for researchers in the same ways as other areas, such as the antimalarial research task 40 years ago. Before the National Action Plan was adopted in 2016, the national major S&T research project was just a new fund for drug discovery and an extension of the National New Drug Fund from 1989 (SDA 1989) and the "1035 project" from 1993 (Chen and Chen 2019). However, the 2016 National Action Plan integrated elements of mission-oriented innovation policy and provided a clearer antibiotics mission for the whole society (including the scientific community). How can we trace the impact of these changes in terms of antibiotic innovation outcomes?

First we look at the difference that the elements of mission-oriented innovation policy explored above have made to R&D investment. We already know that a total amount of 400 million Yuan RMB (approximately USD 60 million) was invested in targeted antibiotic R&D through the MLP major projects between 2016-18 (National Health Commission 2017). Another possible piece of evidence is the increasing research focus on antibiotics in response-mode funding. The National Science Foundation of China (NSFC) is a research fund to support free research which reflects the focus/interest of researchers rather than government-targeted research. Using the method described in Section 3 above we can see that support from NSFC in the area of antibiotics has increased steadily, over the past decade, both in terms of the proportion of the investment (Figure 1), the total amount of money and the number of projects (Figure 2). From 2010 to 2019, the total investment from NSFC into research mentioning "antibiotics" increased from 10.64 million RMB (approximately USD 1.6 million) to 64.82 million RMB (approximately 10 million) and the number of grants also rose from 37 to 139. The largest increase was seen after 2016. If we consider the money invested in antibiotics as a percentage of the total amount each year from NSFC, we find that the percentage of investment in 2010 was only 0.11%, rising to 0.22% in 2019 (Figure 1). Again from 2010 to 2015, the increase of percentage was no more than 0.05% while the increase after 2016 (especially from 2016-2017) was much greater.

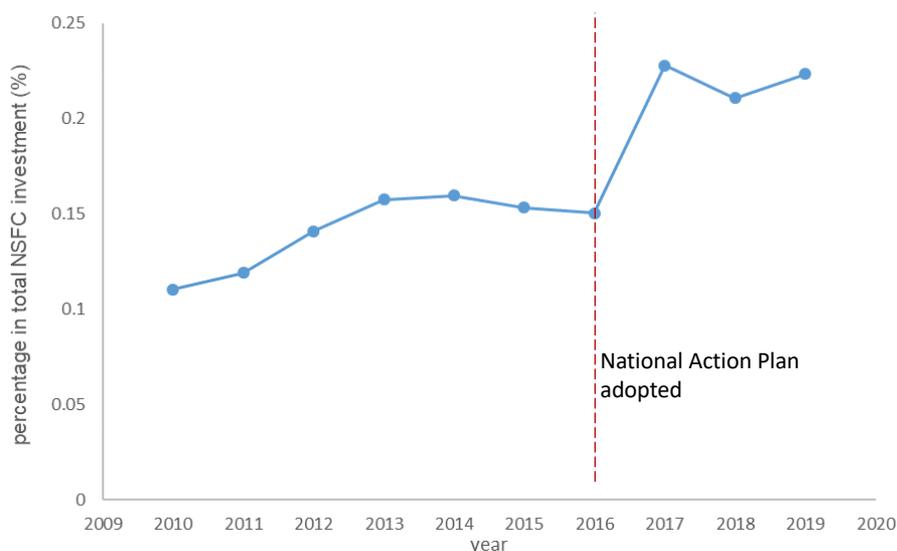


Figure 1. Grants for “antibiotics” research as a percentage of total NSFC investment (source: <http://www.letpub.com.cn/>)

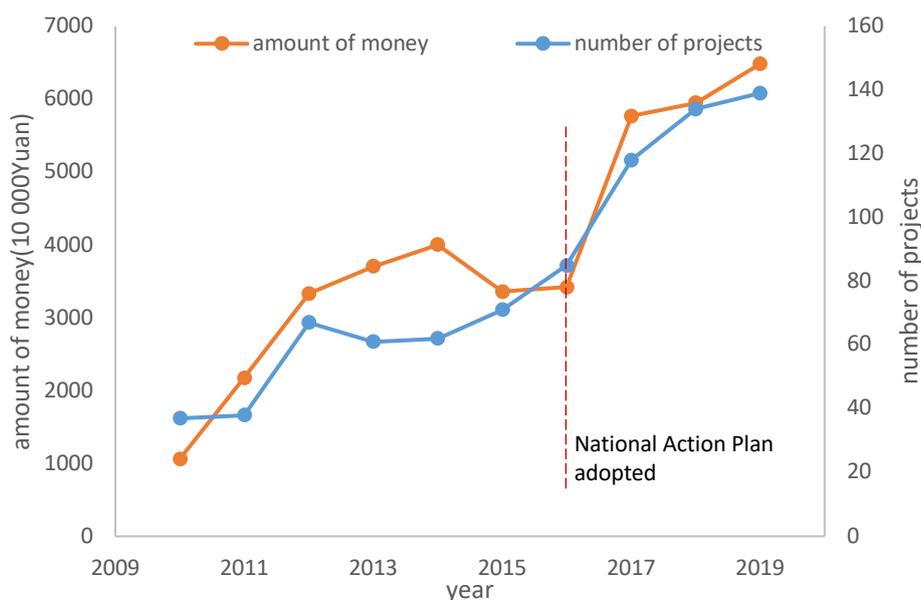


Figure 2. Number of NSFC grants for “antibiotics” research and aggregate amounts invested (source: <https://isisn.nsf.gov.cn/>)

These data seem to suggest an increasing level of interest from academics applying to NSFC in antibiotics and/or an increase in reviewers’ support for antibiotics-related research. Unfortunately, data is not available to allow us to clarify this. A further hypothesis is that the 2016 National Action Plan was responsible for the more rapid increase in antibiotics research funding directly after that period. Even given the increases, the overall amount of funding dedicated through the Major projects and the NSFC (counted in the hundreds of million RMB or tens of millions USD) is small, given the apparent importance afforded to the mission in the policies described in Section 4 above. It is possible that other funding sources (for which data is unavailable) would augment these amounts, however on the basis of the

data analysed here, it does appear that high levels of mission-oriented, co-ordinated R&D funding in this area were not obtained in the pre-Covid 19 era. To provide a comparison, the UK committed approximately USD350 million through a single antibiotics research fund – the Fleming Fund – in 2016 (UK Government 2016)².

5.2 Increasing Publications on Antibiotics

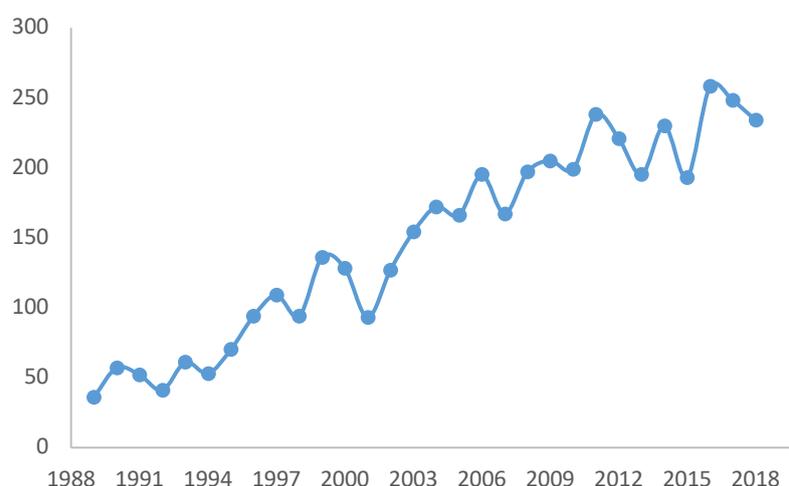


Figure 3. Number of papers on AMR – Chinese authors (source = CNKI)

Another approach to exploring the effectiveness of the mission-oriented innovation policy for antibiotics is through tracing trends in research outputs. From the data collected from CNKI, Figure 3 shows the publication of papers on AMR within the area of Pharmacy, it shows a steady increase from 1989-2019. However, it is hard to say whether AMR has become more important relative to other areas, as China experienced a dramatic increase in its overall publications. Therefore, over that period we compare the papers on AMR with the total number of papers in the Pharmacy area. Figure 4 shows the result - that from the papers on AMR as a percentage of total pharmacy publications, there is no evident increase and the percentage is rising and falling around 0.01%. However, Figure 4 also shows that papers on AMR that were supported by NSFC seem to increase steadily from 2006 and dramatically after 2015. This approximately mirrors the trend in funding seen above, which may be explained by the National Action Plan raising awareness and interest in antibiotics research among independent researchers or reviewers in the NSFC. However, if this rise was a consequence of the increasing numbers of new grants awarded to antibiotics research from NSFC shown in Figures 1 and 2, we would expect a delay of possibly one or two years before resulting publications emerged. An alternative suggestion is that NSFC-attributed submissions of (and/or positive reviews of) antibiotics-related articles in Chinese language journals increased around and following the introduction of the Action Plan, with authors framing their research contribution more in line with the national “mission”.

² Care should be taken in this comparison, however, due to the various approaches to quantification adopted in each case. Within NSFC other relevant work may have been funded, which was not picked up by our chosen search term. The Fleming Fund includes investments in improving laboratory capacity and international surveillance systems.

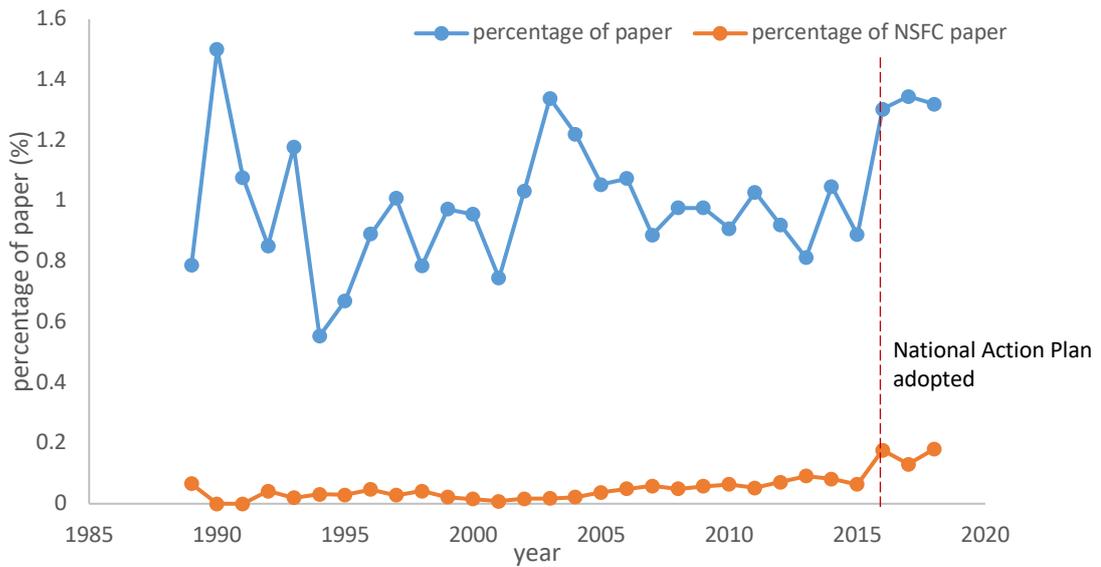


Figure 4. CNKI papers on AMR as a percentage of those in the area of pharmacy (total and NSFC-funded)

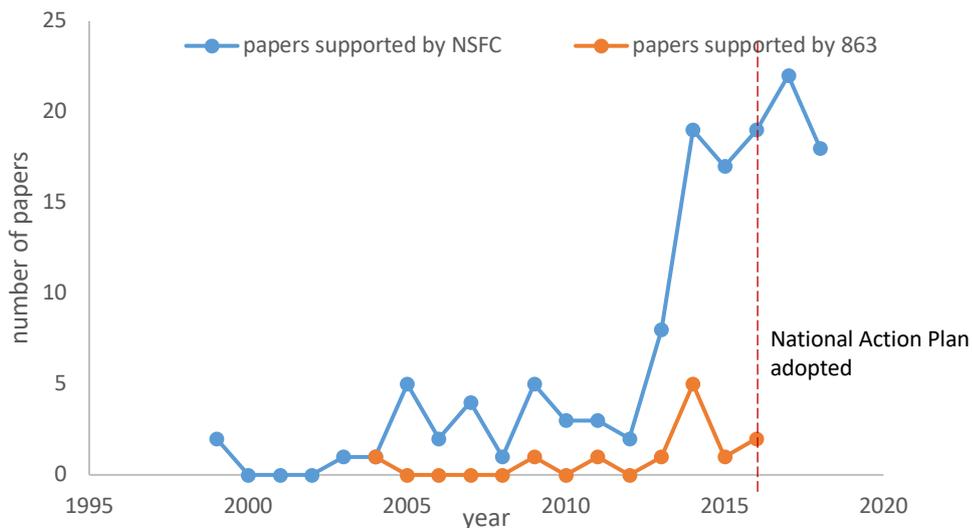


Figure 5. Number of Chinese language papers on AMR supported by different funding sources (source: CNKI)

Figure 5 delineates the growth of papers on AMR supported by China’s major research funds - the NSFC and “863 Program”. Source of funding for papers is directly collected from the CNKI database according to the acknowledgement statements of the papers. The dramatic increase of NSFC supporting papers happened over the most recent ten years, which is consistent with the increase in policy focus. The “863 Program” is an important research funding project for cutting-edge research, however after its reform in 2015, the Program was integrated into the “National Key R&D Plan”. Before the “863 Program” was terminated, the papers on AMR supported by this Program increased significantly in the period after 2010.

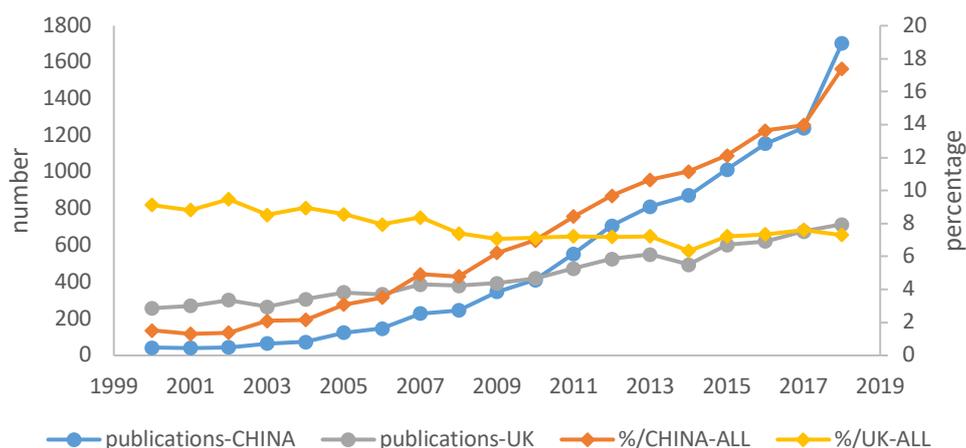


Figure 6. Number of English language papers on “Anti-Bacterial Agents” from authors in the UK and China, and their proportion of world publications in the area of pharmacy (source: PubMed, WOS)

A dramatic increase after 2016 is also reflected in data from international journals. Figure 6 shows the papers on antibiotics from the UK and China published in international journals, both in number and as a percentage of world publications in the area of pharmacy. The UK is consistently a strong research force in this area and published more than 200 papers in 2000 while China only published 43 papers at that time. However, China’s research output in this area has been expanding and overtook the UK in 2007. In 2018, China published 1703 papers, representing 17.38% of the publications in the world, up from 1.52% in 2000. The United Kingdom publications consistently represent around 8% of global publications in this area. The increases in international publications also demonstrates a positive improvement for China in antibiotic research and innovation.

5.3 Antibiotic innovation case studies

In 2019 July 24th, carrimycin was approved by the Chinese FDA after long-term clinical trials. The antibiotic is classified as a Class 1 new drug under the 2016 CFDA classification system - it comprises new chemical entities with clinical value, and has never been marketed anywhere in the world (MOST 2019). Carrimycin was the first new antibiotic in China producing using synthetic biology (MOST 2019) and can be used to treat upper respiratory tract infection. It was regarded as one of the most important achievements of the national major S&T research project. Since its approval by CFDA, the macrolide has been found to display antiviral properties in addition to its antibacterial effects, including against Covid-19 (Yan et al 2021) and received Phase III trials approval from the US FDA for treatment of Covid-19 in December 2021. This is a particularly recent and important example of China’s increasing success the application of new techniques to antibiotics innovation. However, it follows a long history of work in this area.

As a matter of fact, the research that led to carrimycin has taken place for more than 30 years, as illustrated (alongside other drugs) in Table 2. It started in 1988 and was originally supported by “863 Program,” and later the 973 Program and NSFC (MOST 2019). In 2000, preclinical studies of carrimycin were completed. Approval for clinical trials was obtained

from the regulatory department the year after, with phase III clinical trials for upper respiratory tract infection completed in 2009. Only in recent years, this project was mainly funded by the “new drug discovery major project” (MOST 2019). This work was completed by Wang Yiguang, a researcher from the microbial branch of the Chinese Academy of Medical Sciences. The branch was started in 1956 through the first “Long-term Plan for the Development of Science and Technology for 1956–1967,” appealing for development of antibiotics to protect the nation’s health (Yixian 2019). Before the 1990s the major task of this branch was developing antibiotics which had been found in other countries. In recent decades, the discovery of new antibiotics has gradually become the main goal, with carrimycin providing a key example.

Under the support of the major project for new drug discovery, other Class 1 new antibiotic drugs were approved by China FDA. L-ornidazole was approved in 2009, and morinidazole was approved in 2014. These two antibiotics were both mainly developed by pharmaceutical companies (National Health Commission 2018) and are not included in Table 2. Besides the Class 1 new drugs, the new drug discovery major project also supports the development of other drugs. Class 3 new drugs refers to drugs which are introduced to China after having been marketed in other countries, and are equivalent to the original drugs in quality and efficacy. Up till 2017, at least 15 such drugs had been approved by the China FDA (National Health Commission 2018). By 2016, there were also 8 new antibiotics in clinical trials. It seems the national major S&T research project played a critical role.

Antofloxacin hydrochloride is another Class 1 new drug. Research on this antibiotic started in 1993 and was also supported by the “863 Program” and the NSFC (Dong 2018). This new antibiotic was a new kind of fluoroquinolone (Dong 2018) which became the first drug of its kind with indigenous intellectual property rights in China. It has been in production since 2009 and by 2016 had benefited at least 1 million people. In 2018, antofloxacin hydrochloride was included in the China National Reimbursement Drug List (NRDL), providing a market pull incentive.

Research on carrimycin and antofloxacin hydrochloride was mainly completed by research institutions, however the success of both has also involved the engagement of enterprises. Public funding provided the basic support in the early stages, especially in the period of lab-experimentation, whilst cooperation with private firms contributed to the preclinical and clinical trials, as well as the production and manufacturing of drugs. The National Major S&T research project investment in these two new drugs mainly focused on clinical trials, illustrating the important role for government funding in near-to-market research in China.

Table 2 below shows a case study history of four major innovative antibiotics in China, with two more drugs - etimycin and cepthiamidine - included alongside carrimycin and antofloxacin hydrochloride. In all cases, the innovation process was long and received long-term, continuous support from public funds and/or enterprises. The National Major S&T research project of recent years was just one in a series of research funds supporting researchers and companies to continue new drug discovery. Some of these case studies also reveal investments in production (eg. Torch Plan) and others illustrate how the subsidies from China National Reimbursement Drug List (NRDL) have contributed to shaping the market.

In summary, the history of these new antibiotics proves that public funding has long been important for the creation of new antibiotics, especially at the basic research stage. It also reveals that public funding has been involved alongside follow-up investment from entrepreneurs, with some significant successes. The long-term strategy has been expanding projects on new antibiotics at the basic research stage to increase the possibility of drug development and support the preclinical and clinical trials of new candidate antibiotics, which are undertaken through cooperation with entrepreneurs. As the development of new drugs always has a long history, we cannot confirm with any certainty whether recent public investments in R&D have increased (or will increase) the number or type of new antibiotics development in China. As such, we can currently only provide preliminary answers to our second question (How effective is antibiotic innovation in China?)

Table 2 The innovation process of major original innovative antibiotics in recent years.

Name	Etimicin	Antofloxacin hydrochloride	Cefathiamidine	Carrimycin
Class	Aminoglycoside	Fluoroquinolone	β -lactam	Macrolide
Research timeframe	1980s-1997	1993-2009	1974-1994-2000	1988-2019
Research process	<p>In 1980s, a series of chemical modifications were undertaken based on Gentamicin C1a. Etimicin was found, which had the lowest ear and renal toxicity. For further development, this project was supported by the National New Drug Fund 国家新药基金。 Supported by the National New Drug Fund, many other leading institutions and researchers were involved in research on pharmacodynamics, pharmacology, toxicology and quality standards, due to the poor research ability of the major researcher.</p>	<p>Since 1993, researchers started to study fluoroquinolones, and designed and synthesized 62 new compounds. In 2009, antoxacin hydrochloride, which stood out from the competition, was successfully approved, becoming the first new chemical drug of class 1 with novel chemical structure and independent intellectual property rights in China.</p>	<p>In the 1970s, the research group set out to study the semi-synthesis of cephalosporins and small-scale laboratory processes. In 1976 the clinical trials started with help of Shanghai Huashan Hospital. In 1982, cefathiamidine was approved for production by Shanghai Health Bureau.</p>	<p>In March 1986, the state launched the high-tech research and development program ("863 Program"), which aimed to improve China's independent innovation capacity. Meanwhile, genetic engineering technology was flourishing in domestic biology circles, but little research was applied to new drugs. Researchers seized upon the opportunity of a high-tech approach, applied for the antibiotic genetic engineering project in 1988, and the basic research work of Carrimycin began.</p>
Major researcher	Jiangsu Institute of Microbiology	Shanghai Institute of Medicine of Chinese Academy of Medical Sciences	Shanghai Institute of Pharmaceutical Industry	Shanghai Institute of Medicine of Chinese Academy of Medical Sciences
Industrial cooperato r	WuXi Shanhe Group Co. Ltd	Anhui Huanqiu Pharmaceutical Co. Ltd	Guangzhou Baiyunshan Pharmaceutical Co., Ltd	Shenyang Tonglian group co. Ltd

Development process	<p>After Etimicin got support from the National New Drug Fund in 1989, WuXi Shanhe Group started to cooperate with Jiangsu Institute of Microbiology. They worked together on the amplification research and preparation of clinical samples. Etimicin was approved by the CFDA in 1997.</p>	<p>Anhui Huanqiu pharmaceutical company acquired the intellectual property of antofloxacin hydrochloride and its derivatives. They cooperated on preclinical studies and phase I, II and III clinical research, accelerating the pace of new drug research and development.</p>	<p>The drug met difficulties in production at an early stage. At the end of 1980s, Baiyunshan company took over this drug and started to cooperate on the production. It took them many years experimentation to reach high quality production. In 1993, the first factory sample was produced, and the drug was approved in 1994. They then took five years to improve the quality of large scale manufacturing</p>	<p>In 2000, the preclinical study of Carrimycin was completed, the clinical trial approval was obtained from the regulatory department in 2001, the phase III clinical trial was completed in 2009, and the new drug was approved by the technical review in 2014. However the final approval document was only given in 2019 due to a change of standards.</p>
Policy support	<p>National New Drug Fund; Torch Plan; High-tech demonstration project; 1035 project; National Basic Medical Insurance</p>	<p>863 Program; NSFC; The State Technological Invention Award; National Basic Medical Insurance</p>	<p>The State Technological Invention Award; National Basic Medical Insurance</p>	<p>863 Program; 973 program; NSFC; National Major S&T research project for new drug discovery</p>

Sources: from online news and reports.

6. Discussion

Pharmaceutical innovation is capital-intensive, long term and high risk. In the absence of commercial R&D investment, state support has been important to develop and maintain Chinese drug discovery capabilities, which reside mainly in the public sector. The main early focus of Chinese scientists was the production of analogues of drugs developed by foreign companies.

However since 1989, a series of targeted (vertical) policy instruments has been used to support investment in drug discovery (in general, not specifically antibiotics), and to support the development of innovative capacity with the aim of “catching up”. In 2001, a framework for supporting national major S&T research projects was established as a mechanism available across sectors. In recent years, especially since 2006, there has been a more explicit emphasis in China on “endogenous innovation” (Gu and Lundvall 2006), alternatively termed “indigenous innovation” (Wilsdon & Keeley 2007)(自主创新). As a result, the National S&T Major Research Project on new drug discovery has devoted further resources to creating new drugs. Some of these National S&T Major Research Projects have focused on antibiotics and have the potential to become a core element of the first pillar of a mission oriented innovation policy for antibiotics. However, to some extent the National S&T Major Research Projects remain focused on “catching up”, rather than more ambitious, mission-oriented investment in response to the grand challenge of antimicrobial resistance. This is particularly reflected in the modest levels of investment that are apparent from our analyses. However, there is evidence that China’s capabilities in producing novel antibiotics are improving.

From organisational mission to national mission

The mission of creating new antibiotics initially came not from a national plan but rather from the self-appointed mission of individual research institutes. This is most clear from following case studies of antibiotic innovation, which have their origins in research institutes, established with modest resources, that have had an antibiotic-related mission since the 1950s. These institutes have long-established research capabilities, which have benefitted from the increase in resources resulting from market reforms and a series of national R&D programmes.

Before these funding initiatives, the institutes developing antibiotics such as Etimicin and Cefathiamidine faced extreme resource limitations. They have also had to adapt to the introduction of market reforms and associated competition. On the one hand, these difficulties meant that Cefathiamidine’s development took 20 years. However, from the end of the 1980s antibiotic developers were able to access support from both public funding programmes and private enterprises, accelerating the process. Carrimycin has had a less difficult development process as it benefitted at the outset from the support of the “863 Program”. Later on it was also supported by NSFC and National Major S&T Research Project for new drug discovery. Carrimycin’s production drew upon synthetic biological techniques, and hence this was a highly unusual project at a time when most of Chinese research was focused on imitating known drugs.

The above innovations have their origins in the first national research plan for science and technology (1956-1967) which focused on organizing researchers directly by establishing institutes and providing basic funding. This strategy was widely used in defence and space technologies. During the 1980s competitive funding mechanisms for research became more prevalent and the role of central

planning reduced. At the present time most researchers and companies access support under competitive modes of funding. The national research plans and 2006 projects for new drug discovery involved researchers pursuing, in many different directions, innovation for “creating new drugs”, and with no particular emphasis on AMR. While antibiotic drug development is pursued by some researchers, it is a relatively small part of overall activity. The 2016 National Action Plan may provide the opportunity for a clearer mission focused on new antibiotics, and could also provide an opportunity to coordinate the existing elements of mission oriented innovation into a more coherent and cohesive form, which – through enhanced investment and appropriate market shaping – could bring significant benefits.

As the NSFC grant data and historical event analysis seems to reflect, the 2016 national action plan to contain AMR has drawn more researchers into the field of antibiotic drug discovery as well as engaging other ministries beyond the Ministry of Health. The plan may also improve awareness of the challenge of AMR in society as a whole. The National Action Plan may lead to an increase in AMR related basic research, and may lead to increases in research support from different ministries. A growth in basic research here would provide a platform for researchers to obtain further support later on from the national major S&T research project in new drug discovery as well as from commercial enterprises. The National Action Plan could also provide a policy framework for market-shaping - to coordinate the subsidies for new drugs from NRDL, and the subsidies and other preferential policies for industrialization processes, such as the fast track approval process for drugs. Although policy coordination is far from cohesive at present, the joint working mechanism established in 2016 could be used to help strengthen coordination across ministries in the future. These developments illustrate a slow move towards a national mission-oriented innovation policy around antimicrobial resistance, in which political commitments still need to be fulfilled by ambitious, long-term investments.

7. Conclusion

By analyzing the R&D activities, publications and policies relevant to antibiotics innovation in China, this paper reveals how China has been developing its antibiotic R&D and innovation capabilities and at the same time evolving towards a configuration with more of the characteristics of mission oriented innovation policy.

The analysis has revealed the emergence of elements of mission oriented innovation policy including: (1) the establishment of specialist research institutes, dating back to the 1950s; (2) the broadening and deepening of funding through a series of co-ordinated policy instruments such as the national major research project based on the 2006 Medium-Long-Term Plan on Science and Technology and other research plans & major projects; (3) a series of market-shaping policies including the fast track approval of new drugs, reimbursement of treatments for healthcare providers for use of new antibiotics listed in the NRDL, and subsidies for the industrialization and commercialization processes. While many of the specific policy instruments are conceived more broadly than just antibiotics, they include some specific provisions for antibiotics as a priority.

More focused policies related to AMR have been emerging since 2008 in China as this became a growing domestic problem as well as being increasingly recognized internationally as global challenge. In particular, the 2016 National Action Plan to Contain AMR identifies a clear mission to tackle the problem of AMR and provides the opportunity to coordinate and integrate a range of policies into a coherent mission-oriented innovation policy. Specifically, the National Action Plan provides the

chance to reconfigure China's efforts from the mission of "catching up" towards a "Grand Challenge" mission.

The intrinsic contradictions/ tensions between market creation through the fast-track approvals/ NRDL reimbursement processes and the regulations around rational use raise important questions that are peculiar to the AMR case. Mission oriented innovation policy around antibiotics must adopt a different approach to that in other fields from the perspective of market shaping, in order to incentivize innovation but also limit product use. Rather than a "market entry reward" supported by public procurement or subsidies, a sophisticated and finely-tuned approach to antibiotic purchase and use is crucially important. This regulation may reduce the market for antibiotics in the short term but will also protect their value and market in the long term. One potential innovation policy would include the expectation of the limited use of antibiotics but longer-term protection of intellectual property to incentivize stewardship of the drug. Alternatives, currently being piloted in various countries, are attempting to de-link the relationship between sales/ revenue for the pharmaceutical industry and volume of drug used (Gotham et al 2021). The complex interactions between these regulatory approaches and their role in co-ordinating the behavior of different system actors in different contexts require further research, both from a theoretical perspective and through policy experimentation and learning.

Limitations and further research

This study has some limitations: Only high-level trend analysis of publications and grants, using just a few key terms, has been conducted. This is partly due to limited data availability for the majority of funding sources in China. For grants, more detailed analysis could be conducted by moving beyond overall numbers to explore thematic foci and follow developments in different specific areas, such as TCM approaches, and different mechanisms of (and responses to) resistance. The AMR-related research supported by different major funding programmes could also be studied in more depth (e.g. support for areas such as diagnostics, vaccines and other substitutive therapies besides antibiotics). For publications in English, more detailed analysis about the authors and their institutions could be undertaken, while combining/ comparing the MESH data we collected with alternative MESH terms could also be used to provide a fuller picture. The search for antibiotics-related research in CNKI publications in Chinese could try to use antibacterials ("抗菌素") as well as antibiotics ("抗生素").

Further research could reveal experts' and policy makers' perceptions of the National Action Plan and its observed effectiveness, combined with tracking improvements through other metrics such as patents or clinical trials. In particular, it may be important to understand whether and how mission-oriented innovation policy can overcome some of the specific challenges associated with the restricted use of new antibiotics that limit their commercial attractiveness. Given that the National Action Plan arose in response to the 2015 World Health Assembly initiative, the type of approach employed in this study could also be applied in other countries to compare the extent to which, and modalities through which, mission-oriented innovation policies for antibiotics have been adopted. Finally, whilst this study covers the time period up to the arrival of the Covid-19 pandemic, patterns of biomedical investment, policies and increasing attention to antimicrobial resistance mean that further work to trace how China's approach evolves will be important.

References

- Anadón, Laura Díaz. 2012. 'Missions-oriented R,D&D institutions in energy between 2000 and 2010: A comparative analysis of China, the United Kingdom, and the United States', *Research Policy*, 41: 1742-56.
- Bioon. 2007. 'China's Innovative Drug Ceftiamidine Promotes the Development and Application of Antibiotics', Bioon.com.
- Bound, K., Saunders, T., Wilsdon, J. & J. Adams (2013) 'China's absorptive state: research, innovation and the prospects for China-UK collaboration' . London: NESTA
- Cao, Cong. 2015. '23. China', *UNESCO science report: towards 2030*. 622-37, Paris: United Nations Educational, Scientific and Cultural Organisation.
- Chen, Chuan hong, and Kai xian Chen. 2019. *The Road to Pharmaceutical Innovation: Review of 1035 Project (迈向药物创新之路：1035 工程实施回顾)* (Higher Education Press (高等教育出版社): Beijing).
- Chen, Yantai and Adrian Ely. 2011. 'Health biotechnology innovation for social sustainability – a perspective from China' , STEPS Working Paper 47, Brighton, STEPS Centre, <https://opendocs.ids.ac.uk/opendocs/handle/20.500.12413/2221>, accessed
- China CPC/SC 2012. 'Opinions on Deepening the Reform of the Scientific and Technological System and Speeding up the Building of a National Innovation System.' edited by The CPC Central Committee and the State Council. Beijing.
- China, State Council of People's Republic of. 1956. 'Outline of the long-term plan for the development of science and technology from 1956 to 1967.' edited by State Council of Peopel's Republic of China.
- China, State Council of the People' s Republic of. 2006. 'The National Medium- and Long-Term Plan for Science and Technology Development (2006-2020).' edited by State Council of the People' s Republic of China. Beijing.
- Chorzelski, S, B Grosch, H Rentmeister, S Völler, B Landré, J Pfitzner, C Wechselmann, R Busse, S Edwards, C J. 2015. Report for the Global Union for Antibiotics Research Henschke, and Development Initiative Commissioned by the German Federal Ministry of Health. 2015. 'Breaking through the wall: Enhancing research and development of antibiotics in science and industry'.
- Dong, Chunlei. 2018. 'Antifloxacin hydrochloride: A Local Good Drug Developed in 16 years' , *Xinmin Evening News*.
- Ely, Adrian, Adrian Smith, Andy Stirling, Melissa Leach, and Ian Scoones. 2013. 'Innovation politics post-Rio+ 20: hybrid pathways to sustainability?', *Environment and Planning C: Government and Policy*, 31: 1063-81.
- Fan, Jin , and Min Zhao. 2019. 'The road of research and development of etimicin', *Chinese journal of antibiotics*, 44: 1229-31.
- Foray, D., D. C. Mowery, and R. R. Nelson. 2012. 'Public R&D and social challenges: What lessons from mission R&D programs?', *Research Policy*, 41: 1697-702.
- Foster, K. and H. Grundmann 2006. 'Do We Need to Put Society First? The Potential for Tragedy in Antimicrobial Resistance.' *PLoS Medicine* 3(2): e29
- Freeman, C. 1979. The determinants of innovation: Market demand, technology, and the response to social problems. *Futures* 11(3): 206-215
- Gotham, D., Moja, L., van der Heijden, M., Paulin, S., Smith, I., and Beyer, P. 2021. 'Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States.' *Health Policy* 125(3): 296-306
- Gu, Shulin, and Bengt-Ake Lundvall. 2006. 'China's Innovation System and the Move Toward Harmonious Growth and Endogenous Innovation', *Innovation: Management, Policy & Practice*, 8: 1-26.
- Guo, Z. 2016. 'Artemisinin anti-malarial drugs in China', *Acta Pharm Sin B*, 6: 115-24.
- He, Ping. 2019. 'Rational use of antimicrobial drugs under the background of China's medical and health system' reform (in Chinese, 中国医药卫生体制改革背景下抗菌药物的合理使用)." In *theBMJ*, 365.

- Hekkert, M. P., R. A. A. Suurs, S. O. Negro, S. Kuhlmann, and R. E. H. M. Smits. 2007. 'Functions of innovation systems: A new approach for analysing technological change', *Technological Forecasting and Social Change*, 74: 413-32.
- Hicks, Diana. 2016. 'Grand Challenges in US science policy attempt policy innovation', *International Journal of Foresight and Innovation Policy*, 11: 22-42.
- Huang, Yanzhong. 2016. 'Global Health at the G20 Hangzhou Summit'.
- Kattel, R., and M. Mazzucato. 2018. 'Mission-oriented innovation policy and dynamic capabilities in the public sector', *Industrial and Corporate Change*, 27: 787-801.
- Kuhlmann, Stefan, and Arie Rip. 2014. 'The challenge of addressing Grand Challenges', *EU Commission*.
- LetPub. 2019. "国家自然科学基金项目查询(Inquire of NSFC)." In.
- Li, Zhe, and Nan Su. 2014. 'A Study on the New National System for Science and Technology Innovation under the Condition of Socialist Market Economy (in Chinese, 社会主义市场经济条件下科技创新的新型举国体制研究)', *China Science and Technology Forum (中国科技论坛)*, 2: 5-10.
- Mazzucato, M. 2018a. 'Mission-Oriented Research & Innovation in the European Union: A Problem-Solving Approach to Fuel Innovation-Led Growth.' In. European Commission, Directorate-General for Research and Innovation: European Commission, Directorate-General for Research and Innovation.
- Mazzucato, M. 2016. 'From market fixing to market-creating: a new framework for innovation policy', *Industry and Innovation*, 23: 140-56.
- Mazzucato, M., and C. C. R. Penna. 2016. 'Beyond market failures: the market creating and shaping roles of state investment banks', *Journal of Economic Policy Reform*, 19: 305-26.
- Mazzucato, Mariana. 2018b. 'Mission-oriented innovation policies: challenges and opportunities', *Industrial and Corporate Change*, 27: 803-15.
- Mazzucato, Mariana, Heidi Chow, Andrea Laplane, Tiziana Masini, Diarmaid McDonald, Victor Roy, and Ellen 't Hoën. 2018. 'Peoples Prescription: Re-imagining health innovation to deliver public value' In. London: UCL Institute for Innovation and Public Purpose.
- Ministry-of-Health. 2012. 'Administrative Measures for the Clinical Use of Antibacterial Drugs.' edited by Ministry of Health.
- Mossialos, Elias, Chantal Morel, Suzanne Edwards, Julia Berenson, Marin Gemmill-Toyama, and David Brogan. 2010. *Policies and incentives for promoting innovation in antibiotic research* (World Health Organization. Regional Office for Europe).
- MOST. 2005. 'National S&T Major Research Projects: Innovation and new medicines and modernization of traditional Chinese medicine.' edited by Ministry of Science and Technology. Beijing.
- . 2006. 'Introduction of National Science and Technology Major Project.' edited by Ministry of Science and Technology. Beijing.
- . 2019. 'Press Conference of National S&T Project on New Drug Discovery.' Beijing: Ministry of Science and Technology.
- Mowery, David C. 2012. 'Defense-related R&D as a model for "Grand Challenges" technology policies', *Research Policy*, 41: 1703-15.
- National Health Commission. 2017. 'Status Report on Antimicrobial Administration and Antimicrobial Resistance in China,2017.' Beijing.
- . 2018. 'Status Report on Antimicrobial Administration and Antimicrobial Resistance in China,2018.' Beijing.
- National Health and Family Planning Commission. 2016. In 'National action plan to combat antimicrobial resistance (2016-2020)', edited by National Health and Family Plan Commission. Beijing.
- O'Neill, Jim. 2018. 'An earnest proposal for tackling AMR.' In *Project Syndicate*.
- Oldham G, et al. 1997. *A Decade of Reform: Science and Technology Policy in China* (International Development

Research Centre Ottawa. Canada).

- Christel M. 2019. Pharm Exec's Top 50 Companies 2019. *Pharmaceutical Executive*. 39(6), Jun 12, 2019. <http://www.pharmexec.com/pharm-execs-top-50-companies-2019> (Accessed June 14, 2019)
- Qu, Junyan, Yimei Huang, and Xiaoju Lyu. 2019. 'Crisis of antimicrobial resistance in China: now and the future', *Frontiers in microbiology*, 10: 2240.
- Renwick, Matthew J, Victoria Simpkin, and Elias Mossialos. 2016. 'Targeting innovation in antibiotic drug discovery and development', *Health Policy Series of the European Observatory on Health Systems*.
- Rosenberg, N. 1969. 'The Direction of Technological Change: Inducement Mechanisms and Focusing Devices' . *Economic Development and Cultural Change*, 18(1, Part 1), 1–24.
- Sampat, B. N. 2012. 'Mission-oriented biomedical research at the NIH', *Research Policy*, 41: 1729-41.
- Schot, Johan, and W. Edward Steinmueller. 2018. 'Three frames for innovation policy: R&D, systems of innovation and transformative change', *Research Policy*, 47: 1554-67.
- SDA. 1989. 'Interim measures for the administration of new drug research fund projects.' In, edited by State Drug Administration. Beijing.
- Stirling, Andrew. 2009. 'Participation, precaution and reflexive governance for sustainable development' Chapter 9 in Adger, N. & Jordan, A. (Eds) *Governing Sustainability*, Cambridge: Cambridge University Press, pp 193-225
- Tarrant, C., Colman, A. M., Chattoe-Brown, E., Jenkins, D. R., Mehtar, S., Perera, N. and E. M. Krockow. 2019. 'Optimizing antibiotic prescribing: collective approaches to managing a common-pool resource' *Clinical Microbiology and Infection* 25(11): 1356-1363
- UK Government. 2016. Government response to the Review on Antimicrobial Resistance, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/553471/Gov_response_AMR_Review.pdf (accessed 20 January 2020).
- Van Zwanenberg, P., Ely, A. & A. Smith. 2011. *Regulating technology - international harmonization and local realities*, Abingdon: Routledge
- Wagner, Caroline S., and Shing Kit Wong. 2011. 'Unseen science? Representation of BRICs in global science', *Scientometrics*, 90: 1001-13.
- Wang, Zuoyue. 2016. 'The Chinese developmental state during the Cold War: the making of the 1956 twelve-year science and technology plan', *History and Technology*, 31: 180-205.
- Weber, M. & H. Rohracher (2012) 'Legitimizing research, technology and innovation policies for transformative change;/Combining insights from innovation systems and multi-level perspective in a comprehensive 'failures' framework' , *Research Policy* 41, 1037-1047
- WHO. 2011. Antimicrobial resistance: no action today, no cure tomorrow. <https://www.who.int/world-health-day/2011/en/>(accessed 20 January 2020)..
- — — . 2015. Global Action Plan on Antimicrobial Resistance. <https://www.who.int/antimicrobial-resistance/global-action-plan/en/> (accessed 20 January 2020).
- Wilsdon, J. and Keeley, J. (2007) 'China: the next science superpower?' London: Demos.
- Wind. 2018. "Wind-Economic Database."
- Xiao Y, Zhang J, Zheng B, Zhao L, Li S, Li L. 2013. Changes in Chinese Policies to Promote the Rational Use of Antibiotics. *PLoS Med* 10(11): e1001556. <https://doi.org/10.1371/journal.pmed.1001556>
- Xiao, Y. and L. Li. 2016. 'China's national plan to combat antimicrobial resistance.' *The Lancet Infectious Diseases* 16(11): 1216-1218.
- Yan, H., et al. (2021). 'Repurposing CFDA-approved drug carrimycin as an antiviral agent against human coronaviruses, including the currently pandemic SARS-CoV-2.' *Acta Pharmaceutica Sinica B*
- Ying, Guang-Guo, Liang-Ying He, Andrew J Ying, Qian-Qian Zhang, You-Sheng Liu, and Jian-Liang Zhao. 2017. 'China must reduce its antibiotic use', *Environmental Science & Technology*, 51: 1072-73.

- Yixian, Qu. 2019. 'Wang yiguang, a pioneer of the new antibiotic era, used genetic engineering to develop new drugs.' In *The Economic Observer Newspaper*.
- Zhang Jiuchun, Zhang Baichun. 2019. 'Planning Science and Technology: Working out and Implementing the Long-term Program for Developing Sciences and Technology from 1956 to 1967', *Bulletin of Chinese Academy of Sciences*, 34: 982-91.
- Zhang, Qian-Qian, Guang-Guo Ying, Chang-Gui Pan, You-Sheng Liu, and Jian-Liang Zhao. 2015. 'Comprehensive evaluation of antibiotics emission and fate in the river basins of China: source analysis, multimedia modeling, and linkage to bacterial resistance', *Environmental Science & Technology*, 49: 6772-82.
- Zhejiang-Medicine. 2019. 'Nemonoxacin newly entered National Reimbursement Drug List '.
- Zhong, Shuhua. 2009. 'On the Whole Nation System of Science and Technology (in Chinese, 论科技举国体制)', *Studies in Science of Science (科学学研究)*, 27: 1785-92.

Appendix 1: Timeline of relevant policies and their associated innovation system functions and actors

Year	Title	Function	No.	Central government	Health	NDRC	S&T	Agriculture	Food & Drug	Education	Industry	Finance	Land & Resources	Environment	Culture	Press and Publication	SATCM	Military Logistic	Sports	Commerce
2006	Outline of the national plan for medium - and long-term scientific and technological development(2006-2020)	Function 4, 6	1	√																
2006. 2.7	Supporting Polices for National Plan 2006-2020	Function 1, 3, 5, 6	1	√																
2008	National Major Scientific and Technological Special Project for "Significant New Drugs Development" (-2020)	Function 1, 2, 3, 4, 6	2		√		√													
2011	WHO world health day on combating AMR	Function 2, 7			1															
2012. 2.13	The Administrative Measures for the Clinical Use of Antibacterial Drugs		1		√															
2014	12th Five-year National Science & Technology Pillar Program "R&D of Key Technologies for emergency prevention and control" (2014-2017)	Function 2	1				√													
2015	WHO Cnference call for National Action Plan	Function 2, 7	1	√																
2016. 1	Joint working mechanism for the prevention and control of AMR	Function 1, 2, 3, 4, 5, 7	12		√	√	√	√	√		√		√	√	√	√	√	√		

2016.08.05	National Action Plan to Contain Antimicrobial Resistance (2016-2020)	Function 1, 2, 3, 4, 5, 7	14	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
2016.10.25	Outline of the Healthy China 2030 Plan	Function 4, 6	1	√														
2016.10.26	Plan and guidance for Pharmaceuticals development	Function 1,4, 5	6	√	√	√	√		√									√
2017.06.12	The 13th five-year plan for TCM science and technology innovation	Function 4, 6	1			√												√
2017.06.12	The 13th five-year plan for Hygiene and Health Science and Technology innovation	Function 4, 6	6	√		√		√										√
2017.5	National Key Technologies R&D Program of 'modernization of TCM' and 'R&D of Key Food safety technology' (2017-2021)	Function 2,4,6	1			√												

Note: Functions of innovation systems according to Hekkert et al. (2007)

- Function 1: entrepreneurial activities
- Function 2: knowledge development
- Function 3: knowledge diffusion through networks
- Function 4: guidance of the search
- Function 5: market formation
- Function 6: resources mobilization
- Function 7: creation of legitimacy/counteract resistance to change

Appendix 2: Interviewee list

Interviewee	Position	Date of interview
A	Professor of Science and Technology Policy	2019.10.14
B	Official from NFSC	2019.10.15
C	Official from Ministry of Science and Technology	2019.10.15
D	Official from China Food and Drug Administration	2019.10.14
E	Official from Ministry of Industry and Information Technology	2019.10.11
F	Official from China Committee of Health.	2019.10.08

Recent papers in the SPRU Working Paper Series:

May

2021.03. Appraising research policy instrument mixes: a multicriteria mapping study in six European countries of diagnostic innovation to manage antimicrobial resistance. Josie Coburn, Frederique Bone, Michael M. Hopkins, Andy C. Stirling, Jorge Mestre-Ferrandiz, Stathis Arapostathis and Martin J. Llewelyn.

2021.02. Artificial Intelligence's New Clothes? From General Purpose Technology to Large Technical System. Simone Vannuccini and Ekaterina Prytkova.

January

2021.01. Exploring the links between research demand and supply: The case of Chagas. Valeria Arza and Agustina Colonna.

December

2020.20. Riskwork in the Construction of Heathrow Terminal 2. Rebecca Vine.

2020.19. The Origin of the Sharing Economy Meets the Legacy of Fractional Ownership. Francesco Pasimeni.

November

2020.18. Sustainability and Industrial Change: The Hindering Role of Complexity. Tommaso Ciarli and Karolina Safarzyńska.

Suggested citation:

Yuhan Bao, Adrian Ely, Michael Hopkins, Xianzhe Li and Yangmu Huang (2021). Exploring the Antibiotics Innovation System and R&D policies in China: Mission Oriented Innovation? (SWPS), 2021-04. ISSN 2057-6668. Available at: www.sussex.ac.uk/spru/research/swps.

Science Policy Research Unit
University of Sussex, Falmer
Brighton BN1 9SL
United Kingdom

SPRU website: www.sussex.ac.uk/business-school/spru

SWPS website: www.sussex.ac.uk/business-school/spru/research/working-papers

Twitter: [@spru](https://twitter.com/spru)