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Building bridges to operationalise one health – A Sino-Swedish collaboration to tackle antibiotic resistance

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ABSTRACT

Antibiotic resistance is a complex global health challenge. The recent Global Action Plan on antimicrobial resistance highlights the importance of adopting One Health approaches that can cross traditional disciplinary boundaries. We report on the early experiences of a multisectoral Sino-Swedish research project that aims to address gaps in our current knowledge and seeks to improve the situation through system-wide interventions. Our research project is investigating antibiotic use and resistance in a rural area of China through a combination of epidemiological, health systems and laboratory investigations. We reflect here on the challenges inherent in conducting long distance cross-disciplinary collaborations, having now completed data and sample collection for a baseline situation analysis. In particular, we recognise the importance of investing in aspects such as effective communication, shared conceptual frameworks and leadership. We suggest that our experiences will be instructive to others planning to develop similar international One Health collaborations.

1. Introduction

It has become evident in recent years that we need to take a holistic approach to understand the complex global health issue of antibiotic resistance. Research efforts led by single disciplines have produced essential knowledge, but there is a need for a collaborative multisectoral approach that can deepen our understanding of the underlying dynamics – how bacteria, resistance genes and antibiotics are continuously flowing between humans, animals and the environment and how these might be influenced by various factors [1–5].

One Health is the collaborative effort of multiple disciplines – working locally, nationally, and globally – to attain optimal health for people, animals and the environment [6]. In this article we describe a Sino-Swedish One Health research project that addresses gaps in our current knowledge through a cross-disciplinary collaboration, and seeks to improve the situation through system-wide interventions. We also illustrate the early experiences of this project, called 'The Sino-Swedish Integrated Multisectoral Partnership for Antibiotic Resistance Containment' (IMPACT), which involves institutions in both China and Sweden. We do this with a view to contributing to the limited discourse so far on cross-country multisectoral collaborations in One Health.

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2. The context for a one health research project in China

China is one of the largest producers and consumers of antibiotics in the world [7] and high levels of resistant bacteria have been isolated in surveillance programmes and research studies [8–13].

The IMPACT research project is being conducted at a time when antibiotic resistance is gaining increasing attention at the highest of political levels globally, as well as in China [14,15]. The Chinese government has increasingly recognised the challenges that antibiotic resistance pose, has started to take actions across many sectors [15] and has released several policies at a national level for human healthcare [14,16]. As Xiao et al. explain, implementation of these policies have included extensive use of targets, production of guidelines and formulary restrictions, improved education, and liability assignment to institutions and even individuals [15]. There have been clear successes in reducing inappropriate antibiotic use in the past few years, but as these policies have largely been focussed on hospital care in urban areas, it is less clear how much of an effect they have had on the situation in rural populations [17,18]. These policies are linked to and embedded within China's huge and complex set of on-going healthcare reforms.

In recent years both the Ministry of Science and Technology (MOST) and Ministry of Agriculture (MOA) have begun to recognise the influence of animal husbandry on environmental ecology, with research funding being allocated to improve basic knowledge and control mechanisms [7]. National surveillance efforts have started for antibiotic resistance in bacteria from animal origins, and for drug residues on farms. The government is developing methods to monitor antibiotic use in agriculture, as well as plans to evaluate the presence of drug residues and resistance elements in the environment more broadly. The current effectiveness of policies for improving antibiotic use in animal husbandry is hindered by the extremely large populations of animals involved, fragmented systems, and the structural changes currently occurring with large scale intensive production rapidly replacing family farms and back-yard production [19,20].

Further challenges to implementation of policies relevant to antibiotic resistance in China include on-going rapid mass urbanisation, a poorly educated ageing rural population, and a lack of microbiology facilities and expertise for standardised culturing and susceptibility testing of bacteria; however, the development of national policies in several sectors, increasing scientific excellence, and rising public concern for food safety all represent opportunities to improve the situation. Furthermore, the structural changes in both human healthcare and agricultural sectors may themselves provide opportunities for improving previous behaviours and practices.

3. Collaborations between China and Sweden

Addressing antibiotic resistance has long featured on the political agenda in Sweden. This is exemplified by the early banning of antibiotics as growth promoters in animal husbandry in 1986, and by the implementation of national collaborative multisectoral policies against antibiotic resistance in 1995 (Strama, the Swedish Strategic Programme Against Antibiotic Resistance) [21]. The Swedish Government and its agencies have made substantial funding available for research projects and other initiatives that address various aspects of antibiotic resistance. This funding has frequently aimed to stimulate and support international collaborations, recognising that antibiotic resistance is a global concern, and one that cannot be managed within a single country [10,18,22–24].

In 2006, the Chinese and Swedish governments formed a Memorandum of Understanding on several areas within the health sector, and a Plan of Action specifically emphasising cooperation on antibiotic resistance was signed by the Chinese and Swedish health ministers in 2010 [25]. In 2012, a Memorandum of Understanding on agriculture cooperation was signed between the Ministry of Agriculture of China and the Ministry for Rural Affairs in Sweden, supporting enhanced cooperation and knowledge exchange within the field of antibiotic resistance and use [26].

Projects investigating antibiotic use and resistance in China were launched and reported, identifying high levels of ESBL bacteria in rural settings, gaps in knowledge about antibiotics in rural caregivers and rural doctors, and describing recent trends in antibiotic usage across several provinces [10,18,27]. The political support extended to the National Natural Science Foundation of China (NSFC) and the Swedish Research Council (SRC), who co-hosted a workshop on antibiotic resistance in Beijing in May 2013, and formed a joint funding call for research collaborations between the two countries [28]. We report here on one of the funded projects.

4. IMPACT – purpose and scope

IMPACT is a multisectoral five-year research project that investigates antibiotic use and resistance in a rural area of China using a One Health approach. This project involves institutions in China and Sweden that span several sectors (Table 1). The governmental authorities on both sides participate as scientific partners. Some of the partners have previously collaborated on smaller-scale research projects [10,18,27].

The IMPACT research project consists of epidemiological and health systems investigations, as well as laboratory analyses. It includes four phases: (i) Joint problem formulation around a One Health approach to antibiotic resistance, involving all partner institutions; (ii) A baseline situation analysis in a rural area in China, investigating the present situation of knowledge, attitudes, practices and perceptions on antibiotic use and antibiotic resistance across human, animal and environment sectors; (iii) Design and implementation of a package of multi-faceted context-specific interventions to prevent infections, improve antibiotic use in humans and animals, and limit the spread of resistant bacteria in this rural area; (iv) Evaluation of the interventions through a repeated situation analysis. The research goals of IMPACT are listed in Table 2.

We have chosen to conduct this research in a rural area because it is likely to provide a more defined and stable environment in terms of population than an urban setting would over the duration of the study. In addition, there are household pigs living in close proximity to humans, and there are good local systems in place that can help support development and implementation of interventions. The project includes a secondary care hospital in a nearby town as well as twelve villages (six intervention and six control villages), pragmatically selected from the 73 villages surrounding the central town in the selected district. In total 780 households are included in the investigations. In addition to the households, we are working with village doctors and animal health advisors in the villages, through the support from local Centers for Disease Control and Prevention. The research project will use context-adapted versions of previously used methods, including investigations of commensal microbiota from humans, animals and the environment, as well as clinical bacterial isolates from the secondary care hospital [10,22,29–31]; measurements of antibiotic use for humans and animals at household and village level, and in the secondary care hospital [32,33]; and assessments of the knowledge, attitudes, practices and perceptions of antibiotic prescribers, dispensers and consumers [27,33].

This is a mixed methods project, and the expected outcomes are both qualitative and quantitative. Examples of measurable outcomes

Table 1
Partner institutions in IMPACT.

China	Sweden
Zhejiang University (PI)	Public Health Agency of Sweden (PI)
China Agricultural University (co-PI)	Karolinska Institutet (co-PI)
Shandong University (co-PI)	Linköping University (co-PI)
Shandong Academy of Agricultural Science	National Food Agency
Shandong Center for Disease Control and Prevention	National Veterinary Institute

Table 2
Research goals of IMPACT.

- To increase basic knowledge and understanding of the complex routes of dissemination of antibiotic resistance between different sectors (humans, animals and the environment) by a multisectoral and bilateral approach
  - To increase basic knowledge and understanding of factors contributing to irrational use of antibiotics in humans and animals
  - To integrate the resultant knowledge with existing evidence to design and pilot interventions aiming to limit development and spread of antibiotic resistance
  - To promote adequate infection prevention and control and access to effective antibiotics for humans and animals for improved public and animal health and consequently efficient, sustainable animal food production

are prevalence of resistance within each sector (humans, animals and environment) and overlap of resistance phenotypes and genotypes between sectors. Other measurable outcomes include assessing the relationship between presence of a backyard farm in households and the residents' knowledge, attitudes and practices regarding antibiotics; quantifying monthly household usage of antibiotic for humans and pigs; and describing patterns of antibiotics prescribed in village clinics. Results will be compared before and after the multifaceted intervention and between intervention and control villages. Furthermore, we anticipate that the local infrastructure and collaborations created to deliver the One Health intervention can be used in future efforts to improve antibiotic use and contain antibiotic resistance.

5. Operationalising one health

The world has become deeply interconnected: we observe mass movements of humans and global trade of food, with an increase in urban centers and the formation of funnel points in the food production industry. A One Health approach is now needed to help develop our understanding of antibiotic resistance [1,2]. The World Health Organisation (WHO), World Organisation for Animal Health (OIE) and the Food and Agriculture Organisation of the United Nations (FAO) all recognise the centrality for One Health approaches in tackling antibiotic resistance, as demonstrated by the tripartite concept note and the WHO global action plan on antibiotic resistance, where the OIE and FAO have distinct roles [34–37].

At its heart, One Health is a collaborative effort [5,6]. How we interpret and operationalise this collaborative effort in real world research has important implications for the value that IMPACT can deliver. Single discipline and multidisciplinary investigations are vital to generate knowledge relevant to specific situations; integrating the results to produce a deeper understanding of the underlying dynamics as well as tentative solutions is an additional challenge. Cross-disciplinary thinking can more easily recognise how different structures and feedback loops are shared between disciplines [38–40]. As examples, a rural farmer's understanding of antibiotic use in his pigs will likely have implications for how he treats his children when they are ill; and drugstore regulations designed to improve antibiotic use in humans may have consequences for antibiotic use in animals if they are introduced in drugstores that serve both markets.

Our intention of using a multisectoral approach in IMPACT is to address important research questions that individual discipline investigations are not able to, either through observational evidence or methodological developments. By using a One Health approach the interventions, for instance, will be strengthened by being more holistic and realistic. As an example, we will design education sessions on human hygiene together with sessions on hygiene in household farms. Examples of research questions within IMPACT are “Who influences total antibiotic use within a community, and what are their knowledge and attitudes towards antibiotic resistance?”; “How do antibiotic drugs ‘move’ within a selected geographical area?”; “To what extent are clones of resistant bacteria and genetic resistance elements similar within and between different sectors and geographical locations?” and “What are the similarities/differences of clones of resistant bacteria and genetic resistance elements between people, animals and the environment?”.

6. Challenges of cross-country cross-disciplinary one health collaborations

As cross-disciplinary One Health research programmes are a relatively recent concept, there are few published reports that can help guide the development of a new project. Min et al. conducted a scoping review of the limited literature and identified key elements contributing to the challenges and successes of such projects (see Table 3) [41]. Using this as a framework, we present some of our experiences from the first two years of the IMPACT project, and mention two additional themes that we feel are particularly relevant to international collaborations in this context: *culture* and *geographical separation*.

6.1. Communication

Effective communication is central to the success of IMPACT, but also lies at the root of some of the challenges encountered. Crucially, the majority of our communication cannot take place in person. So far we have organised annual meetings in China and Sweden, attended by all

Table 3
Successes and challenges of the IMPACT project, and our strategies to meet the challenges.

Successes and challenges of One Health research projects [41]	Strategies to meet the challenges
Effective communication	• Annual meetings attended by all, including educational presentations, training workshops, and site visits • Separate meetings to review progress • Day to day communication centred on the working groups (online conferencing, telephone calls and email)
Education	• Educational sessions at annual meetings help share discipline-specific terminologies, methodologies and experiences; particularly important for junior members
Conflict among disciplines	• The project includes a large group of researchers who have interpersonal characteristics conducive to collaboration perhaps as a result of careful initial selection • We aim to give all sectors equal importance
Shared conceptual frameworks	• The most important conceptual framework has been elaborating the value of a One Health approach, and this has been presented at several meetings • Joint protocols, including protocols for laboratory work
Leadership	• The collaboration includes two PIs (one in China, one in Sweden), supported by four co-PIs (two in China, two in Sweden) • Each working group has one named leader in China and one in Sweden
Perceived power differentials	• Differences often manifest through invisible features of work and daily interaction, and a key undertaking is to make these features more visible to individual researchers, to reduce the potential feelings of division
Community-based methodologies	• We collaborate with local practitioners to organise infrastructural support
Time and effort required for maintaining and establishing research teams	• We have found time to be a necessary investment, with a period of over twelve months elapsing between funds being awarded and the first samples being collected • The establishment of smaller working groups (see Table 4) was crucial
Support for transdisciplinary research	• Financial support for the project was granted • Early in the research development process we discussed expected publications, and how individual contributions might be recognised

individuals involved in IMPACT, as well as several separate visits with smaller numbers of researchers to focus on specific project tasks. The annual meetings include educational presentations, training workshops, and site visits. Chinese institutions and Swedish institutions have also met separately, roughly every six months to review progress. Day to day communication between these larger meetings is centred on working groups that are responsible for different project components (see Table 4 for a list of working groups prior to the first data collection; the composition was then adapted for the analytical phase). Most researchers are members of multiple working groups. These groups have used online conferencing, telephone calls and email. The discussions are mostly conducted in English, with Chinese translation when needed. The complexity of the project means that individuals have occasionally not been available to take part in certain conversations, so there is a regular need for reviews to ensure that everyone is aware of key developments.

China and Sweden are separated by 7000 km and a time difference of six or seven (7) hours, depending on the time of year. These distances exacerbate several of the challenges described above, in particular our communication. We interact less frequently than we would with a smaller separation, and we make more use of communication methods such as email that are asynchronous. Our exchanges often proceed in step-like increments rather than flowing as a conversation; we also rely more heavily on the textual content of messages than on nonverbal contents such as tone of expression and body language [42], and this has sometimes led to communication errors. We must also recognise that international research collaborations have a crucial role to play in supporting the transfer of research methodologies between geographically separated settings, despite these challenges [43].

6.2. Meeting the challenges

We have used educational sessions at our annual meetings to help share discipline-specific terminologies, methodologies and experiences and to move towards common understanding of the complex issues at hand. This has been particularly important for the junior members of the research teams, many of whom have little previous exposure to other disciplines. Conceptual frameworks were discussed in the drafting of the original funding application. It has been useful to subsequently return to these, particularly when a single discipline would usually investigate a research question in a different manner. The most important conceptual framework has been elaborating the value of a One Health approach, and this has been presented at several meetings.

The IMPACT collaboration includes two principal investigators (PIs), one in China and one in Sweden, who maintain the project's focus on the bigger picture. They are supported by four co-PIs (two in China, two in Sweden). The PI/co-PI group holds monthly meetings, and the minutes are shared with all IMPACT researchers for transparency and trust. In addition, each working group has one named leader in China and one in Sweden. We also have a senior advisor who focuses more on broader observations of the project and its progress.

Many researchers have reported that additional time and effort is needed when conducting cross-disciplinary research [41]. We have also found this to be a necessary investment, with a period of over twelve months elapsing between funds being awarded and the first samples being collected. There was a mixture of expectations among different partners as to how long this period would take, recognising that certain project components require longer to plan than others. In retrospect, it would have helped for us to be more open about our different expectations early on. We have found that reporting requirements set by some funders do not currently recognise the need for such a long period of planning in large collaborative projects. This time and effort also brings opportunities: innovations frequently occur at disciplinary interfaces, side projects may develop within the main project, and smaller collaborations may emerge that will outlast the formal research project.

As Larson et al. describe, we become socialised professionally in different ways as researchers [44]. These differences often manifest through invisible features of work and daily interaction, such as preferred length of meeting times, comfort with uncertainty, and positioning of junior members within a research team. International collaborations face the additional challenge of individuals working and communicating from different cultural backgrounds. A key undertaking is to make these features more visible to individual researchers. This can help reduce the potential feelings of division that arise between individuals from different countries, as well as the frustration from being unable to identify where the tensions originate.

As the number and diversity of participants in a cross-disciplinary collaboration increases, the project naturally becomes more complex. Participants are not passive, however, so it can start to behave as its own *complex adaptive system* that evolves over the course of the research project [45,46]. As the collaboration grows in size there is a risk that any one person feels less individual responsibility and ownership for the whole, particularly when many components are outside their area of expertise. In many ways the success and survival of the collaboration is dependent on purposefully cultivating an ability within the complex adaptive system to respond to the various challenges it may encounter. This requires effective management of information flows between all sub-systems and individuals, combined with an on-going awareness of the role each person is playing in the wider system.

Table 4
Working groups in IMPACT, prior to first data collection.

- Location and participant selection working group
- Questionnaire development working group
- Antibiotic usage data working group
- Hospital working group
- Microbiology and media selection working group
- Environment working group
- Logistics working group
- Data labelling working group

7. Conclusions and implications

Resistant bacteria, genetic resistance elements and antibiotics are not limited by disciplinary or geographical boundaries. Multisectoral research collaborations such as IMPACT mirror this concept, and are encouraged by the recent shift towards the One Health approach in addressing antibiotic resistance.

In today's globalised world the individual researcher is increasingly working in large multi-disciplinary or multisectoral consortia. Challenges in such collaborations require researchers to be open-minded and less concerned with protecting their own scientific area. Everybody involved in the IMPACT project, at all levels in China as well as in Sweden, have been made aware of the challenges in working internationally and across sectors, as we tackle these meta-questions in a transparent and structured way. Succeeding in this “project within the project” is a prerequisite for obtaining results that have a true impact on the continued global engagement against the spread of antibiotic resistance.

Conflicts of interest

None.

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