Irrational use of antibiotics in Iran from the Perspective of Complex Adaptive Systems: redefining the challenge

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Abstract

Background: Irrational use of antibiotics proves major concerns to the health systems globally. It results in antibiotics resistance and increases health care costs. In Iran, many years of research, appreciable efforts and policy making have been of little avail and indicators still show suboptimal use of antibiotics, pointing out an urgent need to alternative approach to understand the problem and generate new solutions. Applying the Complex Adaptive Systems theory, to explore and research in health systems and their challenges and has become popular. Therefore, this study was aimed to better understand the complexity of irrational use of antibiotic use in Iran and the potential solutions.

Method: This research utilized a CAS observatory tool to qualitatively collect and analysis data. Many interviews with key informants were conducted. The data was enriched with documents reviews in order to fully understand the system. MAXQDA software was applied to organize and analyze the data.

Result: We could identify several diverse and heterogeneous, yet highly interdependent agents in the antibiotic consumption system in Iran, operating at different levels. The network structure and its adaptive emergent behaviour, information flow, governing rules, feedbacks and values of the system and the way they interact were identified. The gaps and weakness of the system which needs redesigning or modification were recognized as well. Findings describe antibiotic use as an emerge behavior of the system which is formed by interplay of many factors and actors over time.

Conclusion: The study suggests re-engineering the system by implementing several system level changes including establishing strong, timely and effective interactions between identified stakeholders which facilitate information flow and provision of on time feedbacks, create win-win rules in participatory manner with stakeholders and distributed control system.

Background

Irrational use of medicines poses a formidable challenge to health systems in many countries [1–4]. The practice includes over- or under-prescription, inappropriate self-medication, polypharmacy, incomplete course of medications, overuse of antibiotics and injectable drugs, and non-adherence to clinical guidelines [3, 5, 6]. The World Health Organization (WHO) has ominously warned that still “more than half of all medicines are prescribed, dispensed or sold inappropriately, and half of all patients fail to take medicines prescribed to them correctly”[7]. The far-reaching consequences of irrational use of antibiotics can range from increased morbidity and mortality, enhanced medication errors, increased health care costs, to patients’ mistrust in physicians and health care authorities [7–9]. Among all medicine categories, irrational use of antibiotics has brought about additional undesirable health outcomes like bacterial treatment failure and antibiotic resistance [10–12]. However, despite the enormity of the problem, it has remained a substantial public health problem globally, not least in developing countries [13, 14].

Even with many appreciable efforts to promote the rational use of antibiotics in Iran such as establishing The National Committee on Rational Use of Drugs (NCRUD) and codifying some regulations and guidelines, indicators still continue to show suboptimal prescription and use of antibiotics in Iran [15]. For example, the number of prescriptions including antibiotics is still above the national and international standards. Some

studies have explored the current situation of irrational use of antibiotics in Iran [11, 15–18], pointing out the insufficiency of previous efforts in improving the status quo and, subsequently, the necessity of a shift in policymaking and defining the problem.

Recently, providing healthcare services has shifted from a single prescriber and user in a single setting to multiple providers and users at different levels of settings, confronting health care systems with many unexpectedly complexities and challenges [19]. In fact, like most health problems, irrational use of antibiotics often stems from its multi-disciplinary and complex nature so it should not be reduced to linear root causes [20]. Generally, classic approaches to solving health problems are inadequate as they often tend to ignore the subtle inherent complexities of the problem in favor of its easily visible features [21]. Therefore, in the face of such baffling complexities, achieving public health goal would definitely require going beyond overly simplistic notions [22].

Health systems can be a classic embodiment of a complex system as they involve many autonomous but connected and even dependent actors at different settings, changing is continuous, many feedback loops are running, and the effect of a single intervention in one part may be observed in other parts of the system [23]. Recently complexity science approach to health, settings and organizations has emerged as a promising approach which can provide a more thorough understanding of complex health issues [24–29]. Similarly, applying the Complex Adaptive Systems (CAS) theory, a derivative of complexity science to understand, explore, scale up, evaluate and research in health systems has become popular with researchers in recent years [22, 30–33].

CAS characteristics

- *A multi-agent system with many interactions*

Divers interactive agents are the very substantial part of healthcare systems with power in shaping the system, its behaviour and making decisions [23, 34]. These agents, considered as systems in their own turn, can be a part of other systems [24, 35]. As a result, agents are interacting in a nested, multilevel, and networked system. The interactions between agents in CAS are commonly non-linear [27].

- *A dynamic system with ever-adapting and learning agents*

Agents and whole system alter their behaviors and interactions according to the characteristics of other agents and the impact of external circumstances, in other words they adapt to new conditions [22, 36, 37].The interactions between multi agents, feedback mechanisms and flow of information are key learning sources and drivers of adaptation which is an essential phenomenon in CAS [24]. Continuous adaptation and intermittent changes cause systems to be more dynamic than static.

- *De-central control of the agents*

Agents' autonomous behavior, non-linear interactions and dynamic nature make the central and full control of the system impossible [38]. The outputs of CASs are more yielded from a process of self-organization rather than hierarchical external control [24]. It can be very common for CASs to expose little response to many controlling efforts, or to show a big change in response to a tipping point [27].

- *A system with emergence behavior*

One of the pivotal characteristics that defines a CAS is emergence [33]. The core concept of this feature is that the whole behavior of the system is probably greater and more complex than the sum of individual behaviors [22, 37]. The interplay of elements results in a behavior in the whole system, which cannot be easily observed and predicted [24, 39, 40].

Although health care systems have been acknowledged as CAS by many scientists [23, 26, 27, 29, 36, 39, 41], it seems that it has rarely been translated into practice. Considering a paradigm shift toward description of health care systems as complex systems in recent years and insufficiency of the traditional approaches, it is therefore worthwhile to explore the premises of complexity science to approach health care problems. In fact, there has been little exploration of the potential benefits of the application of CAS to better analyze and provide policy and practical recommendations for the irrational use of antibiotics. Drawing upon the CAS observatory tool, this study aims to observe and prescribe the problem in the healthcare system of Iran through the lens of CAS, and apply the CAS explanatory capability to explain, understand and refine the issue and the system emergent behaviours all in order to provide complexity-informed recommendations for policy and practice.

Methods

The study was designed as a qualitative research utilizing qualitative data collection and analysis methods. Qualitative methods are suitable to explore and explain complex social phenomena as well as social complex systems [42]. They can help us understand social complex issues and address processes that arise over time. Complex Adaptive System theory was utilized to guide formulation of research questions, data collection and analysis. The study used the CAS observatory and explanatory tool[24], which consists of the following five items:

1. Identification of agents, interactions, and system structure
2. Description of the information flow in the system
3. Distinction of feedback loops
4. Recognition of rules and values that run in the system
5. Exploration of adaptation, self-organized and emergent behavior of agents

This study conducted two qualitative data collection methodologies: (I) semi-structured interview to collect data form individuals and (II) Focus Group Discussion (FGD) designed to discuss the use of antibiotics with those who we assumed might express their opinions in a group discussion more openly and comfortably. According to CAS observatory tool the probing questions for interviews and FGD were developed [see supplementary file]. Additionally, interviewees were free to state additional viewpoints on the topic so that we could get more in-depth views of the participants. Having reviewed the available relevant literature, we identified five key agent types at different levels of antibiotics use in Iran as follows: 1.Policy makers, 2.Prescribers, 3.Producers and distributors, 4.Trainers and researchers, 5. Patients or consumers. The first four levels were chosen to be interviewed and the last, i.e. patients or consumers, were assigned to FGD. This categorization provided a holistic understanding of the issue and captured previously unmet and unexplored aspects of the rational use of antibiotics.

Ethical approval was obtained from the Institutional Research Ethics Committee School of Pharmacy and Nursing & Midwifery – Shahid Beheshti University of Medical Sciences. All interviewees provided verbal informed consent in order to participate and audiotape of interview or FGD.

Altogether, twenty interviews and two FGDs were conducted. Data collection was carried out from December 2017 to August 2018. All transcriptions of both interviews and FGDs supplied rich material for analysis. Qualitative analysis of the data was facilitated through MAXQDA 2018 software. The core notions of the CAS observatory framework, as introduced earlier, constituted the main concepts of analysis (thematic analysis). The validity of coding was improved through analyst triangulation, three researchers cross-coded the raw material and discussed the analysis at regular intervals.

Results

We first present an overview of the irrational use of antibiotics in Iran and, then, describe the system as a CAS using the CAS observatory tool.

An overview of the irrational use of antibiotics in Iran

Generally, the irrational use of antibiotics in Iran was acknowledged by almost all interviewees, although some also believed that some progress had been achieved in recent years. The total percentage of prescriptions containing antibiotics has decreased, some new pharmaceutical protocols have just been enforced in hospitals to rationalize the use of most expensive antibiotics and many researches have been done in this field. Nevertheless, the participants pointed to so many case of the irrational use of antibiotics. Patients' adherence to antibiotic therapy is estimated medium to low, they do not follow the instructions properly and do not complete the antibiotics therapy course. Antibiotics self-medication is prevalent especially when patients suffer from common cold. Many community pharmacies deliver antibiotics to patients and customers without prescription and therefore antibiotics are easily accessible to public. Physicians usually prescribe antibiotics irrespective of medical guidelines or laboratory tests because of some constraints such as time and patients' insistence. These constraints sometimes lead to inappropriate dosing, improper combination therapy and irrational prescription of injectable antibiotics. All these behaviors have ultimately culminated in a high incidence of antibiotic resistance.

Antibiotics use system as a CAS

Agents and their interactions

We identified several diverse and heterogeneous agents regarding the use of antibiotics in Iran, organized in subsystems or groups like medical universities, hospitals, patients, etc. Moreover, some interviewees suggested that significant diversity could be seen in similar agents. For instance, physicians, pharmacists and patients' perception and behavior related to antibiotics are not always similar as they stem from different level of knowledge or attitude, experiences and individual and organizational governing values and rules.

All these agents can fall into two major categories: supply-oriented agents and demand-oriented agents. Supply-oriented agents refer to all agents that can provide antibiotics to end users (can be patients or not) or play a role in the process of supplying, for instance by regulating the procedures or training physicians. Demand-oriented agents, on the other hand, refer to all agents that are prone to use antibiotics, both prescribed and unprescribed,

or, like the media, can alter the behavior of antibiotic use in either side. It should also be noted that some agents like physicians can be fuzzy members of both categories as they can affect both the supply and demand sides of antibiotic use. Within these arrangements, agents can be characterized by their properties, role, importance or power and objectives [see Table 1 file].

Table 1- Agents, their properties, role, power, and objectives

Agents or subsystems		Role	Related components	Importance/power	Objectives/ incentives
-d	Ministry of health and medical education (MOH)	It is the main policy-making and stewardship agent that decides about macro health policies. It also regulates and finances all service provisions in healthcare	Deputy of curative affairs, deputy of education and deputy for health. Some components like medical universities existing all provinces all around the country, are defined as a major and separate agent.	The most important governmental agent that oversees all the actions and processes in health care system and is in charge of all things related to public health.	Providing health and hygiene to all citizens.
	Iran Food And Drug Administration (IFDA)	Supervising and regulating all the processes of manufacturing, distributing, and use of antibiotics. It is authorized and financed by MOH	The National Committee on Rational Use of Drugs (NCRUD), General directorate of Pharmaceutical and narcotic affairs	It is the most substantial supervisory body that directly controls all the processes of supply and access to antibiotics. It makes policies related to access to antibiotics and compiles pharmaceutical guidelines through collaborating with other related bodies. It is also responsible for the rational use of all drugs, especially antibiotics.	Enabling access to effective and safe medicines in a rational way.
	Basic health Insurance companies	They reimburse antibiotic drugs.	There are three major basic public insurance companies in Iran. Besides National health Insurance called Iran Health Insurance Organization (IHIO) and Social Security Insurance (SSI), there is also	They are the main enforcing levers of health policies in Iran. They can rationalize the use of antibiotics by developing limitations and special regulations for reimbursing antibiotics.	Trying to minimize their cost.

		Ministry of Defense Health Insurance Organization. There are also many private insurance companies, but they are not usually considered as major players		
Medical universities	They are authorized by MOH. They educate and train physicians, pharmacists, specialists, and other healthcare professionals who can order or deliver antibiotics.	Vice chancellor of Food and Drug administration in medical universities, Educational hospitals and pharmacies, professors, students and medical residents	The power of medical universities is pretty high because MOH and IFDA enforce their supervision of prescribing and delivering antibiotics through Food and Drug Departments of different medical universities. All departments have a RUD committee. They periodically check upon physicians under their supervision to ensure their acceptable prescription practices and provide feedback to them. Additionally, they play a critical role in promoting physicians and pharmacists' knowledge and practice of antibiotics by continuing medical education (CME) programs. they can also supervise all promotional activities of pharmaceutical companies in hospitals,	Training qualified and knowledgeable physicians, pharmacists and other health care professional. Helping health care professionals maintain competence and learn about new and developing areas of their field.

			pharmacies and clinics, etc.	
Research centers	Conducting clinical and non-clinical researches related to the rational use of antibiotics.	-	The outcome of their researches may influence two main processes: policy-making and antibiotic prescription.	Communicating and collaborating with policy-makers and prescribers adequately. Carrying out feasible and practical researches.
Islamic Republic of Iran Medical Council (IRIMC)	IRIMC is the largest national non-governmental organization in which all health care professionals (except nurses) have to register to be granted permission to practice in the country. It regulates health care professionals' collaborations with other associations. It has developed many regulations and guidelines related to medical practice standards.	It has more than 190 branches all over the country in different cities.	It can play an important supervisory role in physicians and pharmacists' practices. Additionally, it can affect the physicians' prescription behaviors through their contribution to the development and enforcement of guidelines as well as educational programs.	Improving and modifying medical affairs in Iran. Supporting patients' and health care professionals' rights. Promoting medical knowledge in Iran.
Scientific and guild NGOs	Providing educational and research services. They support healthcare professionals' rights.	Many scientific and non-scientific NGOs are practicing in different fields of medical sciences.	They play a significant role in other health care professionals' behavior such as nurses, dentists, etc. They also enforce regulations, influence antibiotic prescription practices, and make connections between different groups of healthcare professionals.	Improving education, training and research services. Protecting physicians and pharmacists' monetary and non-monetary rights.
Pharmaceutical companies	Producing or importing necessary pharmaceuticals of the country. Introducing, providing and promoting antibiotics to prescribers and pharmacies through diverse promotional activities.	It includes many manufacturing and importing companies.	They can highly affect both demand and especially supply sides of the antibiotic market. They promote their products through different ways such as giving free samples,	Making more profit through grabbing and maintaining more market share.

			discounts, gifts, etc.	
Prescribers	They prescribe antibiotics to the patients.	It includes physicians (General Practitioners or specialists), dentists and midwives.	After MOH, they are the second important agent in both supply- and demand-oriented group agents. They determine the number and quality of antibiotic prescription.	A wide range of interests from enhancing rational use of antibiotics and patients' quality of life to monetary objectives and visiting more patients.
Hospitals	Providing in-patient care service and also most of the time, out-patients' services.	Physicians, nurses, clinical pharmacists, Pharm-D, pharmacotherapy committee, and antibiotics stewardship committee	Their practice highly affects the volume and the quality use of a wide spectrum of injectable antibiotics.	Controlling antibiotic use, improving the rational use of antibiotics in order to prevent antimicrobial resistance at hospitals
pharmacists	Delivering antibiotics to patients and to the general public. They also have to explain and give consultation to patients about the use of antibiotics in terms of how to use, interactions and side effects, etc.	-	Irrespective of codes of action, they sometimes provide antibiotics to the public and patients over the counter. They occasionally collaborate with pharmaceutical companies to sell more antibiotics. They can also collaborate with physicians to prescribe more antibiotics.	Providing good service delivery and maximizing their profit.
mass media	Improving public knowledge about antibiotics through educational programs and contents.	TV, social networks like Instagram, telegram, Facebook, etc.	They can highly affect public knowledge, attitudes about antibiotics. They also help to modify the general public's life style and alter their perception of antibiotics, physicians and pharmacists.	To attract and maintain more audiences.
Patients and public	use antibiotics (final consumer)	Patients, patients' families	They are the most important agent	Living better and more comfortably.

			and friends, public population	on the demand-side. Their health literacy, knowledge, perceptions, expectations and experiences highly affect antibiotic use.	Having the best treatment in the world for their illnesses. Having the lowest cost services.

After the original mapping of agents, we could breaking down the whole system into four circles as layers or subsystems, into four interdependent layers as subsystems (Fig1). Circle 1 comprises of Ministry of Health (MOH), Iran Food and Drug Administration (IFDA) and insurance companies that make policies, regulate the system, reimburse and provide access to antibiotics. Circle 2 consists of those agents who monitor the implementation of regulations and guidelines, help circle 1 to enforce the regulation and make better policies by providing necessary evidence. Circle 3 includes pharmaceutical companies and pharmacies who produce and distribute antibiotics. However, the core functions of supply and use of antibiotics take place in circle 4. Physicians include general practitioners and specialists, patients, public population, pharmacies and hospitals are overlaid by this circle. Although these circles are operating at different levels and can be broken up, they are highly interdependent with overlaps. Most participants argued that most of current solutions to tackle the irrational use of antibiotics in Iran have failed to adequately take into account all agents, their role and power.

"See Fig1. Subsystems of antibiotic use in Iran"

Nested structured Interaction

Data analysis showed that there are diverse and several interactions and interaction patterns between agents (stakeholders) in antibiotic use in Iran, playing out in a nested structure and also a network system. These interaction identified to be influential in decision making and behaviours in regard to prescription or use of antibiotics, based on rules enforced or information exchanged through these interactions.

We identified three patterns of interactions between agents. Type one represents governance and supervisory-oriented top-down relationships that regulate the activities, supervise the procedures and finance or reimburse medical costs; a good case in point can be several formal governance-oriented and rule-based relationships of MOH with IFDA, top down interactions of medical universities with hospitals, or financial and legal relationships of insurance companies with physicians and pharmacies regarding the reimbursement of service provision and medical costs. Type two represents interactions related to service provision, where the main action of antibiotic consumption occurs. Several informal and formal relationships between physicians, pharmacists, patients and hospitals are subsumed under this rather broad category. Finally, type three embodies reciprocal relationships, where agents have interactions based on professional collaboration or contract-based corporation. For instance, there are collaborative interactions between MOH and IFDA with medical universities and research centers, pharmaceutical companies contract research centers to conduct their clinical trial researches, IFDA have interaction with scientific Non-Governmental Organizations (NGOs) or Islamic Republic of Iran Medical Council (IRIMC) or academia, insurance companies send prescription information which IFDA or MOH or medical universities have requested, hospitals can provide data and information which research centers and medical

universities need for their researches, and pharmaceutical companies have many formal and informal relationships with physicians and pharmacies. Through all these types of interactions, information and financial resources get exchanged, regulations are enforced and antibiotics are delivered to patients or the general public as a whole. Figure 2 shows the contribution of agents' interactions to the formation of a nested and multilevel system.

"See Fig2. Main agents' interactions in antibiotic use in Iran and their contribution to the formation a networked interaction structure

Many participants believed that interactions between key stakeholders in antibiotic use system in Iran were often insufficient, ineffective or non-systematic. For example, interviewees made a point of highlighting the discontinuous and insufficient reciprocal interactions between research centers and policy-making entities like MOH, IFDA, insurance companies and research centers. Inadequate interactions of IFDA with other agents such as IRIMC were mentioned by majority of participants. Lack of adequate supervision on prescribing and delivering antibiotics, incomplete implementation of programs and improper enforcement of rules and regulations were identified as the consequences of current ineffective interactions and inadequate coordination between different parts of the MOH and the whole system of antibiotics use in Iran.

Information flow

Almost all respondents were dissatisfied with the current information flow of the system. Data analysis showed Information regarding antibiotic use circulates inefficiently and inadequately through the systems. For example, insurance companies send prescription-related information to IFDA or MOH, but there have been some logistic problems in recent years that have impeded data transformation. MOH and IFDA not always receive information about antibiotic use statistics from hospitals or medical universities, and some participants revealed that this information flow was sporadic and erratic. Many people in FGDs complained about the incomplete information about antibiotic use imparted to them by physicians and pharmacists. Physicians and pharmacists are supposed to educate patients about the administration of antibiotics and how they should be used while they are prescribing and delivering antibiotics. These improper relationships of patients with physicians and pharmacists may consequently lead to irrational use of antibiotics, as an instance patients do not complete treatment course and discontinue antibiotics use as they get better. Respondents working for research centers or scientific NGOs stated that despite their willingness to collaborate with IFDA or MOH to conduct useful researches and participate in health decision making, the stage had not been set for the smooth flow.

Moreover, many participants criticized the quality and accuracy of information about antibiotics production and distribution run in the system, caused by ineffective and insufficient interaction between IFDA and pharmaceutical companies. Some interviewees argued that sometimes information circulation is done through informal and non-documented channels, and so much of officially documented information exchange slips unnoticed. Additionally, there are some logistic obstacles in the way of data collection and information integration that have made the information flow problematic.

Feedback loops

The main identified formal feedback mechanism in the system of antibiotic use in Iran is about antibiotic prescription information which is yielded through analyzing physicians' prescription and mostly prepared by

basic insurance companies. Such information is sent from insurance companies to IFDA or the vice chancellor of the Food and Drug administration in different medical universities. They report RUD indicators such as the mean item per prescription and the percentage of prescriptions containing antibiotics. Analyzing this information, regulatory bodies evaluate their programs and the effectiveness of their practices toward the rational use of antibiotics. In some cases, they send feedback reports to physicians who have not met prescription indicators and ask them to adhere to guidelines and regulations. Moreover, no systematic feedback mechanisms were identified from MOH, IFDA or insurance companies to prescribers and other practitioners or vice versa in the system

There are some informal and even not easily observable feedbacks that form the behavior of the system as follows:

Antibiotic resistance, caused by irrational use in human and many other variables not included in this study, increases treatment failure of infectious diseases and so decreases patients' proper experience with antibiotics. This in turn can negatively influence patients' adherence to the treatment course, encouraging them to discontinue antibiotic therapy, or consume more potent antibiotics, and also may decrease physicians' adherence to medical guidelines, which can in turn increase irrational prescription of antibiotics and the threat of antibiotics resistance.

Patients' experience with previously used antibiotics may affect the patient-doctor relationship and their trust in physicians as well. Many respondents said that in many cases physicians prescribe antibiotics irrationally because patients do not trust them and insist on receiving newer or more antibiotics. Physicians may receive feedback from patients who are prescribed antibiotics by following their therapeutic responses and observing their symptoms. The patient-doctor relationship influences patients' tendency toward visiting physicians and can cause more self-medication tendency with antibiotics, which can in turn reinforce the quality of the patient-doctor relationship through irrational use of antibiotics and more treatment failure. In addition, providing antibiotics over the counter worsens self-medication through increasing public access to antibiotics without prescription.

Rules and values

Different types of formal rules are identified in antibiotic use including pharmaceutical and medical guidelines and protocols, WHO and international guidelines, laws of IRIMC, codes and regulations of insurance companies, and codes of actions and regulations developed by MOH. Most of them are authorized by MOH and publicly accessible. However, it was identified that they are not always followed by the agents.

Interviewees who were clinical pharmacists argued that not all physicians easily adhere to evidence-based medicine and collaborate with clinical pharmacists to change their antibiotic prescriptions. Some defy pharmaceutical guidelines and dismiss them in favor of their own experiences. Clinical pharmacists believed that physicians' different following rules behaviors may be also influenced by their prior interaction with pharmacists, and also health authorities.

Prescription and use of antibiotics were governed by the agents' perception of formal rules, which can be termed internalized rules. According to some participants, physicians and patients follow their internalized rules more obediently than central and formal regulations. Even some sub systems like hospitals have their own

internalized official regulations and guidelines. For example, some hospitals have developed their own regulations and guidelines about infectious disease, derived from formal regulations and adapted to their contextual properties. We observed that pharmaceutical protocols were performing well in some private and public hospitals and were accepted by clinical pharmacists and Infectious disease specialists. However, some hospitals dismissed them because they believed pharmaceutical protocols should be internally developed on the basis of the internal context of hospitals or there should be a reasonable room for change and adaptation.

However, results of the study revealed that this self-organizational behavior of sub systems are not well regarded by regulatory bodies in Iran.

In addition to rules, organizational, professional and individual values were also recognized as contributing to governing certain types of behavior. They included organizational, professional and individual values. For example, insurance companies have clear and well-established credit and blame mechanisms which aim to restrict physicians' over-prescription of antibiotics. Most participants agreed that rational use of antibiotics greatly matters to governmental authorities due to the significance of antimicrobial resistance, which partly explains the establishment of Rational Use of Drugs committees in vice chancellors of Food and Drug administration and hospitals. Likewise, among RUD indicators, the antibiotic use standard has always been an important indicator for MOH. However, it seemed to be controversial, some respondents argued that the importance of RUD committees had declined for MOH and antibiotics have lost their priority. For example, except in insurance companies, there are no credit or blame mechanisms in governmental organizations related to the rational use of antibiotics and many respondents believed that their efforts to rationalize antibiotics use were not appreciated as much as they deserved. Some argued that the reason of failure to achieve the whole goals of NCRUD was the lack of support of its organizational position by MOH.

In addition to organizational and professional values, individual values also influence the patients and physicians' behaviour in regard to antibiotics. For example, some interviewees stated that sometimes people including physicians may have enough knowledge about the importance of rational use of antibiotics but their knowledge did not translate into attitude and practice.

Some participants noted that the magnitude of the rational use of medicines varies from person to person among policy makers and health care managers. During some periods of times, it might have attracted considerable attention and, under a different person's management, it might have been consigned to oblivion.

Dependent, diverse and multifactorial behaviors different of agents

We classified four major behaviors in antibiotic use system conducted by key agents, all influenced by their information, rules, values, resources, feedbacks and interaction with other agents.

Physicians' prescription behaviours- Variation in physicians' prescription behavior was expressed by a wide range of participants. Generally all participants believed that physicians' prescription behavior is influenced by the quality of their interactions with patients, like their efforts to satisfy patients. Patients' satisfaction seemed to be more important in contexts where physicians compete for more patients and more income. Noting the effect of context, some FGD participants believed that physicians exhibit different behaviors in public and private sectors. Additionally, some physicians argued that they are faced with time constraints in some settings and do not have enough time to explain and convince patients that they do not need antibiotics. However, some

people in FGDs reported contrary experiences with physicians who had spent reasonable time visiting them in spite of a long queue of patients. These co-evolutionary physicians' behaviors makes difficulties to predict the emergent behaviour of the whole system

Pharmaceutical companies and pharmacies behaviors- Data analysis of information provided by this study indicated that the behaviors of pharmaceutical companies and community pharmacies depend on many factors which may not necessarily be relevant to their knowledge, the health care system or its rules, and may even be exogenous to it. For example, their practices are highly dependent on their income and so the economic, political and even the international communication conditions of the country. In recent years, some technical and international communication problems have impeded pharmaceutical export and many pharmaceutical companies have lost their niche market in the Middle East. As a result, they have produced antibiotics in excess of domestic use such that their inventories overflow with antibiotics, and so more efforts to sell antibiotics. Besides external limitations, there have been some restrictions imposed by MOH and IFDA on the procurement of the active pharmaceutical ingredients of antibiotics and pharmaceutical pricing, which can in turn further compound the situation. These forces altogether have driven companies to adapt themselves to an unpleasant situation by enhancing antibiotic sales through promotional activities. It was reported by participants that pharmaceutical companies sometimes provide some products like antibiotics free of charge to pharmacies as part of their promotional activities, offering financial incentives for physicians to over-prescribe antibiotics. These promotional activities seemed to be the most pressing concern repeated by almost all policy makers and prescribers interviewed in this study. On the other hand, economic pressures encourage pharmacies more to deliver antibiotics over the counter to the public in order to increase their revenues. Although these marketing strategies have increased the total use of antibiotics, they can be understood as an adapting behavior of companies and pharmacies.

Policy making and implementation behaviors- Several interviewees discussed that depending on policy makers' willingness to earn short-term outcomes, personal preferences, characteristics and responsibility, contextual constraints and experiences, they may show different behaviors at different health care settings. In addition to personal preferences, it was argued that occasional crises, the context and limitations has led to different rule adherence behaviors.

Patients' antibiotic use behavior- Data analysis revealed that antibiotic consumption behaviour of people are determined by many factors such as socio-economic situation, their perception of and belief in physicians, their perception of self-medication, antibiotics benefits and hazards, and their medical history. For example, some participants choose supplementary medicines and herbal pharmaceuticals when they catch a cold because they believe that herbal pharmaceuticals are more effective than antibiotics and chemical medicines; however, some others cannot implicitly trust herbal medicines because of their unknown side effects. According to their experiences, some people believed in the efficacy of antibiotics, while others thought that their efficacy is not overweighed by their side effects.

Discussion

Many years of research and experimental policy making to improve rational use of antibiotics in Iran has been of little avail and it is still a mystery why all endeavors have yielded few positive outcomes. This rather yawning gap between health planning and real practices have considered by some other studies [43]. Against this

backdrop, this paper is an attempt to offer a fresh insight into complexity of the issue of irrational use of antibiotics in Iran and an in-depth analysis of the possible causes, building on the premises of the complex adaptive system theory.

The main strength in this study is analysis a wide spectrum of different key agents and trying to understand the behaviors of the antibiotics use system through the lens of complexity science.

The main strength in this study is examining a wide spectrum of different key agents and trying to understand the behaviors of the antibiotics use system through the lens of complexity science.

Findings provided a detail description of highly diverse agents and their properties, interactions and behaviors in regard to antibiotic consumption. The results showed that how interactions, past experiences, level of knowledge, preferences, belief in self-medication, and the socio-economic situation all influence patients' and physicians' behaviors continuously. Complexity perspective also acknowledges that as conditions change, agents self-organize their behavior and adapt according to new conditions. We saw that physicians' prescription behavior is adapting and evoked by their own trade-off between various variables such as patients satisfaction, relationships with health authorities, time constraints and interactions with pharmaceutical companies. Sometimes, health care professionals under the impression their history, positive or negative experiences, ignore their knowledge and behave sub-optimally for a host of reasons [44]. In addition, results revealed that the attitude of policy makers and health care managers toward antibiotic use are highly affected by their personal preferences and priorities, interaction with other agents, external pressure and the context in which they are practicing. Such emergent behaviors toward a drug policy had been observed in three different rural counties in China as well [26]. Any intervention in any parts of this system may bring about unexpected outcomes and, therefore, there should be some room for self-organizing and emergent behaviors of agents in order not to be shocked in the face of unexpected behaviors. System developers are encouraged to provide enough opportunities to different actors to enhance their self-organizing quality [45].

The other key findings of this study was interdependency of elements of the system which should be taken into account. It provided insight on how dependent are behaviors of different agents of the system which co evolve by change in the context of the systems or its agents. For example, change in physicians 'prescription behaviour may lead to change in patients behaviours and if one program aims to modify physicians' prescription behaviors, their interactions with patients, pharmacies and pharmaceutical companies have to be considered as well. This is because the change in physicians' prescription behaviors can affect patients' and pharmaceutical companies' attitude toward antibiotics as well.

It also was observed that the goal of different agents of the system are often in conflict which each other. For example while MOH and IFDA try to regulate the system of antibiotics use and reduce health care cost, some others like pharmacies and pharmaceutical companies are seeking for more profit and therefore try to provide more antibiotics. In other words, while selling more antibiotics can save a pharmacy or pharmaceutical company and produce significant profits, or prescribing more antibiotics means more patients' and pharmacies' satisfaction and so higher income for physicians, it increases healthcare costs and antibiotic resistance as a serious health problem. Without a shared goal and values, there is little chance for rational antibiotics supply. It can be argued that unless the solution including an effective interactions between all stakeholders and a

regulation system which takes into account the interests of all key agents , the sustainable and significant reduction of irrational antibiotic consumption seems impossible[46].

The result of this study reveals that some required interactions among agents specially those working in regulatory bodies, IRIMC, research centers, pharmacy industry and practitioners are missing or weak which prevents information flow, building mutual trust or communicating and enforcing rules and values about new regulations and guidelines. Lack of interacting with all stakeholders by health authorities may lead to bring about decisions and policy making which are not comprehensive , evidence-based or participatory, which in turn decrease the chance of being effectively adhered by stakeholders. As argued by participants of this study that health authorities should involve pharmacies and pharmaceutical companies' associations in policy making and truly see them as important stakeholders rather than rivals. Moreover, a key reason for failing many health intervention is the lack of adaptability by target individuals or organizations. A fluent information flow enables a CAS to be agile and dynamic. CAS suggests that to be able to adapt to a new conditions, such as new rules or programs, agents need to have effective interactions, benefits and resources which allow them to access to timely required information, feedbacks, opportunities to adopt the new behaviour [46]

The other interaction which needs modification is the physicians and patients interaction. During a non-professional and insufficient interaction between physicians and patients, mutual trust is damaged and information is imparted to patients in a defective way. Essential information related to antibiotic use is not usually transferred to patients by physicians and pharmacists. Therefore, patients are not educated properly about the importance of rational use of antibiotics and consequently their adherence to antibiotics therapy is decreased. Improve physician-patient relationship may break down this reinforcing loop and help patients to adapt to interventions.

This study showed that how insufficient and non-systematic interactions between agents cause the information of antibiotic consumption to be not adequate and timely accessible to all stakeholders. These information are mainly generated at insurance companies, medical universities, hospitals and IFDAs. Amplifying the information flow in the rational use of antibiotics in Iran calls for more serious attention and should be achieved through the recovery of disrupted interactions, development of required infrastructures and optimal use of the existing potentials.

Moreover, there are interactions which needs to be banned or monitored by developing new rules and regulations. For example, promotional activities of pharmaceutical companies and their interactions with pharmacies and physicians need to be more regulated. Negative impacts of relationship between physicians and pharmaceutical industry such as irrational prescription behaviour, unethical attitude and malpractice in patient management have been demonstrated in previous studies [47, 48]. Furthermore, the conflict of interest rules in Iran health system have been challenged before and the need to stringent regulation to prevent unethical interaction between physicians and pharmaceutical companies is a necessity. It also seems that direct financial relation between patients and physicians needs to be changed as it influences physicians' behavior. Fee-for-service payment system has been substituted for new and modified payment model in many countries.

Although agents in Social CAS are ruled base but they have also high degree of freedom for autonomous behavior. Other studies have also revealed that formal rules should not be overestimated in terms of their power

to centrally control the behaviors and manners because these kinds of rules do not ensure the stability of the policies [31]. Our study showed that, beside the compromised mutual trust between health authorities and other agents, ineffective implementation and central supervision of rules have encouraged autonomous action often against the policy and rules. These kinds of behaviours can clearly be seen in behaviors of pharmaceutical companies, pharmacies and hospitals. Despite many limiting regulations about pharmaceutical promotional activities and prohibition of delivering antibiotics over the counter at pharmacies, antibiotic sale increases at pharmacies. Hospitals disobeyed some pharmaceutical protocols and guidelines because they believed they were not compatible with the pattern of antibiotic resistance in their hospitals. This study suggests that encouraging following the rational use of antibiotics rules and programs is more likely to be successful if autonomy of agents is well regarded, the rules are developed participatory, implemented locally and supervised continuously and effectively. Bounded autonomy of health settings and limited decision authority have also been criticized in other studies[49].

Our finding highlighted the importance of organizational, professional and individual values to influence agents' behaviors. Organizational values of rational use of antibiotics in MOH and IFDA have criticized by respondents and need to be reviewed in terms of their credit and blame mechanisms. Professional and individual values in physicians and patients are also seem to be unable to interpret their knowledge and awareness of the importance of rational use of antibiotics into rational attitude and practice. Some factors like insufficient and ineffective interactions between physicians and patients, facilitated access to antibiotics and physicians conflict of interests have been found as interferer variables in this way.

Conclusion

Understanding the irrational use of antibiotics from a holistic perspective offered by CAS observatory tool, can lead us to different solutions. To this end, this study provides a different description and explanation of the problem contributing to detangle the complexity of the problem. A substantial insight of this study would be noticing the complex nature of antibiotics irrational use problem and better managing unexpected consequences of any policy and program to address that.

The findings of the study showed suggest that the antibiotics use system in Iran needs re-engineering by strengthen some links between stakeholders, weaken or cut some links, improve information flow, taken into account interdependencies of systems components, consider the role of autonomous and self-organized behaviors of agents, and revising rules and values of the system.

It is our sincere hope that this study serves as a stepping stone and an incentive for like-minded researchers to further expand its scope and apply the principles of complexity science into other relevant areas of medicine use and prescription. Developing a dynamic model for irrational use of antibiotics and CAS observatory studies can be some potential areas for future studies.

List Of Abbreviations

CAS Complex Adaptive Systems

NCRUD The National Committee on Rational Use of Drugs

WHO	World Health Organization
FGD	Focus Group Discussion
MHO	Ministry of Health
IFDA	Iran Food and Drug Administration
RUD	Rational Use of Drug
IRIMC	Islamic Republic of Iran Medical Council
NGO	Non-Governmental Organization

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Institutional Research Ethics Committee School of Pharmacy and Nursing & Midwifery – Shahid Beheshti University of Medical Sciences. All interviewees provided verbal informed consent in order to participate and audiotape of interview or FGD.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NK developed the CAS observatory tool and the conceptual framework of the study, assisted data analysis and reviewed the draft. ZS interviewed with participants, analyzed the data, reviewed available documents and drafted the article. FP helped to fully and properly describe the system, comprehensively identified governing rules and regulations, assisted data analysis and reviewed the draft. JS reviewed interactions extracted from data analysis and approved all interplays and feedbacks in the system. AJ helped to develop conceptual framework and reviewed the draft. All authors read and approved the final manuscript.

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References

1. Desalegn AA. Assessment of drug use pattern using WHO prescribing indicators at Hawassa University teaching and referral hospital, south Ethiopia: A cross-sectional study. BMC Health Serv Res. 2013;13:1–6.
2. Hadi U, Keuter M, Van Asten H, Van Den Broek P. Optimizing antibiotic usage in adults admitted with fever by a multifaceted intervention in an Indonesian governmental hospital. Trop Med Int Heal. 2008;13:888–99.
3. Who. The Pursuit of Responsible Use of Medicines: Sharing and Learning from Country Experiences. Vet Rec. 2012;169:78. doi:10.1136/vr.d5420.
4. Mousavi S, Mansouri A, Ahmadvand A. A bibliometric study of publication patterns in rational use of medicines in Iran. Pharm Pract (Granada). 2013;11:38–43. doi:10.4321/S1886-36552013000100007.
5. Basaran NF, Akici A. Patients' experience and perspectives on the rational use of drugs in Turkey: A survey study. Patient Prefer Adherence. 2012;6:719–24.
6. Ofori-Asenso R, Agyeman A. Irrational Use of Medicines—A Summary of Key Concepts. Pharmacy. 2016;4:35–48.
7. Kaplan W, Mathers C. The World Medicines Situation 2011 - Global Heath Trends: Global Burden of Disease and Pharmaceutical Needs. World Heal Organ. 2011;3:1–434. http://apps.who.int/medicinedocs/documents/s20054en/s20054en.pdf.
8. LeGrand A, Hogerzeil HVH, Haaijer-Ruskamp FFM. Intervention research in rational Use of Drugs: A Review. Health Policy Plan. 1999;14:89–102.
9. Nilseng J, Gustafsson LL, Nungu A, Bastholm-Rahmner P, Mazali D, Pehrson B, et al. A cross-sectional pilot study assessing needs and attitudes to implementation of Information and Communication Technology for rational use of medicines among healthcare staff in rural Tanzania. BMC Med Inform Decis Mak. 2014;14:78–90. doi:10.1186/1472-6947-14-78.
10. Sumpradit N, Chongtrakul P, Anuwong K, Pumtong S, Kongsomboon K, Butdeemee P, et al. Antibiotics Smart Use: a workable model for promoting the rational use of medicines in Thailand. Bull World Health Organ. 2012;90:905–13.
11. Mohagheghi MA, Mosavi-Jarrahi A, Khatemi-Moghaddam M, Afhami S, Khodai S, Azemoodeh O. Community-based outpatient practice of antiobiotics use in Tehran. Pharmacoepidemiol Drug Saf. 2005;14:135–8.
12. Machowska A, Lundborg CS. Drivers of irrational use of antibiotics in Europe. Int J Environ Res Public Health. 2019;16:1–14.
13. Rashidian A, Zaidi S, Jabbour S, Jahanmehr N. Identification of Priority Policy Research Questions in the area of Access to and Use of Medicines in EMRO Countries : Focusing on Iran , Pakistan and Lebanon. 2011.
14. Holloway KA, Ivanovska V, Wagner AK, Vialle-Valentin C, Ross-Degnan D. Have we improved use of medicines in developing and transitional countries and do we know how to? Two decades of evidence. Trop Med Int Heal. 2013;18:656–64.
15. Mousavi S, Zargarzadeh AH. Rational Drug Use in Iran : A Call for Action . J Pharm Care. 2014;2:47–8.

16. Hashemi S, Nasrollah A, Rajabi M. Irrational antibiotic prescribing: A local issue or global concern? EXCLI J. 2013;12:384–95.
17. Bastani P, Barfar E, Rezapour A, Hakimzadeh SM, Tahernejad A, Panahi S. Rational Prescription of Drug in Iran: Statistics and Trends for Policymakers. J Heal Manag Informatics Orig. 2018;5 April:57–64.
18. Soleymani F, Valadkhani M, Dinarvand R. Challenges and Achievements of Promoting Rational Use of Drugs in Iran. Iran J Publ Heal. 2009;38:166–8.
19. Kuziemsky C. Decision-making in healthcare as a complex adaptive system. Healthc Manag Forum. 2016;29:4–7. doi:10.1177/0840470415614842.
20. Brown CA. The application of complex adaptive systems theory to clinical practice in rehabilitation. Disabil Rehabil. 2006;28 May:587–93.
21. Kannampallil TG, Schauer GF, Cohen T, Patel VL. Considering complexity in healthcare systems. J Biomed Inform. 2011;44:943–7. doi:10.1016/j.jbi.2011.06.006.
22. Braithwaite J, Clay-williams R, Damen N, Herkes J. Complexity Science in Healthcare – Aspirations, Approaches, Applications and Accomplishments: A White Paper Research. Australian Institute of Health Innovation, Macquarie University: Sydney, Australia; 2017.
23. Agyepong IA, Kodua A, Adjei S, Adam T. When “solutions of yesterday become problems of today”: crisis-ridden decision making in a complex adaptive system (CAS)–the Additional Duty Hours Allowance in Ghana. Health Policy Plan. 2012;27 suppl 4:20–31. doi:10.1093/heapol/czs083.
24. Keshavarz M N, Nutbeam D, Rowling L, Khavarpour F. Schools as social complex adaptive systems: A new way to understand the challenges of introducing the health promoting schools concept. Soc Sci Med. 2010;70:1467–74. doi:10.1016/j.socscimed.2010.01.034.
25. Javadi D, Bigdeli M. Alliance for Health Policy and Systems Research Flagship Report 2014 Examples of complexity approaches to access to medicines in the existing literature. AHPSR Flagsh Rep. 2014;:1–16.
26. Xiao Y, Zhao K, Bishai DM, Peters DH. Essential drugs policy in three rural counties in China: What does a complexity lens add? Soc Sci Med. 2013;93:220–8. doi:10.1016/j.socscimed.2012.09.034.
27. Paina L, Peters DH. Understanding pathways for scaling up health services through the lens of complex adaptive systems. Health Policy Plan. 2012;27:365–73.
28. Peters DH, Paina L, Bennett S. Expecting the unexpected: Applying the Develop-Distort Dilemma to maximize positive market impacts in health. Health Policy Plan. 2012;27 SUPPL. 4:44–53.
29. Karemere H, Ribesse N, Marchal B, Macq J. Analyzing Katana referral hospital as a complex adaptive system: agents, interactions and adaptation to a changing environment. Confl Health. 2015;9:1–10. doi:10.1186/s13031-015-0046-5.
30. Anderson RA, Plowman D, Corazzini K, Hsieh P-C, Su HF, Landerman LR, et al. Participation in Decision Making as a Property of Complex Adaptive Systems: Developing and Testing a Measure. Nurs Res Pract. 2013;2013:1–16. doi:10.1155/2013/706842.
31. Ogbuabor D, Onwujekwe O, Ezumah N. Muddling Through Policymaking: A Complex Adaptive Systems Perspective on Policy Changes in a Free Maternal and Child Healthcare Program in Enugu State, Nigeria. Niger J Clin Pract. 2019.
32. Brainard J, Hunter PR. Do complexity-informed health interventions work? A scoping review. Implement Sci. 2016;:1–11. doi:10.1186/s13012-016-0492-5.

33. Caffrey L, Wolfe C, Mckevitt C. Embedding research in health systems : lessons from complexity theory. Heal Res Policy Syst. 2016;:1–9. doi:10.1186/s12961-016-0128-x.
34. Gilson L, Elloker S, Olckers P, Lehmann U. Advancing the application of systems thinking in health : South African examples of a leadership of sensemaking for primary health care. Heal Res Policy Syst. 2014;12:1–13.
35. Sturmberg JP, Bircher J. Better and fulfilling healthcare at lower costs : The need to manage health systems as complex adaptive systems [version 1 ; peer review : awaiting peer review]. F1000Research. 2019;8:789–800.
36. Zimmerman B, Dooley K. Advances in Health Care Organization Theory. S. M. Mick and M. Wyttenbach; 2003.
37. Marion R. Organizational Extinction and Complex Systems. Inst Study Coherence Emerg. 2016;1 April.
38. Seel R. Culture and Complexity : New Insights on Organisational Change. Organ People. 2000;7:1–8.
39. Tsasis P, Evans JM, Owen S. Reframing the challenges to integrated care: A complex-adaptive systems perspective. Int J Integr Care. 2012;12 JULY-SEPTEMBER 20:190–201.
40. Kurtz CF, Snowden DJ. The New Dynamics of Strategy: Sense-making in a Complex-Complicated World. IBM Syst J. 2003;42:462–83.
41. Plsek PE, Greenhalgh T. Complexity science The challenge of complexity in health care. Br Med J. 2001;323:625–8.
42. Ritchie J, Lewis J. Qualitative research practice. 2013.
43. Lamprell K, Arnolda G, Delaney GP, Liauw W, Braithwaite J. The challenge of putting principles into practice : Resource tensions and real-world constraints in multidisciplinary oncology team meetings. Asia Pac J Clin Oncol. 2019; August 2018:1–9.
44. Pype P, Mertens F, Helewaut F, Krystallidou D. Healthcare teams as complex adaptive systems : understanding team behaviour through team members ' perception of interpersonal interaction. BMC Health Serv Res. 2018;18:570–83.
45. Neely K. Complex adaptive systems as a valid framework for understanding community level development. Dev Pract. 2015;25:785–97. doi:10.1080/09614524.2015.1060949.
46. Keshavarz M N. One step back toward the future of health promotion : complexity-informed health promotion. 2019;34:635–9.
47. Keller F, Marczewski K. The relationship between the physician and pharmaceutical industry : background ethics and regulation proposals. 2016;:398–401.
48. Mandal BK, Yadav SK, Karn A, Sah AK. Relationship between Doctors and Pharmaceutical Industry : An Ethical Relationship between Doctors and Pharmaceutical Industry : An Ethical Perspective. 2012; January.
49. Barasa EW, Molyneux S, English M, Cleary S. Social Science & Medicine Hospitals as complex adaptive systems : A case study of factors in fl uencing priority setting practices at the hospital level in Kenya. Soc Sci Med. 2017;174:104–12. doi:10.1016/j.socscimed.2016.12.026.

Figures

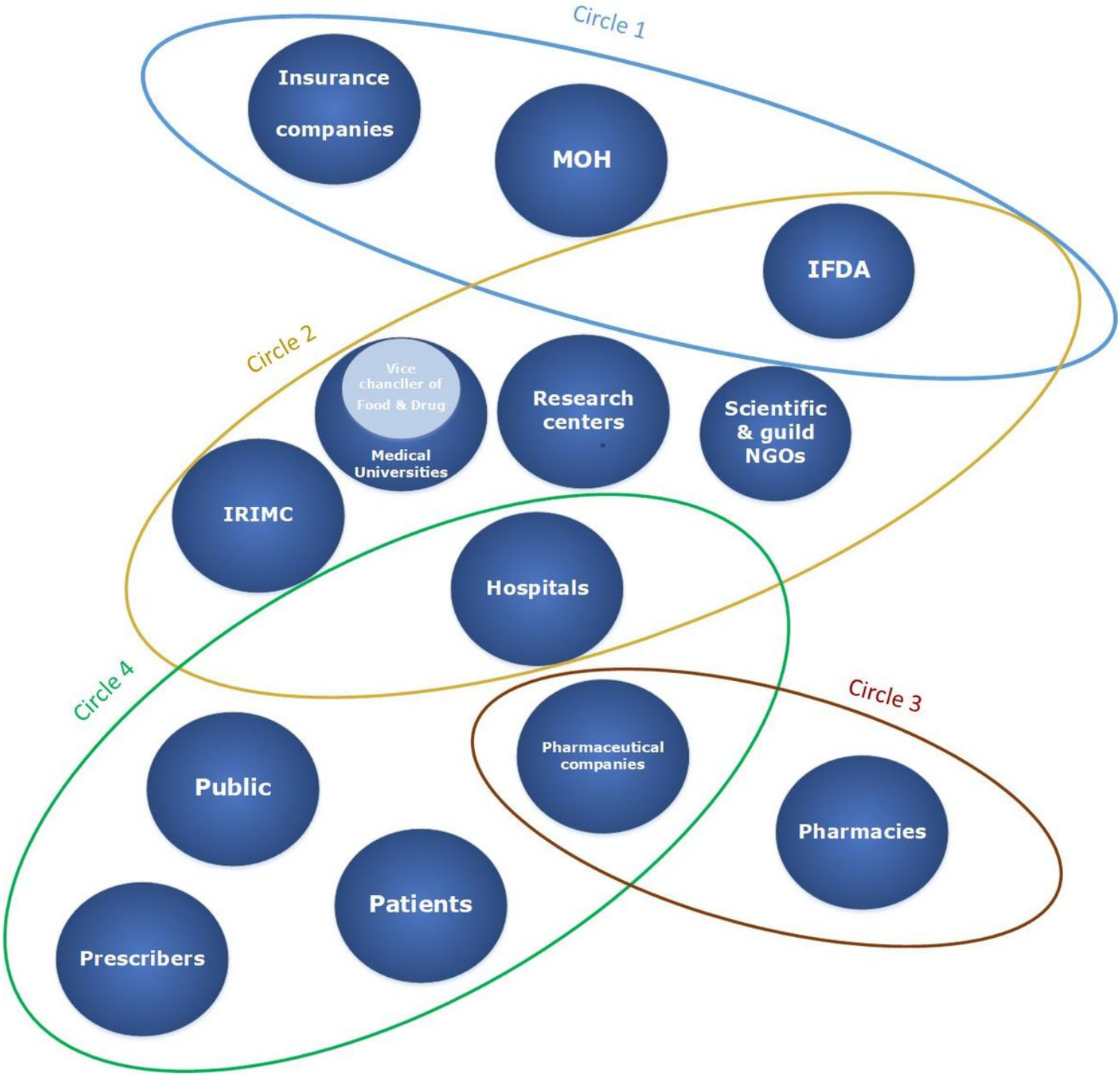

Figure 1

Circle 1 represents agents who make policies, regulate the system and reimburse antibiotics. Circle 2 represents monitoring agents that investigate the implementation of regulations or provide evidence to make policies. Circle 3 points at agents which produce and dispense antibiotics and circle 4 represents agents who contribute in the core function of antibiotic prescription and use “

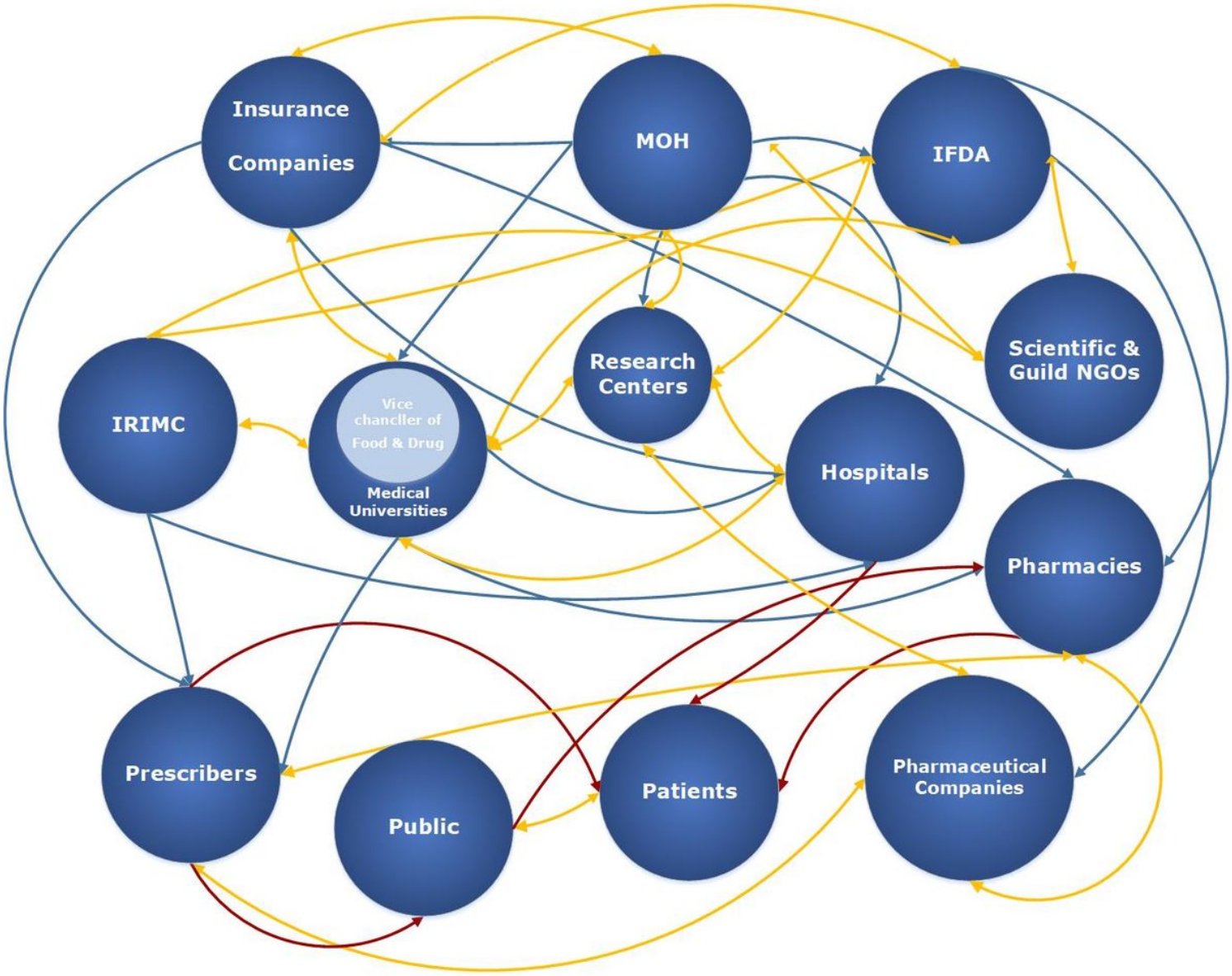

Figure 2

Blue links between agents stand for governance- and supervisory-oriented top down relationships, red links represent interactions related to service provision, and the yellow links show double-faced connections based on professional collaboration or contract-based corporation”

Supplementary Files

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- questionnaire.docx