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Applying the resource interaction approach to policy analysis – Insights from the antibiotic resistance challenge

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ABSTRACT

This paper explores how the Resource Interaction Approach (RIA), namely the 4Rs model and the three settings of developing-producing-using, can be applied to complex policy analyses. We use the global sustainability challenge of antibiotic resistance as an example to define an agenda about how these analytical tools can frame and analyze such problems systematically. We find that these tools offer benefits to policymakers, including flexibility in framing problems, by selecting the focal resources and values to be prioritized, and the ability to visualize the direct and indirect interdependencies that enable or hinder value creation. Moreover, the RIA can point at the resource interfaces that need to change through specific policy interventions, as well as the potential network-level barriers to such changes. We also find that the RIA needs to be complemented by network-level analyses of deal structures and monetary flows in order to better capture the legal and financial dimensions of policy problems and solutions.

1. Introduction

Antibiotics or antimicrobial resistance (AMR) is a major sustainability challenge that could "kill humanity before climate change does," as warned by England's chief medical officer Dame Sally Davis in 2019 (www.telegraph.co.uk). AMR has, in fact, grown into a very serious global problem, which, according to some estimates, may kill up to 10 million people per year starting from 2050 (AMR Review, 2015). Similar to other sustainability problems, AMR is multifaceted, with both health and economic ramifications, and highly complex (Doh, Tashman, & Benischke, 2019; Wells, 2012). It is indeed a "super-wicked" problem (Littmann, 2014), characterized by multiple interdependencies, ambiguity, and many stakeholders still arguing about its nature and possible solutions. Moreover, AMR entails several paradoxes, from the "tragedy of the commons" related to overuse and depletion of a key common resource, such as antibiotics (Hardin, 1968; Ostrom, 1990) to a broken innovation logic and market failure. Therefore, like other sustainability challenges, AMR requires policy interventions and concerted action between public, private, and other spheres of society (Gray & Purdy, 2018). The interdependencies behind this problem and the required concerted action suggest using network approaches like the IMP view (Industrial Marketing & Purchasing) (Håkansson, Ford, Gadde, Snehota, & Waluszewski, 2009; Håkansson & Snehota, 1995) to unravel and understand its complexity, as witnessed by IMP-inspired studies of other sustainability issues (see e.g., Andersson & Sweet, 2002; Frostenson & Prenkert, 2015; Johnsen, Miemczyk, & Howard, 2017).

Antibiotics can be viewed as a "common-pool resource" (Ostrom, 1990) requiring special institutions, such as regulations, to govern its development and use in order to avoid overuse and depletion. However, policies focusing only on the overarching institutions would miss the fact that common-pool resources like antibiotics are embedded in complex socio-technical networks where they are connected and "interact" with several other resources (Baraldi & Bocconcelli, 2001; Håkansson & Waluszewski, 2002). Typical policy suggestions to stimulate antibiotic development include, for instance, "a hybrid model of early payments, a strong commitment by credible purchasers, and the ability to sell on the open market" (Brogan & Mossialos, 2016: 7). However, such policies may have the merit to recognize the need for changing the monetary flows and business deal structures (Håkansson & Olsen, 2015), but they still assume the existence of a homogeneous "open" market for antibiotics, whose traditional exchange mechanisms simply need to be improved or supported. The current AMR policy analyses and discussions accordingly miss the complex interactions and network-level interdependencies that characterize any economic landscape (Waluszewski, Hadjikhani, & Baraldi, 2009), including the antibiotic field.

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Therefore, analytical tools capable of capturing the direct and indirect inter-organizational interactions behind resource development and use can enable framing a wicked problem like AMR in a new way and also provide new insights to help policymakers identify alternative policy interventions to address the problem. In particular, the IMP-inspired "resource interaction approach," *RIA*, and the *4Rs model* (Baraldi, Gressetvold, & Harrison, 2012; Håkansson & Waluszewski, 2002; Prenkert, Hasche, & Linton, 2019) are analytical tools that enable an understanding of *value creation*, or lack thereof, for a specific resource such as antibiotics by penetrating both specific resource interfaces (Baraldi et al., 2012) and more complex resource combinations. Applying RIA for a policy-related analysis of AMR can accordingly provide a novel and multi-faceted picture by showing (1) the socio-technical interdependencies that embed antibiotics, and thus facilitate or hinder value creation, as well as (2) how these resource structures relate to the financial and legal dimensions, which are the typical focus of policy in such interventions as increased R&D subsidies or faster drug approvals (see e.g., Brogan & Mossialos, 2016). These financial and legal dimensions impact value appropriation (Baraldi & Lind, 2017), that is, how the value(s) created through resource interactions are distributed in monetary terms among the involved actors and can be analyzed as the "monetary flows" between network actors and the structure of business deals that govern these flows by assigning specific rights and obligations to these actors (Håkansson & Olsen, 2015).

Against this background, the purpose of this paper is to explore how the RIA and 4Rs model can be applied to a policy analysis of a global sustainability challenge like AMR. Relying on the illustrative example of AMR, we contribute with an agenda showing how a highly complex, indeed wicked, problem can be framed and analyzed systematically through the RIA and 4Rs model to derive new insights relevant for the policymakers dealing with it. In order to assess how certain financial and legal policy solutions relate with actual value creation, this agenda also identifies the need to complement the RIA and 4Rs model with additional analytical tools, such as the notion of "deal structures" and "monetary flows" associated with activated resources in industrial networks (Håkansson & Olsen, 2015).

The paper is organized as follows: after our methods, the next section describes the AMR problem, its causes, various facets, and magnitude. Thereafter, we introduce the RIA and 4Rs model, specifically considering their previous applications in policy-related analyses. The following section applies the RIA and 4Rs model to the empirical setting of AMR, which finally leads to an agenda on how these analytical tools can frame global challenges from a policy viewpoint, considering also their benefits and limitations in doing so.

1.1. Methodological considerations

This paper presents a conceptual study aiming to assess how RIA (Baraldi et al., 2012; Håkansson & Waluszewski, 2002) can frame the problem of AMR in new ways and identify new aspects relevant to policy analyses. We use the multi-level, qualitative case of AMR (Yin, 1993) as an illustrative example to build our conceptual study. Accordingly, we do not aim at conveying a full analysis of the AMR problem, which would require a separate dedicated study or indeed a stream of several papers, each one with detailed case studies focusing on particular resources, value(s), and network connections. In particular, in this paper, we opted to start our analysis of the AMR issue from the focal resource of antibiotics, moving then to the interactions with other resources embracing it, at a micro- and meso-level, and connecting it with complex networks associated with the global problem of AMR (see also Aggestam, 2017). The case should then be regarded as the empirical arena to which we apply an existing analytical framework, the RIA.

Exploring how RIA can be applied as a possible analytical tool for policy differs clearly from defining abstract rules that policy should always follow or formulating specific policy recommendations, because RIA and 4Rs, like other IMP-inspired models, are non-normative. Building on the importance of the interaction context recognized by the IMP tradition (see Håkansson & Snehota, 1995), RIA can help identify specific problems or alternative solutions, e.g., which resources to intervene on specifically – yet, the model can only present selective descriptions of an empirical phenomenon (Snehota, 1990). Therefore, the use of RIA as a tool for policy analysis would still require policymakers to set their own priorities on specific resources and facets of a problem. In fact, RIA and the 4Rs model stress the complexity of resource interactions and the multiple values at play and hence require decision-makers, especially if policymakers or managers, to make very clear choices about which values, resources, and interfaces they want to prioritize in their analyses and interventions. These are analytical tools that are capable of identifying many different solutions and, in this sense, retaining a certain flexibility in comparison to other normative tools striving toward optimization of pre-determined variables and parameters.

In applying RIA to the AMR problem, the following steps were followed. First, we explored this issue in terms of value creation and value destruction and then selected a focal resource, antibiotics, considering which aspects of this resource provide value. Further, we chose to define this value from a policy perspective in terms of, for instance, durability or maintained efficacy, i.e., preserving the value of existing antibiotics over time, in order to ensure future use, or novelty obtained by introducing new antibiotics. Thereafter, we identified the resources affecting these and other values of antibiotics, both in terms of the negative and positive impact resulting from existing interfaces or lack thereof. The resources were then mapped within the three settings of development, production, and use to grasp indirect interconnections of interfaces between the three settings: this step helped to unfold the actual connectedness (or lack thereof) between the settings, which is crucial to eventual value creation (or preservation) for the focal resource. We also identified shallow or missing interfaces, as well as those deep interfaces that either hinder or even may destroy value. The very last steps involved assessing how RIA can capture and make sense of a selection of existing policies (a total of 6) and identifying benefits and limitations of RIA for policy analysis.

In our analysis, we focused on two main types of connections between empirics and selected analytical tools from RIA: (1) how these tools can capture the complexity of AMR, considering its context, various elements, and processes (see Meier & Dopson, 2019) and (2) how these tools can be applied to understand relevant policy interventions, both ongoing and under discussion. This confrontation between empirics and analytical tools suggested eventually the need to combine several models and constructs into an emerging RIA-based framework capable of framing policy issues, as presented in our agenda in the concluding section (see also Fig. 3).

The steps above relied on extensive empirical materials about AMR, which we collected through multiple sources of primary data (Miles & Huberman, 1994) between 2014 and 2020: (1) direct participation in four main policy-related projects (DRIVE AB, the Global AMR R&D Hub, and two projects sponsored by the Swedish Public Health Agency and the Swedish Innovation Agency), where the authors held management functions and contributed to devising specific incentives to stimulate antibiotics R&D, improve antibiotics use and availability; (2) unstructured and semi-structured interviews with over 100 representatives of key stakeholders in the antibiotics field (10 big pharmas, including large generics manufacturers and contract manufacturers, the European Federation of Pharmaceutical Industries and Associations, the Swedish equivalent LIF, 25 SMEs, their association BEAM Alliance, about 20 academic labs); (3) dozens of close interactions, meetings, and seminars with funders of antibiotics R&D, national and transnational regulatory agencies, as well as public health authorities and health technology assessors in Sweden and the UK. All this data provides the authors with both extensive and deep knowledge of the antibiotics field, its structure, processes, problems, and possibilities as well as barriers to change, which are summarized in the next section.

2. Empirical background: The global challenge of antibiotic resistance

When introduced in the 1930s, antibiotics appeared immediately as a miracle drug and soon became the cornerstone of modern medicine being applied not only in direct treatment of bacterial diseases but also for preventing infections and enabling key treatments such as surgery or chemotherapy (So, Ruiz-Esparza, Gupta, & Cars, 2012). However, despite their miraculous abilities, antibiotics also carry an implicit weakness: the more an antibiotic is used, the larger the portion of resistant bacteria. By being exposed to several antibiotics strikes over the years, some strains of previously treatable bacteria have become resistant, making them extremely difficult to kill and turning them into a serious threat to public health (Adeyi, Baris, Jonas, et al., 2017).

Unfortunately, this phenomenon of "breeding" antibiotic resistance has been going on for the last 80 years and has been aggravated by the fact that much of the antibiotics use over the years has not been motivated by medical reasons, that is, the presence of a bacterial, as opposed to e.g., viral, infection. In low-income countries, antibiotics are often used irrationally as a preventive means against the many infections, bacterial or otherwise, caused by lack of clean water and sewages. Further, in low- and medium-income countries, antibiotics are sold over the counter without medical prescription, which makes it impossible to delimit their use to bacterial infections.

However, misuse or irrational use of antibiotics happens also in high-income countries occasionally in human care, but especially and recurrently in animal farming, where antibiotics are irresponsibly given to cattle as part of their "daily feed" just to minimize the space allocated to each animal and avoid the costs of individual control to prevent infections (Nathan & Cars, 2014). The size of the AMR threat is already worrisome, with current deaths due to resistant bacteria estimated at around 700,000 yearly across the globe (Hoffman & Outterson, 2015), and the most pessimistic estimations pointing to between 10 and 50 million deaths yearly in the world already by 2050 (AMR Review, 2015; Adeyi et al., 2017; The Economist, 2019).

Regarding the opportunities of developing new antibiotics to hinder the galloping resistance, the sad truth is that we are losing the race (Nathan & Cars, 2014). It is becoming increasingly difficult from a scientific point of view to develop new antibiotics, and, despite the huge medical and societal value of antibiotics, drug developers have continued to leave the field over the last 20 years due to low profits (Boucher, Talbot, Bradley, et al., 2009; DRIVE-AB, 2018). Today, only 3–4 big pharma companies are still active in the development of antibiotics, of what used to be 25 large pharmaceutical R&D labs in 1980 (Outterson, Powers, Daniel, & McClellan, 2015). During the same period, academic research on antibiotics has also been considerably downsized because of lack of public funding. No truly new antibiotics have been launched in the last 30 years (Kinch, Patridge, Plummer, & Hoyer, 2014).[1] Furthermore, the success rate of an antibiotic project is much lower than for other drugs (Payne, Gwynn, Holmes, & Pompliano, 2007), and clinical trials are more expensive to conduct due to difficulties in recruiting patients with the "right" infection (Katz, 2006).

Antibiotics not only entail higher failure rates, R&D costs, and times (Morel & Mossialos, 2010; Spellberg, Bartlett, Wunderink, & Gilbert, 2015), but they also mean lower and more risky revenues than other drugs (Projan & Shlaes, 2004). New antibiotics necessarily yield low sales because they should target specific resistant bacteria and their use will be delimited to preserve efficacy over time through antibiotics stewardship programs (Boyles, Whitelaw, et al., 2013). New antibiotics are basically kept as "reserve weapons," which will further reduce already low sales volumes. No "block-busters" can be expected in the antibiotics field: the most optimistic estimates are $250 million annual revenues, facing average R&D costs of about $600 million (DiMasi, Hansen, & Grabowski, 2003), and commercial failures can occur, like Achaogen's product that generated less than $1 million in sales during its first year on the market, causing the firm to go bankrupt in April 2019. Antibiotics, thus, represent a "broken market" (Kesselheim & Outterson, 2011).

As pointed out by Waluszewski, Baraldi, and Ciabuschi (2018), there is indeed a paradoxical situation compared to most innovation areas, where increased use of an innovation normally is a sign of success and brings economic benefits: the antibiotic resistance following widespread use would reduce the therapeutic value of the product, making its sales decline. The typical innovation logic is thus untenable for antibiotics; instead, there is a quest for economic models and incentives able to delink revenues from R&D costs (Outterson et al., 2015). Several studies suggest that the support and engagement of governments and transnational agencies are needed immediately to recreate the necessary structures and processes in the antibiotics field (Kinch et al., 2014; AMR Review, 2015).

In order to develop new effective antibiotics, one needs a clear idea of which bacteria to prioritize, something that in turn requires globally coordinated efforts of infection surveillance to spot where and when these "super-bugs" appear. Moreover, infection control is probably the best way to address AMR because it minimizes the global spread of resistant bacteria (Barlam & Gupta, 2015). But when antibiotics are needed, another problem emerges: knowledge on how to provide exact dosage and optimize the use of antibiotics (launched 50 years ago) is still lacking, and there are no economic incentives to conduct expensive clinical studies on old generic antibiotics without protection of IPRs (Intellectual Property Rights).

Another pressing situation related to old antibiotics, which further aggravates AMR, is recurrent global shortages (Davis, 2018). The widespread use, indeed abuse, to a large extent, is caused by the very low price of antibiotics in high-income countries, which, in turn, is a consequence of pressures from national healthcare systems to minimize costs. In order to contain costs, the manufacturing of many old antibiotics and their input materials have therefore been offshored to low-cost production countries, such as India and China, now accounting for over 50% of the world's antibiotics production (Roland Berger GmbH, 2017). These transnational supply chains entail low margins for most actors (FDA, 2019), delimiting the investments in key resources, such as buffer stocks or modern production facilities capable of minimizing pollution (another major cause of AMR) and the risk of accidents, a major cause of shortages. Shortages harm patients directly through lack of correct medications and increase antibiotic resistance indirectly because a shortage requires using antibiotics which should instead have been "preserved."

Antibiotic resistance is indeed not simply an extremely complex problem, but also one entailing multi-layered interdependencies that cause potential conflicts between the parties involved (Gray & Purdy, 2018). Therefore, any policy analysis of antibiotics resistance needs to take multiple perspectives of the socioeconomic structures and their necessary changes for addressing the *whole* problem of AMR (Cars, 2014). While it is clearly impossible for any analytical model to capture the full complexity of the problem presented in this empirical background, in the following sections, we consider how the "resource interaction approach" (Baraldi et al., 2012; Håkansson & Waluszewski, 2002) can be applied to provide new insights to help policymakers gain a novel, multi-faceted picture of the AMR challenge.

[1] Only marginal improvements of old antibiotics appear also in the current global R&D pipeline (DRIVE AB, 2018; Theuretzbacher, Outterson, Engel, & Karlén, 2019). There are several reasons behind the lack of innovation in the antibiotics field: all "low-hanging fruits" have already been gathered, making it increasingly difficult to find attractive compounds (Payne, Miller, Findlay, Anderson, & Marks, 2015).

3. The "resource interaction approach" (RIA) and its policy applications

The analytical and theoretical models applied in this paper are tools that focus attention on and select particular facets of a phenomenon under study: they focus on the resource dimension of inter-organizational networks. In particular, the "resource interaction approach," RIA, enables to penetrate resource combinations and connections in these networks, which positively or negatively affect value creation for one or more resources (Baraldi & Strömsten, 2006). RIA also considers how these resource interactions occur in the different settings where a focal resource such as antibiotics is developed, produced, and used (Håkansson & Waluszewski, 2002). The main advantage of utilizing RIA and the 4Rs model is that they can grasp the interconnectedness between resources and, hence, the direct and indirect effects on the creation of values for specific resources (Baraldi et al., 2012; Håkansson & Waluszewski, 2002). The RIA and 4Rs model can describe how different resources interact with each other in affecting the value of a focal resource, for instance, antibiotics. Such a mapping can, in turn, be the ground for policy analyses, ranging from framing the problem to identifying possible solutions based on these interaction patterns.

3.1. Interaction ascribes a resource its specific features and value

Interaction is conceptualized as *a process* allowing organizations to combine material and immaterial resources systematically over time and space (Baraldi et al., 2012; Håkansson & Waluszewski, 2002; Harrison & Håkansson, 2006). Resources are assumed to be heterogeneous, that is, a resource's value and properties are determined by the other resources with which it is combined (Håkansson & Snehota, 1995; Snehota, 1990). Likewise, any resource can be defined on the basis of its ability to add value to other resources (Baraldi et al., 2012; Håkansson & Waluszewski, 2002). *Indirectly* connected resources influence the value of a resource, too. Thus, it is not possible to define a priori the value of a resource; rather, it is the *outcome of interaction* that will determine the current value and properties of a resource (Snehota, 1990). Resource interaction is thus a continuous process of adaptation, where resources will be shaped and reshaped, rejected, and reconnected to each other.

3.2. The 4Rs model

The 4Rs model categorizes resources into four types: *Products* are physical artefacts created and shaped through buying-selling interactions (Baraldi, 2003; Håkansson & Waluszewski, 2002). *Facilities* are physical resources located at specific organizational units and employed to transform products, such as production plants, hospitals, and warehouses. *Organizational Units* are instead a social type of resource, including the structure, routines (e.g., for product development and investment decisions), and competence, such as the knowledge and skills of an organization's personnel. An important feature of the resource type organizational units is their ability to perform not only internal routines and processes but also to engage in external interactions with other organizational units, which can lead to the next type of social resource. *Relationships* are a social resource that emerges when organizations interact over time and develop adaptations. Relationships can include various other resources being exchanged between organizations, from knowledge to products: the more resources involved in a specific relationship, the larger the interdependencies between the counterparts (Håkansson & Waluszewski, 2002).

The *interface* between two or more resources is a key concept in the 4Rs model (Baraldi and Bocconcelli, 2001; Baraldi et al., 2012; Prenkert et al., 2019): it is in the boundaries or contact points between resources that actual effects of interaction appear, such as the emergence and utilization of a particular value of a resource (Baraldi & Strömsten, 2006), and can be traced back to specific interactions between specific resources (Baraldi, 2003; Håkansson & Waluszewski, 2002). Resource interfaces can be classified into *technical* interfaces, such as how a facility affects a product's quality or durability, and *social* interfaces, such as how two organizational units affect each other through communication and other forms of exchange (Baraldi et al., 2012). The presence and the *depth* (or lack thereof) of interfaces among relevant resources can positively or negatively affect value creation: for instance, a particularly deep social interface between two organizational units can give rise to a business relationship which supports the development and production of a new product.

3.3. Three settings embodying different economic logics

Physical resources such as products can create value only if they become embedded in three main network settings: the *developing,* the *producing,* and the *using* settings, each one populated by different resources and logics (Håkansson & Waluszewski, 2002). Each setting has its own economic logic motivating an organization to engage in value creation for a specific resource (Håkansson & Waluszewski, 2002; Ingemansson, 2010; Linné, 2012; Rosenberg, 1994; Shih, 2009). However, these three settings are closely related, and the same organization may engage in more than one setting, for instance, a hospital involved in both testing and using a drug.

The developing setting is characterized by uncertainty: investing in the development of a specific resource entails high initial costs without guarantees for future returns. The innovative features of the resource under development are essential: a radically new resource will require larger changes to be "accepted" in the established structures than an incremental change supporting already made investments (Baraldi, Gregori, & Perna, 2011; Håkansson & Waluszewski, 2002). Introducing something radically new requires high costs, in terms of adaptations of all interrelated resources, internally and over organizational borders (Håkansson et al., 2009; Håkansson & Waluszewski, 2002; Kline & Rosenberg, 1986). Incremental changes that follow already established resource structures, instead, demand fewer adaptations and are thus easier to achieve. To become an innovation, any resource under development will have to, sooner or later, also become embedded in producing and using settings, requiring further adaptations. It is a matter of adapting to different logics and structures that enable the producing and using settings to create value from the specific resource.

The producing setting focuses on defining if and how a new resource can generate value for potential users, because it is the users who bring revenues to eventually sustain production (Håkansson & Waluszewski, 2002: 152–3). The production logic also concerns how to achieve economies of scale in production, and thus reduce costs and enhance value per unit of output (Perna, Baraldi, & Waluszewski, 2015). However, scaling up production entails frictions due to path dependency and heavy investments in place in production structures (Hughes, 1987; Rosenberg, 1982). The more a new resource clashes with already established resource structures in the production setting, the more difficult and expensive it will be to embed it. A producer has to consider if the investments made for a new resource and its production costs will exceed the value for users, expressed especially as revenues (Håkansson & Waluszewski, 2002). An extensive knowledge about the users' needs and what features of a specific resource are valued is crucial in order to assess potential revenues.

The using setting has a more flexible economic logic than the previous two settings, since users can potentially profit from using a resource in different ways. Users can directly obtain benefits from actual use, or reduce variable, fixed, or total costs, by introducing a new or modified resource into their processes (Håkansson & Waluszewski, 2002). In the case of pharmaceuticals in public healthcare, all these possibilities apply, depending on drug and disease and healthcare system. For example, a new drug that replaces surgery helps in reducing costs compared to previous treatments. A drug treating a previously untreatable disease adds an entirely new value to the using setting. Similar to the developing and producing setting, in a using setting, a

radically new solution requires greater efforts to become embedded, but it can potentially generate even larger economic gains. The argument also holds true the other way around, that is, the smaller the change, the smaller the opportunities for gains for users (Håkansson & Waluszewski, 2002; Utterback, 1994).

Bringing together the notions of developing-producing-using settings and the 4Rs model offers the generic analytical framework depicted in Fig. 1 below, showing various resources anchored in the three settings and the interfaces between some of them.

3.4. The "resource interaction approach" in policy studies

Applications of the RIA to policy issues have focused mainly on the innovation process, often on the commercialization of science-based solutions and policy attempts to support these transitions (see Linné & Shih, 2013; Perna et al., 2015; Shih, 2009; Waluszewski, Baraldi, Linné, & Shih, 2009). Waluszewski, Hadjikhani, and Baraldi (2009) compare three different nations' institutional frameworks for science, policy, and business; specifically, they pinpoint how the differences influenced the embedding of a biotech solution into use.

The Developing-Producing-Using framework has also been utilized to illustrate the effects of policy in the different moments of the innovation process. Shih and Linné (2016) show how strong political involvement in innovation both restricts and supports important resource interactions. Their studies show that Chinese state actors mobilize important resources throughout the whole innovation process: in development, production, and use, whereas Western innovation policies commonly support mostly the developing setting, leaving the producing and using settings to "market forces." The political context in China provides the state with tools to dictate business behavior, such as how resources are combined, i.e., resource interactions (Linné & Shih, 2013; Shih & Linné, 2016). Perna et al. (2015) and Waluszewski, Baraldi, and Perna (2017) argue that there is a clash between local innovation-support policies and global use of resources in innovation processes stretching over transnational networks. The clash is due to the disconnection between activated resource structures and monetary flows (Håkansson & Olsen, 2015), implying that costs and benefits are unevenly distributed among the actors in the transnational network, which counteracts the expected effects of national policy interventions (Perna et al., 2015; Waluszewski et al., 2017). In fact, these monetary flows depend on the business deals negotiated between actors, which eventually assign to each actor specific contractual obligations and rights over resources as well as distribute the costs and revenues associated with resources (Håkansson & Olsen, 2015). These contracts and other legal arrangements form, in turn, complex "deal structures" (Ibid), connecting the actors in a network in ways that may not reflect their actual efforts in value creation or even hinder certain specific resource interfaces and combinations. In other words, value appropriation by specific actors, in terms of the monetary flows determined by the current deal structures, may be disconnected from value creation in terms of actual resource interactions and combinations (Baraldi & Lind, 2017). Therefore, policy interventions may need to intervene in the legal domain of deal structures in order to influence the monetary flows to specific actors and eventually also influence value creation processes involving specific resources.

Waluszewski and Wagrell (2013) demonstrate the contradictions in policies to support healthcare innovations, with new medical devices receiving strong monetary support in the developing setting, thanks to

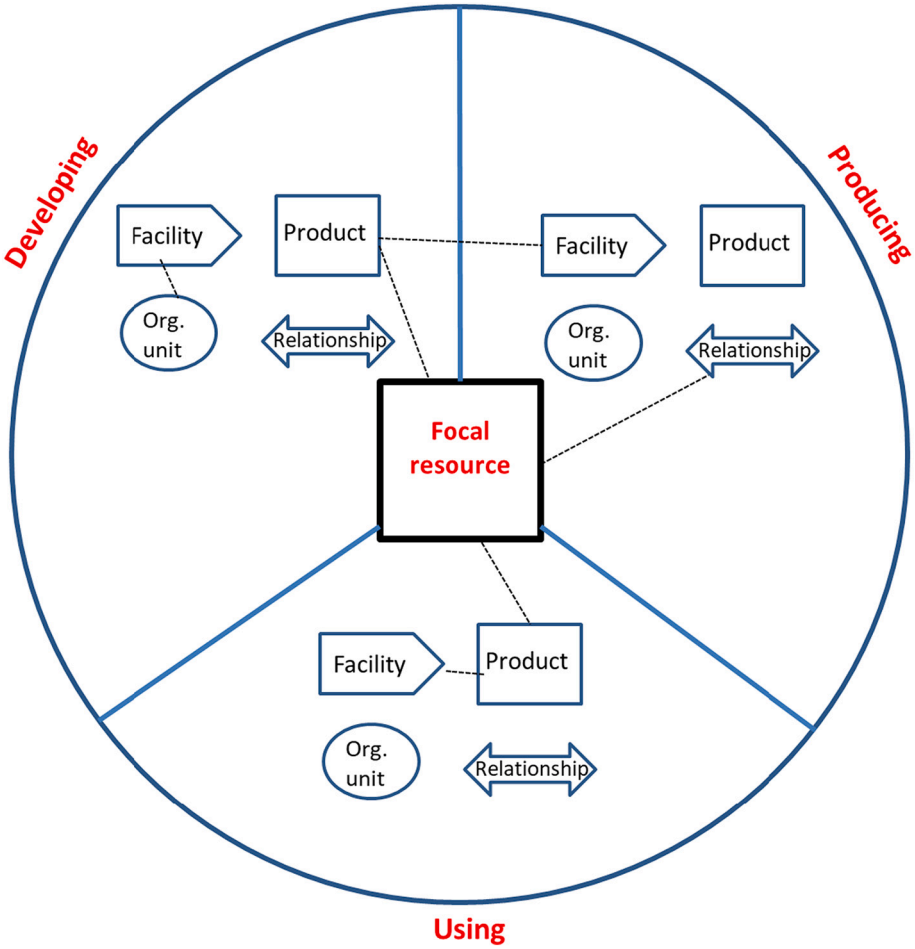

Fig. 1. A framework to capture resource interaction in the three settings.

public investments in the scientific development of new solutions, whereas public procurement regulations hinder the widespread use of the same innovations. Similarly, Wagrell (2017) shows that the various policies applied to each setting impact the possibilities to combine resources in new ways differently: such possibilities are enabled and supported in the developing and producing settings, but neglected or even prohibited in the using setting by, for instance, public procurement and policy tools monitoring the supply of healthcare services with lock-in effects that hinder the embedding of new solutions into widespread use (Ibid).

All in all, policy-related studies using RIA and 4Rs highlight how policy interventions can influence value creation, such as innovations, by directly affecting resource interactions and combinations. Moreover, policy can also influence value appropriation through changes in the deal structures and hence monetary flows, which can, in turn, affect resource structures in five main ways: *financing* the purchase of or other activities on resources, *enabling* or *blocking* certain interfaces and combinations, *evaluating* resources in the sense of attributing them a clear monetary value, and *distributing costs and revenues* among actors and also over time (Perna et al., 2015: 119–20).

3.5. Applying the "resource interaction approach" to antibiotics resistance

After describing the key elements, facets, and magnitude of the AMR problem (Section 2) and the basic analytical toolbox of RIA and 4Rs (Section 3), we can now apply the generic framework of Fig. 1 to the empirical setting of AMR. We frame the AMR issue by analyzing its various elements through the 4Rs model (Baraldi & Bocconcelli, 2001; Håkansson & Waluszewski, 2002), its *four resource types*, the core notion of *resource interface* (Baraldi et al., 2012. Prenkert et al., 2019) and of *embedding resources* for value creation into the three *settings of developing, producing, and using* (Baraldi et al., 2011; Håkansson & Waluszewski, 2002). As a way to define a roadmap on how to use RIA for policy analyses, at the end of this section, the RIA and 4Rs will also be used to delve into already proposed *policy interventions* to address the AMR issue.

3.6. Defining the empirical and the policy problem in terms of value creation and resource interactions

A key starting point for applying RIA to policy issues, such as AMR, is defining the empirical problem as well as the policy problem through the key tools and concepts of RIA. Relying on the background provided in Section 2, we can define the empirical AMR problem as an issue of "value destruction" and simultaneous "lack of value creation" in the antibiotics field. This problem is manifested in existing products becoming ineffective (i.e., losing their therapeutic effect) due to antibiotic resistance, that is, their therapeutic value is being "destroyed" via use and especially overuse, while too few new therapeutically effective antibiotics are being developed and introduced to the market, making more and more infections untreatable. The latter is indeed a problem of lack of innovation, which RIA, accordingly, expresses as inadequate resource combinations and interfaces (e.g., between competences of R&D organizational units and clinical trials routines at hospital units), which hinder network embedding in the three settings of developing, producing, and using (see e.g., Baraldi et al., 2011). Another concomitant facet of the empirical problem of AMR is that even old, albeit still effective, antibiotics lack availability – another key value for patients – due to recurrent shortages caused by inadequate resource combinations and interfaces in supply networks or by the restrictive distribution strategies of pharma's organizational units.

How can we then define the policy problem associated with the above empirical problem of AMR? Identifying a policy problem concerns defining the variables and indicators that policymakers consider as threats to key societal values like welfare or well-being, and which, accordingly, require policy interventions to correct the normal functioning of social and economic interactions. If we take the perspective of public health policy, AMR causes a major problem in terms of patient suffering and deaths because many infections are becoming increasingly untreatable. As we discussed above, untreatable infections depend in turn on deficiencies in value creation. Therefore, according to the RIA's analytical tools, we can define a general policy problem in terms of the need to *support value creation processes in the antibiotics field*. And indeed, public policy interventions to sustain value creation in this field appear motivated by the "market failure" described in Section 2 and the inability or unwillingness of private actors and other organizations alone to contribute and recombine resources in ways that can improve antibiotics R&D, production, and use.

Therefore, a tentative and broad RIA-based definition of the policy problem of AMR is the need to *support value creation through changes in selected resource interfaces*, both forging new interfaces and breaking established deleterious interfaces (Baraldi & Strömsten, 2006). The identification of which particular resources and interfaces to intervene on, how, and how much (including the level of policy investments) should be made through detailed studies departing from key relevant resources involved in the AMR problem. For instance, considering the real-world problem of lack of innovation, excessive use and lack of availability of antibiotics, three more specific policy problems can be phrased respectively as follows: (1) stimulating antibiotic R&D by creating new combinations of resources across the network that can support innovation – a policy problem that would focus on the developing setting; (2) achieving responsible use by breaking down resource interfaces that consolidate irresponsible use – a policy problem that would focus on the using setting; (3) improving drug availability by creating resource interfaces that reduce shortages – a policy problem that would focus on the producing setting.

3.7. Selecting an anchorage point for policy analysis: choosing a focal resource

The next step in applying the RIA, in research as well as in policy analyses, is to depart from a *focal resource* or set of interfaces, as done, for instance, by Waluszewski, Hadjikhani, and Baraldi (2009), with a key production facility (a protein separation tool) capable of highlighting national innovation contexts (within biotechnology) through seven selected interfaces. As for AMR, the sheer complexity of the problem opens to the analyst many possible focal points of departure: for the using setting, *hospitals* would be the focal facilities and/or organizational units, while for the developing setting, *academic labs* or a particular *chemical compound* would be the possible focal resources. Finally, for the producing setting, pharmaceutical companies' and especially generics' *manufacturing plants* would be essential resources to consider. However, there is a resource that is pivotal in all three settings, namely antibiotics, which is also the resource whose value is endangered the most by AMR. Therefore, in this paper, we opt to use antibiotics as the focal resource for our policy analysis, also considering the many values that policymakers can be interested in creating and supporting for this resource.

In fact, policymakers may be interested in different facets of the AMR problem, e.g., *conserving existing* antibiotics as opposed to *developing new* ones, which reflects a focus on two quite different values of the same focal resource: *durability* as opposed to *novelty*. Other relevant values of antibiotics for policymakers can be *accessibility*, which would require making them widely available, and *profitability*, which would require higher prices and/or larger sold volumes, with clear negative effects on durability because of escalating resistance.

Depending on the chosen facet of AMR or the chosen value of antibiotics, the analysis can depart from different resources or interfaces and identify resource combinations relevant for that particular facet or value. For instance, if one focuses on conserving the value of existing generic antibiotics, the organizational units of academic labs dealing with basic research are less relevant than the production facilities in the

established manufacturing structure and the hospitals as well as the animal farms, which are the organizational units most involved in using antibiotics. The specific resources that are particularly salient for the various facets of AMR or various values of antibiotics can then be clustered into more de-limited network sections, each one associated with the three settings of development, production, and use of the focal resource.

Summing up, for our exploratory study of RIA-based policy analysis, we choose to depart from antibiotics – both existing/old and new ones under development – as focal resource, placing them accordingly at the center of Fig. 2, surrounded by the other relevant resources grouped within the three settings of developing, producing, and using (Håkansson & Waluszewski, 2002). As we shall see, it is possible that one and the same resource appears in more than one setting (Baraldi et al., 2011); for instance, hospitals are not only part of the using setting, but can be involved in clinical trials of new antibiotics and hence are also part of the developing setting, similar to the resources bacteria and patients. Fig. 2 also displays the selected interfaces involving antibiotics, namely those particularly deep. We show both direct and indirect interfaces (Baraldi et al., 2012). For example, a direct interface is between antibiotics and the SMEs developing them, while indirect interfaces are those that do not include antibiotics but indirectly affect them, such as the interface "Big pharma-CROs" during clinical trials.

In order to provide a multi-faceted view of the AMR problem and possible solutions, other focal resources can be selected (e.g., hospitals or pharmas) in order to construct several case studies and alternative maps to Fig. 2, each one with a different resource in the center. Moreover, case studies would need to be grounded in particular instances of the selected focal resource, such as a particular antibiotic (e.g., colistin or vancomycin) or pharmaceutical firm (e.g., distinguishing also between SMEs and large pharmas). However, in our following analysis, we will remain at a general level of the whole product group "antibiotics," leaving it to future case studies to conduct specific analyses of particular antibiotics.

Nonetheless, even at the abstract resource type level, it is possible to specify more clearly the general policy problem that we identified above by considering the selected focal resource as a point of departure for policy analysis. In particular, after selecting the focal resource – antibiotics – and its relevant values – e.g., novelty, durability, accessibility, or profitability – the problem that policy aims to solve can be expressed in terms of positive or negative effects on these values deriving from other resources and their interfaces. As already mentioned, the 4Rs model suggests that the negative effects originate from a series of unfavorable interfaces and resource combinations around the focal resource, antibiotics, whose value is consumed without control and eventually becomes depleted, while no new antibiotics are replacing the old ones getting depleted.

We can then express the aim of policy in relation to the focal resource antibiotics in dual terms: (1) to facilitate and enhance *value creation*, such as introducing novel antibiotics or making old ones more available and (2) to support *value preservation*, that is, avoiding value depletion of both new and old antibiotics. Therefore, a key element in the following steps of this policy analysis will be to identify the main direct and indirect interfaces for creating and preserving value around antibiotics, as well as the *changes* in these resource combinations and interfaces that are necessary to create more value (e.g., launch new antibiotics) or better preserve the existing value (e.g., improve their use and thereby prolong their efficacy).

3.8. Zooming in on the focal resource and its heterogeneity

Before delving into the resources embedding antibiotics, a useful analytical step is to look even closer at the focal resource: antibiotics are a resource characterized by great heterogeneity (Penrose, 1959). There are several types of antibiotics from a *chemical* point of view, with some (e.g., methicillin) afflicted by a lot of resistance, making them less effective in treating even common bacteria. Another important distinction is between narrow- and broad-spectrum antibiotics, with the former being more precise in killing only specific bacteria, and accordingly causing less resistance, but requiring exact knowledge of which bacteria

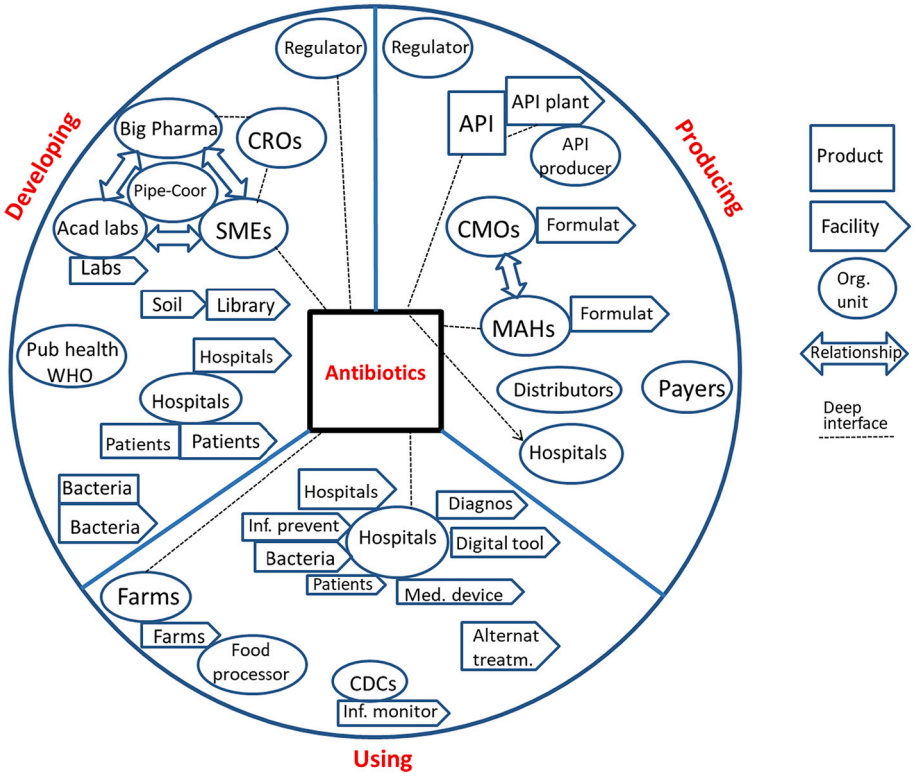

Fig. 2. Key resources and interfaces affecting the value of antibiotics in the developing, producing, and using settings.

cause an infection.

Another more general distinction is between old and new antibiotics, especially those currently "under development," which might fail at any point in the R&D pipeline, according to particular "risks of failures" depending on the stage they reached, e.g., an antibiotic in preclinical phase has a 97% risk of failing (Okhravi et al., 2018). An economically important feature distinguishing new from old antibiotics is also that new ones are covered by exclusivities such as patents allowing high revenues, which usually fall by about 80% the year an antibiotic goes "off-patent."

Antibiotics also differ in terms of production process, whether fermentation (a natural process based on yeast), synthetic or semi-synthetic, as well as if the antibiotic is a combination of two different substances (e.g., piperacillin-tazobactam). These two product features entail important interfaces with production facilities, with complex manufacturing, such as fermentation and combination antibiotics, increasing the risk of shortages, which eventually push the use of sub-optimal antibiotics and hence also increase resistance against the latter. Finally, an important product feature is the formulation of antibiotics (tablets/pills, intravenous liquids, ointments, or drinkable mixture), which has key interfaces with specific patient groups being able to take them (e.g., infants hardly tolerate intravenous antibiotics, and the elderly have often difficulties in swallowing pills); in this way, patients are indirectly connected with the production facilities where formulation occurs. While we will continue our exploratory policy analysis by considering an abstract antibiotic, a full analysis would require conducting multiple case studies on specific antibiotics, in order to account for the above heterogeneity of the focal resource we selected. In order to obtain a multi-faceted and more complete picture of the networks involved in the AMR problem, a series of case studies should be performed selecting, for instance, antibiotics belonging to the following categories: narrow vs. broad-spectrum antibiotics, generic vs. new antibiotics (including antibiotics still under development), and various formulations of antibiotics.

A similar kind of variety as for antibiotics exists also for all the other resources mapped on Fig. 2; for instance, while we indicate SMEs as a single type of resource, it indeed represents about 200 companies quite different from each other in terms of e.g., specific size (from zero to up to 200 employees) and origins (e.g., academia or industry spin-offs), but they share an engagement in antibiotics development, even if they focus on different types of antibiotics and each one conducts unique R&D projects. Therefore, specific case studies should be performed departing from particular SMEs and striving to represent their variation in terms of size and origins, for instance.

In the next steps of analysis, we delve into the resources and interfaces that affect the value of antibiotics in the three settings of developing, producing, and using (see Fig. 2).

3.9. Key resources and interfaces in the developing setting

The main resources involved in the development of new antibiotics are listed in Table 1, which also highlights their key features and interfaces affecting the value of antibiotics.

One of the main challenges in developing antibiotics is that these drugs are expected to attack an organism, a *bacterium*, which has invaded another organism, a patient, without causing damages to the other organism and all other beneficial bacteria found, for instance, in the patient's gut. Bacteria present an enormous heterogeneity: not only are there about 30,000 species of bacteria that are known and classified (Dykhuizen, 2005), with probably billions, if not trillions not yet discovered, but bacteria also mutate genetically continuously, which is indeed the root cause of AMR. Therefore, there is virtually an infinite number of bacteria: each bacterium can be slightly genetically different from others in the same species, which makes it resistant to a particular antibiotic.

Due to these challenges in the interface antibiotic drug-target bacteria, antibiotics R&D is a demanding and truly multi-disciplinary effort. As very few Big pharmas remain involved in antibiotic R&D, and interactions with academic labs have been limited, also due to the reduction in numbers and competence pool of the latter, *collaborative R&D platform* plays an important role. These are policy-initiated inter-organizational projects, also known as "Pipeline Coordinators," whereby academia, SMEs, and big pharma companies collaborate to develop new

Table 1
Resources and interfaces in the developing setting of antibiotics.

Resource	Type and features	Key interfaces
Soil/terrain	*Facility:* provides natural compounds (fungi)	Input to academia and SMEs to start R&D
Chemical libraries	*Facility:* includes previously identified compounds (tested or untested)	If public, free to access; if proprietary, can be kept secret or require payment
Bacteria	*Facility:* natural machinery that attacks patients and needs to be stopped *Product:* process material consumed during R&D projects to test the efficacy of a compound	Key interfaces with patients. Exchanged between laboratories and R&D developers. Antibiotic developed to target specific bacteria, which react by mutating
Patients	*Facility:* human bodies as machines under attack, defended by antibiotics *Product:* infected patients' specimens are process materials exchanged in clinical trials	Close interface with infecting bacteria and antibiotic tested in clinical trials. Specimens are key inputs exchanged between hospitals, CROs, and drug developers at listed prices
Academic laboratories	*Organizational unit:* skill in basic research in microbiology and early drug discovery teams *Facility:* advanced DNA analysis tools (more sophisticated than those of other organizations)	Despite an essential role to start R&D and contribute compounds to other developers, went from a few hundreds to about one hundred: declining knowledge pool
Big pharmas	*Organizational unit:* R&D teams, market and strategic analysis, distribution and investment functions	Pivotal interface with antibiotics via go/no financing routines/decisions. Only about 5 firms left in antibiotic R&D
SMEs	*Organizational unit:* about 200 new firms established as academic or industry spin-offs	Deep interfaces with their drug molecule and with CROs to conduct R&D projects; shallow interfaces with other units
CROs (contract research orgs.)	*Organizational unit:* the largest units capable of conducting clinical trials on antibiotics	The only organizations with deep interfaces with customers, i.e., Big pharmas and SMEs
Collaborative R&D platforms	*Organizational unit:* policy-initiated projects whereby academia, SMEs, and Big pharma collaborate to conduct R&D *Relationships:* deep interfaces between some partners	Can include deep internal social interfaces between partners (up to 50). Important interface with antibiotics R&D projects via their role of "pipeline coordinators"
Hospitals	*Organizational unit:* doctors and nurses performing clinical trials *Facility:* beds for hospitalized test patients	Interfaces with CROs for clinical trials, but usually no deep interface or relationship to maintain independence
Regulatory agencies	*Organizational unit:* has routines and procedures to evaluate and approve new antibiotics. Ability to adapt to special difficulties of antibiotics R&D: faster and anticipated approvals already in Phase 2	Deep interface to antibiotics by adapting approval routines. No interface allowed to antibiotic owners (SMEs and Big pharmas) to remain independent
Public health agencies	*Organizational unit:* national and transnational monitoring of infections and pathogen priority setting (WHO)	Orient antibiotic R&D toward most dangerous bacteria and occasionally fund specific R&D projects

antibiotics, usually funded by public money (for a review of the concept, see Baraldi, Lindahl, Savic, Findlay, & Årdal, 2018, and for a specific example, see Kronlid & Baraldi, 2020). These platforms can be viewed both as key organizational units, which contribute to the much needed development of truly new antibiotics, and as highly complex combinations especially of social interfaces and, if these interfaces are well developed, also deep relationships between the partners they include, which in some cases can be over 50. Another group of organizational units with a key role in the developing setting are *regulatory agencies* in charge of evaluating and approving new antibiotics; to account for the complexities of antibiotic R&D, these units have made important adaptations, such as the US FDA which applies faster evaluation routines and allows for the launching of products already in Phase 2, i.e., years before having results from hundreds of patients. This adaptation corresponds to a deeper interface with antibiotics in general (see the dotted arrow in Fig. 2), but no relationship or even shallower interface with a specific developer (SME or big pharma) is allowed in this area.

As mentioned above, an important analytical step is to assess if there are missing, too shallow, or unfavorable interfaces that negatively affect the policy problem at hand, namely the creation of value via developing and launching new antibiotics. As for the depth of the interfaces (Baraldi et al., 2012; Baraldi & Waluszewski, 2007), our exploratory analysis seems to indicate that this developing setting presents predominantly *shallow* interfaces. While SMEs are strongly dependent on their antibiotics projects (see the central dotted arrow in Fig. 2), big pharmas are not particularly connected to such projects and often terminate them because of insufficient monetary flows. Only CROs have somewhat deeper social interfaces with their customers (see the dotted arrow connecting CROs to SMEs and big pharmas), even though these interactions can hardly be viewed as full-blown and long-term business relationships (Håkansson & Snehota, 1995), and are accordingly not displayed as such on Fig. 2. This situation explains the attempts by policymakers to create or reinforce some of these interfaces, for instance, by funding collaboration platforms like Pipeline Coordinators, which indeed include or also stimulate actual deeper relationships between their partners (Kronlid & Baraldi, 2020). The identification of these missing or shallow interfaces is clearly a preliminary result which needs to be verified via more detailed analyses and multiple case studies, using as focal resources different specific antibiotics or some of the other most salient resources in the developing settings.

3.10. Key resources and interfaces in the producing setting

Table 2 features the main resources involved in producing and distributing antibiotics, as well as their key features and interfaces affecting the value of antibiotics in the producing setting.

It is not only the development of new antibiotics that is challenging but also securing a steady supply of existing antibiotics to patients, as witnessed by the increase in antibiotics shortages, which points at barriers to creating a key value such as availability of these essential products. Problematic interfaces appear both on the demand and the supply side of the networks involved in the producing setting. Considering that the heterogeneity in the need for antibiotics is spread among hundreds of hospitals and thousands of doctors, it is quite difficult to forecast the volume of each specific antibiotic that needs to be produced and distributed to specific clinics and pharmacies. A further problem is that payers have pushed down the prices of antibiotics to levels that leave very limited profits for the various organizational units in the supply chain (from wholesalers to MAHs, and from CMOs to API producers), making it difficult for them to invest in upgrading their own production facilities, with clear consequences in terms of supply risk and even pollution.

Creating values such as availability and avoiding destruction of the therapeutic value of antibiotics through wastewater emission requires well-functioning interfaces in the various steps of the typical supply chain, going from API plants to formulation plants and all the way to hospitals and patients. However, price pressures from payers push low margins all the way upstream in the supply networks, at the level of API plants, where the risk of both delays due to production accidents and pollution is the highest. Any delay or shortage at that stage will then trickle and amplify downstream in the network; even if formulation plants are modern and more flexible, the problem is that they will simply be out of input materials from API plants. In this situation, it is particularly interesting that the *relationships CMOs-MAHs* are usually more developed than those between other organizations in the producing setting; in particular, MAHs tend to keep API producers at arm's length

Table 2
Resources and interfaces in the producing setting of antibiotics.

Resource	Type and features	Key interfaces
API (active pharmaceutical ingredients)	*Product:* the key component giving antibiotics their curative power. Usually patented, but no exclusivity for old antibiotics	Until patent expiration, APIs have deep interface with the pharmas owning them; then they are open for all generic producers
API producers	*Organizational unit:* both manufacturers of generics (80% volumes from China and India) and manufacturers of new proprietary APIs	Producers of generics focus only on the API-step of production for many antibiotics, while proprietary producers are vertically integrated and focus on a single product
API manufacturing plants	*Facility:* very large batch sizes and inflexible, many plants getting old, lacking investments due to low profitability from antibiotics	Deep negative interfaces with antibiotics due to emissions causing AMR in waters, and accidents/stops causing shortages
Formulation plants	*Facility:* process API into final drug (e.g., pill or injectable), smaller batch size, upgraded and modern, thanks to higher profitability	Owned by MAHs or CMOs, located close to end markets (US/EU), lower pollution and accident/stop risk
CMOs (contract manufacturing orgs.)	*Organizational unit:* specialized in formulation/ packaging. Some global players with billion Euros in turnover	Deeper interfaces with their MAH customers than with the latter's specific products, including antibiotics
MAHs (market authorization holders)	*Organizational unit:* Pharma firms holding the patent for a new or the right to sell a generic antibiotic on a specific market	Some MAHs own formulation plants, esp. for new antibiotics. Large MAHs sell many products, and some specialize in generics
CMOs-MAHs	*Relationship:* close connections, established with large volumes and long-term contracts	This interface covers multiple products of an MAH and awards continuity and adaptations in the supply of selected products
Regulatory agencies	*Organizational unit:* can be same as those granting approval for new drugs, but here they approve plants for production	Major impact of local regulators, not only US (FDA) or EU (EMA) on which plants can produce: risk of weak emission controls
Distributors	*Organizational unit:* wholesalers and pharmacies performing logistics and sales, via ordering routines, inventories, and IT tools	Strong impact on antibiotic availability for patients, depending on competences and routines; lacking in low-income countries
Payers	*Organizational unit:* decide prices and reimbursement, and contracted volumes in public as well private healthcare systems	Strong impact on antibiotics' profitability by defining price levels and on the certainty of demanded and produced volumes
Hospitals	*Organizational unit:* both clinics and single doctors select antibiotics, formulations, pack size: express very heterogeneous needs	Affect production by ordering specific antibiotics, depending on the patterns and volumes they need of specific products

to minimize purchase prices, whereas they would need to create more mutual relationships with API producers to improve coordination.

Summing up, if we look at the depth of interfaces in the producing setting, some have become *too deep* but with negative effects; e.g., old API plants pollute the environment, causing resistance and eventually making the focal antibiotic ineffective, or are the sole supply plant still in operation, causing global shortages in case of accidents (see the dotted chain of interfaces in Fig. 2 going from API plants through a focal antibiotic and finally affecting hospitals). Other interfaces are instead *too shallow* to sustain value creation, such as purely standard interfaces and arm's length relationships between API suppliers and generic manufacturers or MAHs, or are even *missing*, such as limited communication and coordination between antibiotics suppliers and hospitals on when shortages will occur, or lack of long-term contracts between antibiotics suppliers and payers, especially in public healthcare systems, often due to public tendering regulations (Waluszewski & Wagrell, 2013). The deleterious or missing interfaces that we identified here are the result of just an exploratory analysis and need to be verified by studying various antibiotics via detailed case studies, as the nature of the interfaces in the respective supply and distribution networks may vary, considering also the different geographic configuration of their supply chains as well as if they are exclusive as opposed to generic antibiotic.

3.11. Key resources and interfaces in the using setting

The use of antibiotics involves those presented in Table 3 as main resources. The table also shows the key features and interfaces that affect value creation or depletion for antibiotics in the using setting.

The using setting of antibiotics is highly heterogeneous, especially because it includes both human use and, at least until strong conservation measures will be introduced, animal/farming use. *Hospitals* are organizational units that have a major interface with antibiotics, being their key user, because only hospitals and doctors are allowed to prescribe them in most healthcare systems. However, these organizational units' ability to preserve the value of antibiotics depends on their knowledge of AMR, routines to prevent infections (e.g., simply handwashing), which vary greatly from place to place, and routines to contain irrational use, including sophisticated stewardship programs such as antibiotics rounds or availability of 24/7 diagnostic services. In particular, *diagnostic devices* are facilities that can allow, if widely used, precise and rational use of antibiotics. They can have different focus (from simply spotting viruses vs. bacteria to more sophisticated indicators of bacterial species and their resistance to specific antibiotic), different speed (the faster the better in order to enable quick decisions about which antibiotic to use on a patient), and different precision (the higher the precision, the more complex and expensive the device). The ideal but not yet available tool would be very rapid (below 4 h), inexpensive, relatively precise, and small enough to keep in doctors' offices, where daily decisions need to be made rapidly.

However, even if widely implemented in hospitals around the world, rapid and precise diagnostics and stewardship programs would not help to preserve the value of antibiotics, because a major blow comes from massive irrational use of key antibiotics in animal and fish farms. Large-size farms even use critical, reserve antibiotics like colistin mixed with fodder as a growth-promotion factor to prevent infections, instead of dedicating sufficient space for animals to reduce infection risk.

The interfaces among the above resources in the using setting present similar and possibly even more serious issues than those in the producing settings: there are *too deep* interfaces that need to be cut between antibiotics (including critical ones) and animal farms, which literally abuse them; but most interfaces are quite *shallow*, including the interface between the organizational units of hospitals and diagnostic devices, which, even if available, tend not to be implemented, witnessing the many barriers to using medical devices despite their potential value (Wagrell, 2017). We identified these deleterious or shallow interfaces on the basis of a general analysis of the using setting. Therefore, these preliminary results can be considered as hypotheses that need to be confirmed and verified via more detailed analyses including a series of specific case studies on single antibiotics to verify, for instance, the differences in how the value of new, as opposed to old, antibiotics is preserved. Additionally, case studies using different hospitals in different countries as a focal resource would also help to gain a broader and more multi-faceted picture of how resources interact in the using setting.

Table 3
Resources and interfaces in the using setting of antibiotics.

Resource	Type and features	Key interfaces
Medical devices	*Facility:* tools applied to perform treatments, ranging from surgery to chemotherapy and ventilators in intensive care units	If not perfectly sanitized, they spread the resistant bacteria infections to many patients
Hospital buildings	*Facility:* design/structure, e.g., space and barriers between patients and ease of sanitizing rooms	Can affect strongly the diffusion of infections
Hospitals	*Organizational unit:* both clinics and individual doctors are usually the only ones allowed to prescribe antibiotics	Major interface with antibiotics, being the main user. Great variations in ability to "preserve" antibiotic value via stewardship
Diagnostic devices	*Facility:* can detect and distinguish infections (e.g., viral vs. bacterial), with varying precision and speed	Important interface to preserve antibiotic value if rapid results and widely used, but hard to implement routinely and broadly
Digital support tools	*Facility:* can facilitate diagnosis, selection of right antibiotics, and optimal dosage	Similar to diagnostics, can improve strongly rational use of antibiotics
Farms	*Organizational unit:* animal and fish farmers seek savings by reduced space and revenues by using antibiotics for growth promotion *Facility:* too narrow spaces between animals increase the risk of infections	Negative interface currently destroying antibiotic value: account for a major share of irrational, unmotivated use of antibiotics on healthy animals to promote growth, which triggers AMR
Food processors	*Organizational unit:* purchase meat/fish from farmers, some global players (e.g., McDonalds)	Can push positive effects (e.g., require no-antibiotic meat) or amplify negative ones (spread meat with resistant bacteria)
Alternative treatments	*Facility:* e.g., phages, viruses engineered to kill bacteria	Substitute for antibiotics, reducing pressure to use and saving their value for future use
Infection prevention solutions	*Facility:* clean water, sewage systems and vaccination programs to avoid bacterial infection in humans and animals	Strong contribution to save antibiotic value by not using it: e.g., massive savings in Norway thanks to a vaccine for salmon
CDCs (centers for disease control)	*Organizational unit:* Monitor antibiotic infections in specific areas, verifying the rate of resistant bacteria per area/country	Can influence doctors' prescriptions by indicating local outbreaks and resistant bacteria strains, hence affect use.
Infection monitoring systems	*Organizational unit:* usually run by CDCs with routines for data collection and spread, global coordination by WHO *Facility:* IT systems and global databases	Complex resource combinations trace infections locally and globally to prepare for pandemic and orient antibiotics use (e.g., GLASS www.who.int/glass/en/system).

3.12. Connections between the developing, producing, and using settings

After analyzing the resources and interfaces inside each setting per se, the next analytical step for policymakers is to consider how the three settings are related. This analytical step embraces a more aggregate level of analysis than single interfaces and settings, thereby providing a novel,

more comprehensive, and multi-faceted view of the AMR problem, which has usually been considered (see e.g., DRIVE-AB, 2018; Outterson et al., 2015) as arising from three separate, or even conflicting, issues of *innovation* (the developing setting), *availability* (the producing setting), and *stewardship* (the using setting). In this regard, the RIA allows to both zoom-in and penetrate into specific resource interfaces inside single settings and to zoom-out and capture the indirect, hidden, connections that stretch across settings, as the involved resources are all part of a large, more complex network, shown in Fig. 2.

In fact, RIA and 4Rs can analyze these complex networks by "breaking them down" into portions, such as the developing, the producing, and the using settings, but these analytical tools can also capture the connections or missing connections between these portions/settings of the larger network, which can be the sources of both problems and solutions in the AMR challenge, because these connections or missing interfaces between settings can impact value creation. Other theoretical and analytical tools that do not consider inter-organizational interactions, interdependencies, and complex resource combinations would be unable to trace these indirect, often hidden, connections behind value creation processes (Baraldi & Strömsten, 2006).

We already stressed, as a preliminary result, the *lack of deep interfaces* within each setting. Likewise, from our exploratory analysis, it is not possible to identify deep interfaces that connect the three settings for creating and sustaining the value of antibiotics. There are instead mostly single resources which connect the three settings because they appear in two or more of them. As shown in Fig. 2, these resources are hospitals (involved in three settings), bacteria and patients (involved in the developing and using settings), regulators (involved in the developing and producing settings), and possibly MAHs for the proprietary antibiotics they developed themselves. It seems like the three settings do not only strictly follow their own different logics (Håkansson & Waluszewski, 2002), but the lack of economic and natural sustainability in the production and the use of old antibiotics has also transmitted negative effects on the development of new antibiotics. The RIA can trace these indirect effects from inappropriate use of antibiotics by farms and hospitals in the using setting, which causes restrictions in use and hence sales, to reduced profitability for MAHs and other organizational units in the producing setting, which, in turn, reduces the financial means and the number of organizational units still active in the developing setting.

This exploratory analysis also shows that physical resources are too loosely connected, that is, interfaces are too shallow to create value in a context where physical resources would need to be mutually adapted, such as diagnostic tools and hospital facilities (in the using setting) or API and formulation plants (in the production setting); or physical resources are "wrongly" connected, that is, interfaces are deep but connect resources in ways that destroy key values like therapeutic efficacy or availability, with negative effects such as increased resistance or antibiotics shortages.

Social resources are also too loosely connected; this implies a lack of coordination, which would be needed to jointly develop new antibiotics, and market competition on generics, which further reduces the value of old antibiotics. Across all three settings, there is a striking *lack of full-blown relationships* as a resource type in the network of Fig. 2. The only full-blown relationships we could identify are around Pipeline Coordinators, between academic labs, SMEs and big pharmas in the developing setting, and between MAHs and CMOs in the producing settings. Instead, between most business-related organizational units, there are predominantly standard and arm's length relations, corresponding within the 4Rs model to not so deep interfaces between organizational units (see e.g., CRO-SMEs in the developing setting), rather than full-blown relationships. Moreover, relationships between some types of organizational units are considered as inappropriate and therefore avoided, such as between public payers or hospitals, on the one hand, and MAHs or pharmaceutical firms, on the other hand; and especially between the latter and regulatory agencies, which must retain absolute independence from private parties.

The lack of full-blown relationships and of deep interfaces connecting the three settings appears clearly from our exploratory analysis. However, further and more detailed case studies are necessary to verify these findings and to understand two additional key issues that would help policy efforts in supporting value creation in the antibiotic field: (1) which conditions favor the emergence of those few full-blown relationships that do appear and (2) which particular resources are pivotal for value creation and, accordingly, need to be connected through deep interfaces within and across the three settings.

3.13. Capturing and evaluating policy interventions in the antibiotics field with the RIA

A final step in our exploration of how RIA can be applied to policy analyses is to use our tools to examine available interventions to address AMR and how RIA can help refine and develop them further. However, we are not applying RIA here in order to devise new interventions, because this is a highly demanding task which would require a dedicated study and indeed a string of papers, each one focusing on specific policies. We delimit us to selecting six of the main policy interventions and solutions already proposed or underway, two for each of the three settings, and to considering how the RIA, in general, can inform future policy interventions by capturing new facets of the AMR problem. A general principle is that, using the lens of the 4Rs model, any policy interventions addressing AMR needs somehow to *change or create interfaces in the resource network* of Fig. 2 in order to improve value creation or avoid value depletion around antibiotics – the focal resource we have selected for our explorative study. Accordingly, we now assess if the six selected interventions can be explained and refined by means of the RIA.

Two policy interventions addressing the development setting are Pipeline Coordinators and market entry rewards (MERs). Pipeline Coordinators aim specifically to promote collaboration and reinforce especially social interfaces, including building relationships between key organizational units in this field. Therefore, this policy intervention is fully captured by and in line with the 4Rs model and RIA. Moreover, these analytical tools can also suggest refining Pipeline Coordinators by helping policymakers identify the specific resource interfaces that these new organizational units should create or reinforce (e.g., between a specific antibiotic, academic lab, and selected hospitals for clinical trials) as well as how these interfaces on the developing setting can be connected to the using and producing settings; for instance, which particular social or physical interfaces would be needed and should be part of the analysis prior to creating and funding a new Pipeline Coordinator? And how would it interact with other similar organizational units already established in the broader network, including those in the using setting?

MERs are lump-sum payments of several billion dollars given to developers of a new antibiotic upon launch, as a way to improve its profitability and reduce the risk of termination of an antibiotic project due to financial reasons. MERs do not intervene per se by directly changing any specific resource or interface on Fig. 2. These incentives only increase the monetary expected net-present value (ENPV) of new antibiotics (Okhravi et al., 2018), but it is not possible to pinpoint which specific interfaces they might indirectly help forge or reinforce via the 4Rs model. Hence, MERs are policies not captured by RIA alone and would require additional analytical tools capable of penetrating the financial and contractual dimension of interorganizational networks, as discussed below. However, MERs are commonly discussed in the literature and policy circles as financial interventions that rely on the market mechanism and competition to reward the "best" product and developer (DRIVE-AB, 2018). Therefore, this literature and policy framing of MERs do not consider the fact that MERs will indeed also affect the interactions between organizational units that compete for MERs and the very ways in which they will combine their resources, such as labs and antibiotics compounds, with those of other units. These other organizational units

can be both other developers competing for the same reward and units holding complementary resources, such as patient specimens necessary for clinical trials or venture capital necessary for developers to survive until they can launch to market their product. A resource interaction-based approach would allow one to identify and hopefully pre-empt a MER's potential indirect negative effects of which can spread across the network, such as barriers for developers to access patients' specimen at hospitals due to ongoing competitive races to obtain a MER.

Two policy interventions currently discussed for the producing setting are (1) premiums/penalties for respectively sustainable/polluting production in order to contain environmentally driven AMR and (2) reshoring API production back to Europe/US in order to improve availability. Both policies take into account the "negative" deep interfaces discussed above. A new insight that the 4Rs model would stress is to weigh in carefully the effects of these policies on indirect interfaces. For environmental sustainability premiums/penalties, one must clearly define at which level of the supply chain they are applied as they will have different effects, including unwanted ones; for instance, if applied at the API plant, environmental penalties may cause shortages if there is only one or too few plants in operations globally. Therefore, RIA would suggest to refine an intervention like environmental premiums/penalties by starting from mapping the supply network for selected antibiotics from MAHs, through formulation plants (often owned by CMOs) and all the way up to API producers and plants. Breaking negative (high-pollution) interfaces with API producers via penalties should be an option only if there are alternative API producers. However, if there are no such alternatives, it might be a better option to improve those negative interfaces through premiums that can be transferred upstream as funds for upgrading API plants.

As for the other policy measure proposed for the producing setting – reshoring API production – applying the RIA would suggest that this intervention requires recreating interfaces when plants are (re)built in a new country, which may oppose the re-embedding of resources, such as organizational units, if local knowledge of chemical production is no longer available. Nonetheless, the unexpected consequences may be global overcapacity and antibiotics being sold underpriced to animal farming, causing even more AMR. Hence, the RIA can advise about considering both the resource-related barriers to implementing API reshoring and the potential indirect negative effects elsewhere in the network of this policy. All in all, both selected policies addressing the production setting can be analyzed and refined through the RIA.

Two important policy interventions for the using setting are (1) stewardship programs based on the use of rapid diagnostics and (2) banning antibiotics use as growth promoter in animal farming. The two measures address, respectively, missing and "negative" deep interfaces shown in the resource network of Fig. 2. For the first intervention, the RIA and the 4Rs model can provide new insights by pinpointing the difficulty in implementing rapid diagnostics due to the many resource-related barriers, such as a hospital's accounting and evaluations routines (Wagrell, 2017), to embedding in the healthcare setting even strongly needed new technologies. Moreover, the RIA can suggest how the new diagnostic solutions and other resources in the using context, such as patient samples or organizational routines (e.g., the opening hours of hospital laboratories or dedicated analyst teams), can be adapted to each other to facilitate embedding into large-scale use. As for the animal use-related ban, the RIA can help policymakers consider its indirect effects on local farms if the ban is not truly global, such as comparatively higher costs only for farms respecting the ban as opposed to those not required to do so by more lenient governments, with the risk for the former of being outcompeted. Further, the RIA can stretch the analysis to even broader effects of this policy ban, such as increased prices of meat and fish for the direct customers of farms, namely food processors, and then eventually also for consumers.

Summing up, RIA and the 4Rs model can help policymakers identify the lack of deep positive interfaces in general and specifically the lack, or weakness, of organizational relationships in the whole network embedding antibiotics (see Fig. 2). Hence, a generalized and important policy measure that RIA suggests is promoting the development of such relationships, as they are the cornerstone of improved interorganizational collaboration and coordination, two elements which have been sorely missed in the antibiotics field. RIA and the 4Rs model can capture the content and effects of the above policy interventions, except for MERs. A possible explanation is that these analytical tools penetrate well the *value creation* side of the AMR problem, i.e., the social and material effects of the combination and re-combination of activated resources, and possibly also the *value measuring* side, i.e., how value is measured in its various dimensions. However, RIA alone is not equally capable of penetrating the *value capturing* side (Baraldi & Lind, 2017), which is related to monetary flows and deal structures (Håkansson & Olsen, 2015), as will be discussed in the concluding section.

However, despite the current limitation of the RIA in capturing the financial and legal dimensions of networks, this research toolkit can bring unique new insights to policy analyses, especially of a complex issue like AMR. In particular, RIA would require policymakers to pay greater attention to indirect, hidden network effects that should be considered before a policy is designed; and then, while that policy is being implemented, RIA would require following it up to monitor these indirect effects in order to take corrective actions if negative, possibly unexpected, consequences would appear for the resources and interfaces targeted by a policy interventions. The general logic of RIA-based policies would be to make explicit, target, and possibly exploit the micro- and meso-level interactions and interdependencies that characterized the interorganizational networks behind both a global sustainability challenge like AMR and its potential solutions. In doing so, the RIA differs clearly in its contribution to policy analyses from other theoretical approaches. Even if we cannot conduct a full comparison here, we can identify some clear differences between the RIA and three influential approaches in current policymaking: two approaches focusing on resources, namely the Resource Based View, RBV (Grant, 1991), and Resource Dependency Theory, RDT (Pfeffer & Salancik, 1978), and one approach focusing on the system level from a more macro perspective than RIA, namely Innovation Systems (Edquist, 1997). These three approaches have analytical merits and have contributed important insights to policy, but there are also facets of policy problems that they cannot capture, and which the RIA instead can illuminate.

In particular, RBV (Grant, 1991; Lavie, 2006) has the ability to highlight the importance of unique resources and resource bundles that, to be successful, organizations need to control internally; hence, RBV can suggest to policymakers *which* deficiencies in the resource bases of key organizations should be filled. However, RBV cannot say much about *how* to fill those deficiencies, nor can it capture interdependencies and resource interfaces outside the single organizational unit, or indirect, hidden network-level effects, which, instead, the RIA is particularly apt in identifying. RDT (Pfeffer & Salancik, 1978; Hillman, Withers, & Collins, 2009) is good for identifying organizations' need to create interorganizational relations to handle their resource deficiencies, causing resource dependence on external actors; hence, RDT can also suggest to policymakers the type of relations that they can promote to compensate organizations' limited resources (e.g., interlocking directorates, alliances, or even vertical integration). However, RDT does not penetrate into the specific configuration of interdependencies and how external resources need to be combined, for instance, via particular interfaces, to solve these dependencies, which are instead the key insights brought by the RIA. Moreover, RDT focuses on dyadic relations, not the network-level connections between organizations, which are the main focus of RIA. Finally, the Innovation systems approach (Edquist, 1997; Sharif, 2006) enables policymakers to see the importance of connecting various material and immaterial elements to build robust systems supporting innovation in a specific location. However, this approach does not penetrate the micro-level interactions between specific resource elements and also restricts the system under investigation to specific geographies, such as regions or countries, whereas the

resource interfaces behind AMR and also potential solutions cross all possible geographical boundaries, in all three settings of developing, producing, and using, which RIA can clearly capture.

4. Conclusion: An agenda for applying the RIA to policy analysis

By relying on the concrete example of AMR, this paper has explored how the resource interaction approach (RIA) and the 4Rs model can be applied to conduct policy analysis. On the basis of this exploration, we propose the following steps to define an agenda for applying these tools to policy issues:

1) *Defining the empirical and the policy problem:* the RIA stresses that, for instance, AMR entails an empirical problem of value destruction and/or lack of value creation, which implies that policy needs to support value creation processes through changes in selected resource interfaces, including those that would allow conservation of value for future use.
2) *Selecting a focal resource as an entry point to start analyzing complex networks*: for AMR antibiotics can be selected, but one has to consider that with the selection of a focal resource one will obtain a particular picture of the network, as the focus of policy actions would be on the values of this resource. Moreover, selecting a focal resource also implies redefining in more specific terms the empirical and policy problem mentioned in point 1: for instance, as a problem of lack of innovation of new antibiotics, or insufficient availability, or excessive and irrational use. Therefore, to open up the analysis, the following are also advisable:
3) *2.1) conducting multiple case studies:* this parallel stream of analyses allows to obtain a multi-faceted view of the problem at hand and possible solutions. In practice, this step means selecting also other focal resources too (e.g., hospitals, pharmas, or different types of antibiotics) to construct several case studies and alternative network maps, each one with a different resource in the center.
4) *Zooming in on the focal resource and its heterogeneous value creating features:* this step should be conducted within each of the parallel case studies and would further contribute to a multi-faceted picture of the problem at hand. Identifying many possible values can in fact open up for multiple specifications of the policy problem at hand and also of more potential solutions.
5) *Identifying the main resources and interfaces affecting value creation:* this step includes placing these resources and interfaces too in the three settings of developing, producing, and using for each of the selected case studies.
6) *Tracing the connections between the three above settings*: this step aims to understand if the settings are well connected or not in order to create and/or preserve value. This part of the analysis corresponds to identifying missing or shallow interfaces which hinder value creation (e.g., limited collaboration among organizational units for antibiotic R&D), or deep ones that destroy value for the focal resource (e.g., excessive use of antibiotics in animal farms).
7) *Capturing and evaluating selected policy interventions by means of RIA, the 4Rs model, and network-level analyses of "deal structures" and "monetary flows"* (Håkansson and Olsen, 2015). A complete application of these tools would also embrace a further step, no. 7, not performed in this paper, of *devising new policy interventions* by using the RIA.

Complementing RIA and 4Rs with the constructs of deal structures and monetary flows enables capturing *regulatory/legal* and *financial issues* too. IPRs motivate actors in their decisions on key resources and investments, especially in highly regulated fields like pharmaceuticals; and the forecasted and actual financial flows are essential in motivating or demotivating actors to act and decide on resources. In fact, AMR, like many sustainability problems, is not only a matter of "value creation" and "preservation" but also of "value appropriation" (Baraldi & Lind, 2017), that is, how much value specific actors receive in the form of money/returns around a focal resource. Several of the policies proposed to address AMR aim to change the monetary flows accruing to various actors, such as MERs or higher unit prices per antibiotic, and legal rights, such as who will own the IPR on subsidized antibiotics. Thus, a more comprehensive policy analysis framework based on RIA can be depicted in Fig. 3 below, which adds the further layer of monetary flows and deal structures to the model in Fig. 2.

4.1. The potential contribution of the RIA to policy analyses

An analytical framework composed of RIA, deal structures, and monetary flows, would mainly provide two new insights to the policy analysis:

(1) Better understanding of the extent to which deal structures and monetary flows reflect the actual resource interfaces and combinations that affect value creation. Previous studies (Håkansson & Olsen, 2015; Perna et al., 2015; Waluszewski et al., 2017) indicate that the legal and monetary dimension of networks *does not reflect at all* the social/material resource structure. Indeed, part of the AMR problem derives from a *mismatch* between the *societal value* of antibiotics (for public health) and the *monetary flows* to developers and producers of antibiotics. This is why several policy suggestions concern financial incentives to *increase such payments*, and others promote *new methods to assess the monetary value* of antibiotics, moving beyond health economics' focus on direct patient outcomes in order to embrace the interdependencies between various treatments, including more complex and indirect forms of value (DRIVE-AB, 2018; Wagrell, 2017). Hence, part of the policy solution in AMR, like in many other fields, such as environmental pollution, is a change in value measuring (Baraldi & Lind, 2017). Only by making explicit all values and costs related to a key resource (such as the cost of resistant infections or antibiotics shortages) can solutions be found on how to improve value creation and also influence value appropriation by specific actors.
(2) Ability to identify how modifications in the deal structures and monetary flows can induce changes in the activated resource structures, that is, concrete innovations which create or preserve value for society and key users. Any such change would be more accepted and easier to implement if part of this value can be appropriated monetarily by key actors (e.g., SMEs or large corporations). In fact, policy discussions on incentives to antibiotics R&D stress that public interventions need to attract new private investments as well (DRIVE-AB, 2018), rather than lead to "nationalizing" this field; and private investments are easier motivated if private actors can capture a share of the financial gains.

Next to the two aforementioned insights, applying RIA offers several other benefits to policy analyses. Firstly, these analytical tools offer policymakers a great *flexibility* in choosing the points of departure for the analysis (any resource or interface of relevance) and in selecting particular value(s) to be prioritized. Such a flexibility derives from RIA and 4Rs being non-normative models per se, which implies that they require policymakers themselves to make clear choices on the values and variables to be prioritized. Another benefit of these models is that they make it possible to *analyze both physical* and *social resources* involved in the problem at hand. Moreover, they have the *ability to visualize* the many resources and interfaces involved in value creation (or lack thereof) and to capture complex connections between resources, including *indirect interdependencies* and *hidden network effects* (e.g., from API plants all the way to hospitals).

Another benefit is that RIA allows for *identifying shallow or missing interfaces that hinder value creation* (given the selected focal resources

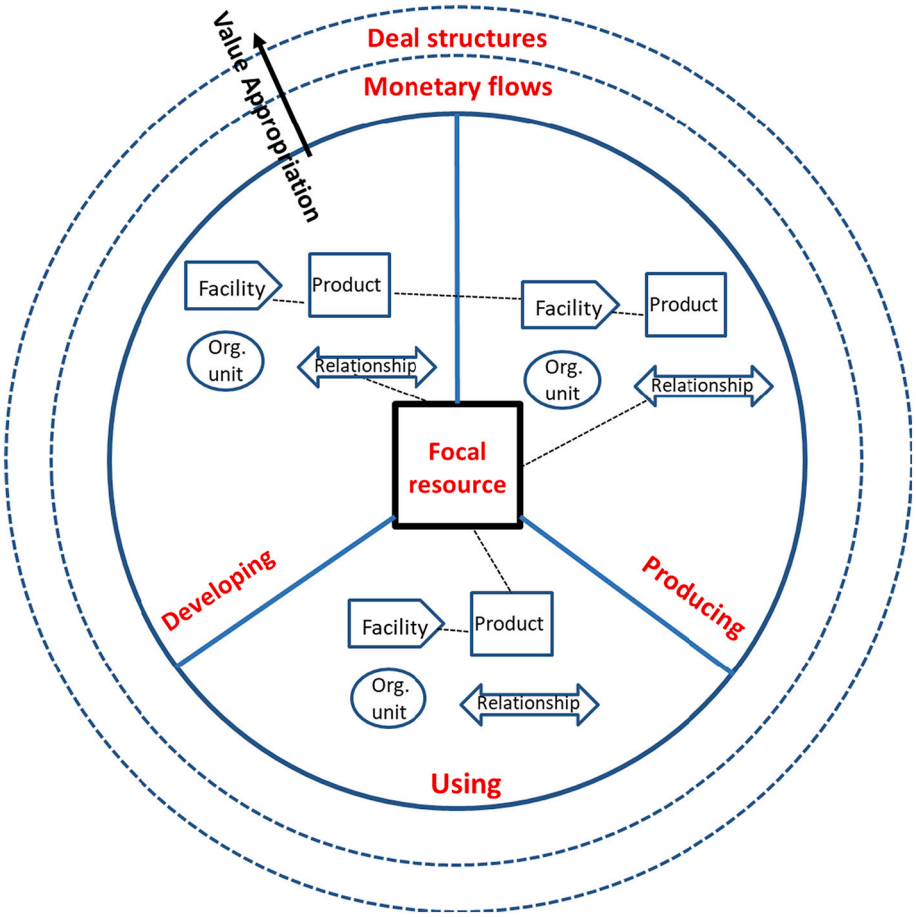

Fig. 3. A developed framework to capture resource interaction, monetary flows, and deal structures.

and values), as well as *deep interfaces that cause value depletion or other negative effects*. Shallow interfaces entail that the connections between resources that would be needed to create value are so weak that value creation cannot happen. However, there can also be interfaces between resources that are deep but connect resources in the wrong way, namely in ways which destroy value, such as the deep interface between farms and antibiotics. This interface entails overuse and hence accelerates resistance for antibiotic that should be reserved for exclusive use for certain patients in extreme cases. Finally, the models considered in our study have the advantage of *capturing several potential* solutions to the problem at hand, depending on the identified problematic interfaces and how these resources and interfaces can be changed. This benefit also stretches to RIA pointing out the network-related barriers to such changes required by implementing the proposed policy solutions – barriers which originate, for instance, from the friction and heaviness of the overall resource structure (Baraldi et al., 2012; Håkansson & Waluszewski, 2002).

These contributions of RIA to policy analyses clearly distinguish this toolkit from other theoretical approaches that we considered in Section 4, such as RBV, RDT, and Innovation Systems. While the full appreciation of a complex and multi-dimensional problem like AMR would require a holistic approach based on multiple theoretical perspectives, the RIA can still contribute to highlight new and unique facets of this problem. In particular, most of the theoretical perspectives informing policy assume that the empirical field is less interconnected and interdependent than what the RIA reveals, and that solutions to empirical problems arise from more competition, instead of the collaborative interactions which are the hallmark of the RIA. If we recognize that interactions, interdependencies, and interconnectedness are basic features of the economic landscape (Håkansson et al., 2009), then we can assume that these micro-level interconnections will also create consequences for the broader system, at macro- level. While reaching this broader, holistic perspective on a complex policy issue like AMR would require a dedicated theoretical development and is beyond the scope of this paper, we have hopefully shown a potential direction to reach that goal by discerning highly complex network-level patterns through a set of micro-level interactions and connections. Further research can thus look for the impact of these network patterns and micro-interactions upwards in the macro-system.

This bottom-up approach to framing and addressing policy problems is clearly different from the macro perspective applied, for instance, by the Innovation Systems model (e.g., Edquist, 1997), which starts from the overarching level to search for patterns and causal factors. While these factors may be easy to identify, as they are often selected from established lists of system components, their causality may be quite difficult to demonstrate because the mechanisms causing macro-patterns are often multiple and found at the intricate micro-level, filled with intertwined complex interdependencies. Thus, devising policies that address the underlying causes of a complex problem like AMR requires conducting detailed micro-level analyses, such as the ones allowed by the RIA, at some point in the policy development process.

Despite potential contributions, there are also limitations in applying RIA and the 4Rs model to policy analysis, which depend on their logic and focus. Firstly, these models do not cover well issues at the *actor-level* (Håkansson & Snehota, 1995) such as culture, traditions, perceptions, and persuasion, which in sustainability challenges are pivotal for consumer/patient behavior and can influence it through e.g., communication campaigns. Further, these tools do not capture well *groups and individuals* independent from particular organizations, such as communities of professionals or experts, who can be important sources of

knowledge and action in many sustainability challenges.

This paper is a first attempt to explore how RIA can be applied to complex policy problems. Much research and refinements are still necessary before these tools can be fully applied in policy analyses and their ability assessed more concretely. To start with, further research is necessary to make a comprehensive and systematic comparison of RIA and 4Rs with other analytical and theoretical tools currently used within policy, such as stakeholder analyses, cost-benefit analyses, Innovation Systems (Edquist, 1997), and Regional Clusters (Porter, 2000). Moreover, we only identified the need to combine RIA and 4Rs with deal structures/monetary flows, which has so far occurred in single cases of policy efforts, but such combined models, as in Fig. 3, need to be applied on more general policy analyses of global challenges. Next to these conceptual developments, it is also important that further and more comprehensive applications of RIA to policy issues like AMR build on detailed and multiple case studies, capable of offering multi-faceted views of the empirical problem at hand. Further research should also apply RIA and 4Rs where they likely fit best in terms of unit of analysis, that is, policy interventions that operate on specific resources and interfaces, especially if they engage interorganizational networks, such as Pipeline Coordinators (see Baraldi et al., 2018).

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