DRIVE AB RE-INVESTMENT IN R&D AND RESPONSIBLE ANTIBIOTIC USE

Work Package 2, Task 4: **FINAL REPORT**

Solutions from other industries applicable to the antibiotic field

2016-01-12

Official title of WP2 Task 4: Assess reward and business models in other industries that promote conservation and that address key challenges similar to antibiotics

Task 4 team:

Enrico Baraldi, Francesco Ciabuschi, Jens Eklinder, Carl Kronlid, Ross Leach, Olof Lindahl, Ka Lum, Kevin Outterson, Jens Plahte, Kellie Ryan, John-Arne Røttingen, Susan Wood, and Christine Årdal

Contents:

1. Introduction

1.1 The aim and scope of this report

The main aim of Task 4 of Work Package 2 of the DRIVE-AB Project is to identify, describe and select a number of reward and business models from other industries that could be adapted to reinvigorate innovation in antibiotics, while facilitating access and responsible use. In practice, these "models" entail various types of solutions of organizational, economic and legal kind, stretching from new contracts to traditional monetary (dis)incentives, and from new financing schemes to the introduction of new organizations and infrastructures.

This report reviews and discusses 19 new other industries' solutions, identified and selected in Tasks 4.1-4.4, which will be delivered to Task 7. These 19 solutions are those resulting from a complex process of selection and refinement which included at most 28 solutions. Importantly, compared to previous versions and lists of these solutions, **a new order and numbering of solutions applies in this report.**

Further, compared to previous templates used in Task 4, the solutions are reported here in the new template specifically developed for Tasks 4.5-4-6.

After describing the methodology applied during Task 4 (section 2), this report introduces and reviews the 19 solutions (section 3), and concludes with a brief analysis and discussion of their roles and relations (section 4).

The next step in the "journey" of these solutions, when they reach Task 7, will be a further and more demanding selection process (probably via a Multi-Criteria Decision Analysis, MCDA) conducted by a broader panel including experts with diverse competencies.

1.2 The template summarizing the 19 solutions

Section 3.2 presents the 19 solutions based on a template aimed at summarizing the essence of each solution, while making them also comparable with each other. After a descriptive title and identification number, the template indicates which *challenges* in the antibiotic field a solution is expected to address. Next, the template explains *how the solution will operate*, including its *optional features*. Then, taking a higher abstraction level, the template extracts the key *economic, organizational and legal variables* that the solution is expected to affect. In order to provide a balanced view on each solution, the template also indicates the associated *critical factors, risks and disadvantages*.

1.3 Grouping the 19 solutions

The 19 solutions are presented under five headlines, with three to five solutions per headline. Solutions falling under the same heading present similar features in terms of the challenge they address in the antibiotics field, their underlying mechanism or the variable they aim to affect. A more elaborate discussion of these five groups is provided in section 3.1.

2. Research methodology chapter

2.1 The research process

The Task 4 Team consisting of the authors of this report set out its work in spring 2015, and a Terms of Reference document (ToR) and a detailed Research Protocol were developed to plan, manage and coordinate the work. The main activities were as follows:

1. Targeted literature review
2. Panel brainstorming discussions with experts
3. Provision of additional proposals by Task 4 and WP2 team members
4. Write interim report presenting business models and reward mechanisms
5. Scoring and screening of solutions from other industries, using simplified Multi-Criteria Decision Analysis (MCDA), termed Single-Criterion Decision Analysis (SCDA)
6. Adapting the selected solutions for use in the antibiotics field
7. Presenting selected solutions adapted for use in antibiotics innovation (white paper)

Given that the reward models existing in other industries can be presented under headings completely different than "reward model" and "business model", such as "strategy", "industrial structure", "competitive advantage", "supply chain", "value creation", etc., we decided that a structured literature search would not be feasible within the scope of the DRIVE-AB project. Due to the difficulty in finding research specifically conducted in order to find economic models transferable to the antibiotics field in other industries, eventually the literature review was limited to a sole source addressing explicitly this aim: Jaczynska, Outterson & Mestre-Ferrandiz, 2015, *Business Model Options for Antibiotics. Learnings from other industries*, Chatham House/Big Innovation Center report. (1)

The Team decided on an approach to identify novel reward models somewhat different from that pursued by the Big Innovation Centre and Chatham House team. That report presents business models and reward mechanisms formulated explicitly by representatives of other industries, that is, managers with extensive experience of a *specific* industry. In contrast, for the present report we selected for our panels individuals who are expert and knowledgeable (also from a theoretical point of view) of *several business models and economic solutions from a broad variety of industries*. In other words, an explorative approach was chosen, using a metaphor of “casting a large net with a wide mesh to catch big fish”. The intention with using an exploratory approach is thereby to identify as many, and as novel, solutions as possible. One expert panel was convened in Oslo, and another in Uppsala, mainly consisting of management scholars, business developers at incubators, representatives of funding agencies etc. to facilitate creative "out of the box" thinking.

This open methodology will be complemented by a more stringent approach taken in Task 7 with the aim of evaluating the merits, relevance and feasibility of alternative solutions and in doing so, possibly narrowing down the final number of solutions that subsequently will be fed into the computer-based modelling of Task 9. Taken together, Tasks 4 and 7 can thereby be seen as constituting a funnel where Task 4 starts out wide to capture a broader range of possible solutions and gradually narrows them down before handing over the remaining solutions to Task 7 for further and closer scrutiny and selection before handing a final list of solutions to Task 9.

In methodological terms the process was based on *focus group discussions* and expert *knowledge elicitation*. First, according to reference (2) what distinguishes *focus group discussions* from simply simultaneously interviewing several informants is that the interaction between the focus group members is key to generating the desired research data. Our focus group discussion research design, or panel brainstorming sessions, aimed at facilitating spontaneous generation of new ideas *on site*, immediate critical discussion, as well as collective development of those ideas.

Second, reference (3) addresses useful methodologies for the general purpose of revealing, representing, preserving, and disseminating expert knowledge. The “experts” were identified in a heuristic manner by using team members’ personal networks and “snowballing” (i.e. asking prospective panel members to suggest other members). The criteria for involvement were that expert panel members should have competence in business models that encompass multiple industries, with

as broad experience, perspective and vision as possible. Each panel would consist of 6-7 individuals. Panelists would be recruited in Oslo and Uppsala to save on travel costs. Prospective expert panel members were approached by phone calls, followed by a formal invitation by email.

The Uppsala panel:	**Uppsala University, 15 April 2015**
Moderators and organizers:	**Experts:**
Enrico Baraldi, Professor, Uppsala University Francesco Ciabuschi, Professor, Uppsala University Olof Lindahl, Research Fellow, Uppsala University	Jens Eklinder, Research Fellow, HiG Lars-Gunnar Mattson, Professor Emeritus, Stockholm School of Economics Benjamin Ståhl, Management Consultant, Blue Institute Nhils Forslund, Business Developer, UU Innovation Lars Jonsson, CEO, Uppsala University Holding Company AB Göran Lindström, Associate Professor, Uppsala University

The Oslo panel	**NIPH, 21 May 2015**
Moderators and organizers:	**Experts:**
Jens Plahte, Senior Adviser, Norwegian Institute of Public Health Christine Årdal, Senior Adviser, Norwegian Institute of Public Health	Marcelle Askew, SprinJene/independent consultant Ingunn Carelius, KPMG Ole Kristian Hjelstuen, CEO, Inven2 Per Ingvar Olsen, Professor, BI Norwegian Business School Widar Salbuvik, independent/self-employed

The expert panelists were provided with a package of briefing material, including a table of challenges in the antibiotics field (see Annex 2) to introduce them to the subject matter and provide a common frame of reference for the discussions. In particular, panel members had been explicitly asked in advance to prepare for the discussion sections by considering several challenges typical of the antibiotics field and to let these challenges guide their suggestions of business models from other industries (see Annex 1 & 2).

The panel sessions, each lasting about three hours, were set up as *unstructured interviews*, which basically entails asking open-ended questions (i.e., What business models and reward mechanisms in sectors you are familiar with could be feasible in the antibiotics field?) in a moderated group conversation. Unstructured does not mean disorganized or unplanned, it simply means that the conversations unfolds in an organic manner without following a previously written interview guide.(3)

Subsequently, based on the notes and recordings made during the two panel sessions, 15 proposed solutions were singled out by the authors of this report, using a common table template for all proposals. Interestingly, despite their geographical and cultural closeness, the Oslo and Uppsala panels provided solutions substantially different from each other and with minimal overlap, concerning only "managed services/service contract" solutions. Further, we added to these 15 solutions, the 6 reviewed by Jaczynska, Outterson & Mestre-Ferrandiz, 2015. Finally, we also invited the entire DRIVE-AB WP2 team to submit proposals: 7 additional proposals were submitted, making up a collection of a total of 28 solutions. When preparing the list of solutions to be refined, adapted to the antibiotics field and eventually moved to Task 7, two solutions from other industries were excluded from the list of 28 because they already exist in the medical/life science space and hence moved directly to Task 7 ("Investment fund with guaranteed mechanisms" and "PPPs"), leaving a total of 26 solutions.

Given that MCDA likely will be applied in other workstreams in WP2 we decided to use Task 4 as a "testing ground" for running such processes within the WP2 Team. The objective was to discard at an early stage solutions that should be deemed inadequate or infeasible, but without seeking to arrive at a predetermined number of selected solutions. We decided not to apply features of a more sophisticated MCDA, such as ranking the selected solutions and performing sensitivity analysis, but to obtain a more simple decision, in terms of Go/No Go for the proposed solutions.

The Task 4 team leads proposed twelve scoring panel members; four persons from each of the three stakeholder groups represented in the WP2 team, i.e. EFPIA members (pharma), academic, and policy. The three WP2 leads endorsed the proposal.

The scoring process was very simple. The collection of 26 solutions and a scoring table were distributed by email, and the table included seven indicators:

- The solution contributes to general scientific or methodological progress in the field
- The solution reduces R&D costs to the developer or increases financing for R&D
- The solution contributes to increased revenues to the developer without incentivizing overuse
- The solution contributes to resolving weaknesses in regulatory requirements
- The solution contributes to conservation of new antibiotics
- The solution contributes to universal access to new antibiotics
- The solution contributes to reducing risks and uncertainties for the actors operating in the antibiotic field
- The solution contributes to creating a convincing argument in our final recommendations

The twelve scoring panelists were requested to respond either "yes" or "no" to the question of whether any one solution deserved further consideration, making our approach akin to a Single-Criterion Decision Analysis (SCDA). According to the protocol any solution given less than three "yes" votes would be discarded. Only one solution ("Tax exemptions for start-up founders") received as little as two votes and was accordingly discarded, leaving 25 solutions for further processing, especially for the important phase of adaptation to the antibiotic field.

Seven of the 25 remaining solutions were considered to be similar to each other, as they relied on basically the same mechanisms of action, and were accordingly merged into three solutions (see below). Moreover, one solution was found to be applied already to antibiotics diagnostics ("Innovation prizes") and hence moved directly to Task 7; and another solution was deemed to be too general for being tested via computerized models in Task 9 ("Innovative motivation") and hence definitely discarded. Therefore, the present report includes a total of 19 solutions (see section 3.2).

Importantly, while the sources (our panelists, the BIC/Chatham House report, or the WP2 team members) initially described the solutions in terms of how they operate in their respective originator industries, the present report describes the way each solution would be adapted to the antibiotics field. The work of translating the solution from the original industry in order to adapt to the antibiotic field was conducted collectively by the authors of this report, with one author making a proposal, verified further by the others. Further research, analysis, screening and assessment of the solutions will be performed by the Task 7 Team.

2.2 Adapting the original industry solutions to the antibiotics field

As mentioned above, an important step in defining the 19 solutions was to translate them from their original context into solutions adapted to the antibiotics field. The template used to present the 26 solutions evaluated during the SCDA was helpful in this direction as it included, after the explanation of how the solution operates in the originating industry, a field specifically dedicated to "adaptation to the antibiotics field": here Task 4 members started envisioning how the original solution, or some component and variant of it, could work in the antibiotics field, considering its actors, specific challenges and other contextual aspects. Importantly, this template also indicated the critical factors to make the solution viable in the antibiotic field, considering the potential barriers it would encounter when moved from its original industry.

This work prepared the ground for expressing the original solutions as concrete and specific "interventions" taking the shape of, for instance, a particular *incentive*, a *contract*, a new *organization* or form of *collaboration*, or a new *financing scheme* conceived as an explicit response to one or several problems/challenges afflicting the antibiotics field. Problems and challenges addressed are in fact one of the first items in the templates used in Section 3.2 to present the solutions and, thereby, frame their major purpose. The authors also identified features of the solutions that could be optional, of that could represent variants of the solution.

When moving from the original industry solutions to the 19 ones adapted to the antibiotics field, some "refined" solutions remain rather similar to the original solution, such as the "Fully refundable R&D tax credit" (No. 11 below) or the "Antibiotics Mitigation Bank" (No. 15 below). Other solutions have instead undergone major changes for the sake of adaptation: for instance "Insurance, Fire protection infrastructure" (No. 4 below) was originally more of a traditional insurance scheme with premiums paid by public/private organizations or individual to have privileged access to new antibiotics; "Standardization bodies…" (No. 7 below), originating from telecom, had to be changed to fit the particular nature of competition among pharmas; and "Reducing the need for antibiotics…" (No. 16 below) was originally about national public support to energy-efficient investments but was made into a broader and more strategic intervention covering all kinds of measures that can reduce the need of antibiotics.

In the work of adaptation of the original solutions to the antibiotics field, we have also merged solutions which were similar into a single one: for instance "Contracts for Difference" and "Risk Corridors" have been merged into a single "Shared risk model" (No. 2 below), where Risk Corridors are now presented as an optional version of the main solution; or the three original solutions of "Performance-based selling", "Contract for availability/gain share" and "Price per service" were merged into "Value-based subscription based on KPIs" (No. 3 below).

3. Results

This section first describes the five groups in which we gathered the 19 solutions and then lists and reviews each of the 19 solutions. Finally, we comment on the differences between otherwise similar solutions.

3.1 The five groups gathering the 19 solutions

The five groupings indicate either broad categories of mechanisms to address problems in the antibiotics field – visible in three of our groups (*New modes of value creation, R&D collaboration, Procurement and funding coordination*); or the main challenges in this field – visible in two of our groups (lack of *Financing* or of *Conservation*). We summarize here the basic features of the five groups, stressing the novelty of the solutions they include in terms of the principles according to which they operate in the five groups:

New modes of value creation: This group includes four solutions which have in common shifting the focus from the economic value derived from units of a product sold to other types of values associated with antibiotics. These values include preparedness and drug availability (solutions No. 1 and 2), but also more complex indicators (KPIs) such as reduced numbers of resistant infections or decreased costs for healthcare (No. 3). The fourth solution in this group looks even beyond antibiotics and the enormous, but sometimes neglected, value of preventive investments in infection surveillance and control, which would in turn further increase the value of antibiotics when used more cautiously (No. 4).

R&D platforms and collaboration: This group includes three solutions which all entail collaboration in antibiotic research or development, coupled with the creation of physical or virtual infrastructures and meeting places for conducting R&D or discussing and sharing research results. The collaboration characterizing these three solutions concerns the main categories of actors involved in R&D: (1) collaboration between the actors (ideally countries) jointly investing in an R&D infrastructure (solution No. 5), (2) collaboration between the actor providing an innovation platform and those actors (ideally smaller companies or individual scientists) using it (No. 6), and (3) collaboration between various actors (typically companies) conducting R&D activities (No. 7).

Coordinated procurement and R&D funding: This group includes three solutions which shift from the previous group's focus on providing general conditions which favour the conduct of R&D, to providing more concrete incentives to R&D activities oriented to meeting specific targets. Organized within a public centralized or coordinated procurement, these incentives can cover targets at different stages of development and be paid either before (solutions No. 8 and 10) or at/after approval of a new drug (solutions No. 9).

Financing schemes: This group includes four solutions which all focus on the sources and mechanisms for financing the R&D activities mostly of SMEs, including public national tax budgets (solution No. 11), public/private investment funds (No 12 and 13) or more complex schemes involving private equity markets and larger companies (No. 14).

Conservation: This group of five solutions address the challenge of excessive or inappropriate use of antibiotics by suggesting disincentives affecting the behaviour of users in healthcare (solutions No. 15 and 17), also of patients (No. 16), of drug distributors and producers (No. 18 and 19). Thus, these conservation-promoting mechanisms intervene at different levels of the value chain stretching from developers to final users of antibiotics.

3.2 The 19 solutions

New modes of value creation:

R&D platforms and collaboration:

Coordinated procurement and R&D funding:

Financing schemes:

Conservation:

Descriptive title of the solution	Solution number: 1

Service or supply contracts for second and third line antibiotics based on fixed annual subscription fee

Problem(s) or challenge(s) in antibiotics that is being addressed:

Unprofitability of R&D investments if revenues are based on unit sales. High volume unit sales drive resistance.

Description of how the solution will operate:

After an open tender, a wholesaler representing public hospitals signs a contract with a pharmaceutical company requiring it to supply a specific drug up to a specified annual quantity in return for a fixed annual fee. The contract should include provisions for supply of additional volumes for emergency situations, such as larger outbreaks or epidemics. In essence, the national supply of second and third line antibiotics would become a public service.

Tenders for such contracts should be stated in terms of appropriate product specifications based on clinical needs, but in a sufficiently broad range of indications to stimulate or maintain competition between suppliers. Contracts could be entered for periods of one to three years. Whenever appropriate, contracts should be awarded to multiple suppliers across a price range rather than to a single company, in order to reduce risk for companies and to maintain competition in the longer term.

Any logistical tasks, such as keeping central stocks, could be outsourced to a commercial wholesaler. The revenues to pharmaceutical firms are represented by the fixed annual subscription fee and, thereby, delinked from the actual number of sold antibiotics, R&D costs, and manufacturing and other variable costs.

Optional features or variants of the solution:

-This solution could work in tandem with public R&D funding, which would reduce proportionally the annual subscription fee paid by the healthcare system to drug developers.

-Contracts could be made exclusive for a national territory, i.e. a national public wholesaler could enter sub-contracts on similar terms with private hospitals, for instance.

-Contracts could reward drug suppliers based on Key Performance Indicators (see Solution No. 3, Value-based subscription), instead of for simply making available a pre-specified annual quantity.

Effect on fundamental economic, organizational or legal variables:

Delinking revenues from unit sales, *anticipating cash-flows* and *reducing uncertainty* for pharmaceutical companies. Introducing a new organization, a central pharmaceutical wholesaler office for the national public health services (which already exists in some countries, e.g. Norway). New type of value created: ‘drug preparedness’ rather than ‘drug consumption’.

Critical factors to make solution viable, risks, or (potential) disadvantages:

For a second or third line antibiotic the annual volume actually dispensed could be so low, in particular if stewardship measures are successful and resistance to first line drugs remain low, that the implicit resulting ‘unit price’ could become excessively high.

This solution might not work in a country with a predominantly private hospital system.

The duration of the contracts would have to accommodate entry of additional suppliers in order to become a predictable incentive for the companies. It is assumed that the manufacturing processes can be adjusted to limited volume outputs without incurring excessive costs in plant maintenance etc.

Source(s), concrete implemented examples and originating industry:

The Oslo and Uppsala panels. Industries: managed services in Industrial Equipment, Telecom Equipment, Defence.

Descriptive title of the solution	Solution number: 2

Shared risk model (Contract for Difference and Risk Corridors)

Problem(s) or challenge(s) in antibiotics that is being addressed:

Lack of investment into antibiotic R&D due to high risk and uncertainty around commercial return for pharmaceutical companies. Pushing for unit sales accelerates resistance.

Description of how the solution will operate:

The government and the pharmaceutical company agree on a total societal value for a novel antibiotic. Based on this total value, the government would guarantee an annual fee or cap to the pharmaceutical company for access to innovative antibiotics through the length of the patent. In years when actual sales revenue falls below the agreed cap the government provides a top-up payment to reach that level. In years when sales revenue exceeds the agreed cap, the pharmaceutical company rebates the government its excess profits minus the cost of goods to cover usage above the cap.

A contract with a cap option entails a risk sharing by limiting upside as well as downside risk both for the government and companies: the level of potential cost exposure is largely predictable for the government and uncertainty around revenue is removed for pharmaceutical companies.

Optional features or variants of the solution:

-The risk-sharing contract could be limited to only 2-3 years, until a market is established, and focus on an agreed 'break-even' point for profits. For example, the first 10% under 'break-even' point (loss) is covered by the company, the next 10% of loss is split 50-50 between government and the pharmaceutical company, everything else beyond that would be covered by government. The same holds true for profits: the first 10% of profit would belong solely to the pharmaceutical company, the next 10% would be shared 50-50, and any profit above that would go to government (i.e. pharmaceutical company would provide drug at cost).

-The agreement can cover a single pharmaceutical company or multiple companies at once.

-The agreement could be with local authority/health care plan as opposed to a national approach.

-This model incentivizes new antibiotics R&D, but may cover also already marketed antibiotics.

Effect on fundamental economic, organizational or legal variables:

Delinked revenues from sold volumes. Greater certainty on return and better cash-flows in early sales period improve project NPV. Risk and loss sharing incentives R&D investment for products with greater uncertainty on returns.

Critical factors to make solution viable, risks, or (potential) disadvantages:

A critical factor is how to set the annual fee (in the absence of a simple mechanism like a cap on price fluctuations in the energy sector): there is a need to develop a process or mechanism to determine the value of antibiotics. Setting the cap and collar levels and any other incentives built into the contract will be based on an assessment of cost and incentives for AMR. However, this could be challenging across a number of stakeholders without formal assessment process in place to determine the value of antibiotics.

Individual agreements would need to be made for each new antibiotic as it enters the market and a standardized methodology would need to be implemented to assure consistency across agreements.

The government needs to ensure funding available for the entire life of an antibiotic's patent. The solution would only apply to new antibiotics and not generics.

The economic results of the contract are uncertain: governments choosing to sign the contract risk that the worst-case scenario (massive epidemic) never materializes and could end up paying more to pharmaceutical companies than without the contract, while governments choosing not to sign the contract risk that the worst-case scenario materializes and end up paying more to pharmaceutical companies than they would under the contract.

Source(s), concrete implemented examples and originating industry:
Contract for Difference between UK Government and the company EDF Energy for nuclear power plant. US healthcare system, Medicare Part D plans and Affordable Care Act Plans. Latest contract between Astra-Zeneca and UK Government

Descriptive title of the solution	Solution number: 3

Value-based subscription based on Key Performance Indicators and gain sharing

Problem(s) or challenge(s) in antibiotics that is being addressed:

Unclear or underestimated value of antibiotics for suppliers and users. Low or unpredictable sale levels. Need of de-linking suppliers' revenues from units sold. Lack of responsible use.

Description of how the solution will operate:

Antibiotics suppliers are paid according to a subscription contract based on the value to healthcare of having certain antibiotics available and using them responsibly. This value, expressed in terms of Key Performance Indicators (KPIs), reflects the health impact of the antibiotic and includes direct benefits such as reduced patient mortality and morbidity, but also indirect benefits such as reduction of local healthcare costs and, especially, reduced risk of antibiotic resistance, both of local outbreaks and broader societal effects. The subscription contract can cover either a single hospital or an entire region with several healthcare facilities.

This solution also entails improved communication and deeper collaboration between antibiotic suppliers and healthcare, including representatives of suppliers ("antibiotic supply & use managers") working close to hospital staff to implement measures targeting the agreed KPI, thus working to fulfil the obligations of the supplier under the subscription contract.

Next to the fixed contract remuneration to suppliers, this solution also includes a variable component which depends on the achievement of specific goals in terms of the values obtained by the healthcare facility. These values can be measured by various KPIs, such as particular therapeutic effects for patients, cost reductions for healthcare, reduced number of ward-related resistant infections. These metrics can then be used for defining the economic gains/savings obtained from reaching these goals which can be shared between antibiotic supplier and healthcare facilities.

Optional features of the solution:

The contract can operate at several levels: (1) cover one single antibiotic, with the local "antibiotic supply & use manager" representing a single brand; or (2) cover several antibiotics by the same or different suppliers, with the local "antibiotic supply & use manager" role played by a brand-independent third party. The latter option permits coordination across several drugs, optimizing use.

Effect on fundamental economic, organizational or legal variables:

Introduction of new KPIs as basis for new, value-based, pricing model: new metrics making explicit the value/benefit of a solution for customers and rewarding suppliers based on this value. Reduced incentives to sell additional pieces of product. Focus on the performance/effect of products in the customer's using context. Improved information flows and collaboration between customers and suppliers. Sharing of savings and gains in operations between customer and supplier.

Critical factors to make solution viable, risks, or (potential) disadvantages:

It is difficult, and riddled with complex negotiations, to set the fixed price component of the subscription contract, for a single hospital and especially for an entire region. Similarly, selecting the KPIs for defining the gain sharing mechanism is difficult and open to complex discussions between antibiotic suppliers and healthcare. Moreover, monitoring the KPIs is demanding and also requires enhanced collaboration and information sharing between healthcare and antibiotic developers: the former may not be willing to let pharmaceutical companies gain insights into their operations.

Finally, this subscription model de-links revenues from sold quantities, but it does not necessarily reduce quantities utilized by healthcare. Therefore, specific KPIs have to capture the adverse effects of resistance and define thresholds of antibiotic use at which payments to suppliers start declining.

Source(s), concrete implemented examples and originating industry:

Uppsala Panel, Chatham House, BIC report, 2015. Industrial equipment (e.g., energy), defence, corporate information (Dun & Bradstreet), antibiotic Health Impact Fund (aHIF).

Descriptive title of the solution:	Solution number: 4

Insurance & "Fire Protection" infrastructure

Problem(s) or challenge(s) in antibiotics that is being addressed:

Lack of investment in antibiotic R&D. Uncertainty in predictions of future antibiotic targets. Inadequate investment in surveillance, conservation, access and stewardship.

Description of how the solution will operate:

The epidemiology of AMR is uncertain, which increases company risk in attempting to predict the epidemiological course of bacteria like CRE. We need a drug that targets such bacteria, but sales will hopefully be very small and difficult to predict. Viewing this problem as insurance and "fire protection" infrastructure allows for adequate investment many years in advance, not tied to the sales of a particular antibiotic.

The value of insurances resides in protecting against uncertain future risks: we are not upset if the insurance does not "payout" because the building did not burn down. Moreover, (fire) protection and surveillance infrastructures are valuable as preventive measures reducing the risk, provided they are created well in advance of the adverse events.

The global antibiotic market is currently about US$35 billion. Viewed as insurance, a 10% premium payment per year ($3.5 billion/year) could be invested to ensure the continued viability of this essential type of drugs. To further the fire protection analogy, some investments financed by this pool of funds would be in development of new antibiotics (fire trucks), some in local and global surveillance (smoke detectors), some in infection control (fire prevention), and some in public goods to respond to epidemics (hydrants). The weakness in some other models of focussing only on financing new drug R&D would be addressed by a purposeful balance between investments in drug innovation, conservation (via prevention) and access.

The insurance/fire protection model puts all of these investments on a more stable basis, delinked from the sale of any particular antibiotic. The implementing mechanism could be national, regional (e.g., EU) or global, with the premium tied to antibiotic sales in the relevant geographic area. However, the premium would be paid by governments, not by patients. The obtained funds could then be re-invested by national governments, a regional or a global organization (or combinations of these) in accord with a framework. Then, these funds can be distributed to infrastructure builders and drug developers based for instance on the following solutions: No. 5-6, No. 9-10 or No. 12-13 (see below).

Optional features or variants of the solution:

-Subsidies for building appropriate prevention infrastructure in low-income countries, akin to social insurance or public provision of fire protection without regard to income.

Effect on fundamental economic, organizational or legal variables:

Stable and automatic allocation of public funds to balanced investment mix in surveillance, infection control, stewardship, and new drugs.

Critical factors to make solution viable, risks, or (potential) disadvantages:

Governments must think about long-term risk management of this problem, with appropriate levels of infrastructure investment.

Most of the funds will come from G20 countries, but many of the prevention and detection investments will be made in low- or middle-income countries (LMICs).

While insurance reimburses for the cost incurred when a risk occurs, this model will not reimburse, but will invest to prevent or reduce the risk. Thus, the funds must be properly invested and with ample time margins in order to get the most "bang for the buck" in terms of global health impact.

Source(s), concrete implemented examples and originating industry:

Rex & Outterson (forthcoming). Based on earlier work at Chatham House and Big Innovation Centre.

Descriptive title of the solution	Solution number: 5
Jointly financed R&D infrastructure and antibiotic supply with "fair returns"	
Problem(s) or challenge(s) in antibiotics that is being addressed:	
Lack of development in a high-risk and uncertain setting. Need of very high investments.	
Description of how the solution will operate:	
A number of countries join forces to finance a common antibiotic R&D platform/infrastructure consisting of equipment, facilities and manpower. The baseline financing is proportional to each country's GDP (or similar indicators) and concerns both the creation of the permanent structure of the platform (capital expenditures) and some operating costs. However, this platform can then be used both by "member" and "non-member" countries to run specific projects, whose running costs are covered by the specific countries taking the initiative for each project. "Fair returns" proportional to the funds provided by the member countries and the countries financing specific projects can then be defined with several principles: (1) via the volume of supply contracts to the R&D platform obtained by a specific country's suppliers and/or (2) via a share of the antibiotic's revenues proportional to that country's investments (or free access to corresponding volumes of the new antibiotic).	
Optional features of the solution:	
-The platform/infrastructure can operate by performing R&D projects only for "member states" or also for "non-member states". -"Fair returns" can be expressed either in financial terms or in volumes of new antibiotics, or both. -The platform can even include scientists/experts loaned by pharmas in exchange of tax breaks or other incentives.	
Effect on fundamental economic, organizational or legal variables:	
Joint R&D investments for an infrastructural, fixed part, proportional to a country's economic power, and for a project-specific part, depending on a country's specific therapeutic interest: risk sharing based on both economic capacity and particular needs. Distribution of economic gains to financing countries based on their share of financial contribution.	
Critical factors to make solution viable, risks, or (potential) disadvantages:	
The basic logic of the "fair return" mechanism would favour richer countries, even if it can work as an argument to gain national acceptance of this type of public investment. While the resulting new antibiotics can also be made globally available by the platform, linking "fair returns" to volumes of global product sales may jeopardize conservation goals. Therefore, it is critical to devise adequate mechanisms for how fair returns are calculated. A further complexity concerns the choice of specific R&D projects to be conducted on the platform: unless the platform is particularly well-endowed in terms of physical and human resources, there would be constraints as to the number of projects it can run simultaneously, and hence consensus between countries with different public health priorities would be necessary.	
Source(s), concrete implemented examples and originating industry:	
Big Science: particle physics research at CERN.	

Descriptive title of the solution	Solution number: 6

Antibiotic Innovation Platforms

Problem(s) or challenge(s) in antibiotics that is being addressed:

Lack of innovation and of innovative firms, such as SMEs.

Description of how the solution will operate:

A platform is created offering, at minimal or reduced costs, physical space (laboratories), scientific infrastructure and advice in R&D activities to small, resource-constrained actors such as start-ups, SMEs and individual inventors or scientists in the antibiotic field. Similar to an incubator, the innovation platform helps these antibiotic developers take their projects to specific development milestones, ideally to Phase II, but also possibly beyond.

The innovation platform can be public or private: if private, the platform can partly own the developing companies, take a percentage on the revenues generated by the final product, or on the solution-related revenues if these are delinked from actual sales volumes.

While the core scientific/technical focus should be on developing new antibiotics, the platform can also include important solutions to the root problem of AMR, including new diagnostics, preventive measures and all other supplementary and complementary technologies. Many solutions can come from the clinics and be rather simple to develop (e.g., antibacterial surfaces or infection-protection tools), but they lack champions to start the innovation process due to several barriers, which the platform can help overcome. With a broader scientific/technical scope, the innovation platform would be able to attract more interest. There is also space for several innovation platforms, specializing on different technical areas or with different geographical locations.

Optional features or variants of the solution:

-If publicly owned, the platform could also guarantee purchases by healthcare, while influencing the way products will be eventually distributed, posing restrictions to obtain responsible use. Moreover, a public platform (especially if at transnational level) can also promote equitable access of the antibiotic it helps develop.

-The platform may also provide funding to finance the R&D activities of start-ups and SMEs.

Effect on fundamental economic, organizational or legal variables:

Reduced barriers to entry in the antibiotic field for smaller actors. Reduced R&D costs thanks to sharing of a physical and knowledge infrastructure. Preferential channel to healthcare.

Critical factors to make solution viable, risks, or (potential) disadvantages:

A risk is that the platform will be induced to push unit sales of the developed product, unless other revenue streams from the innovation, delinked from product volumes, are found. Control by a governmental/international public agency over the platform can mitigate this risk.

The platform should be open in character, ideally accepting to support innovative ideas that would not find financing and support from private investors (e.g., VCs), and therefore willing to accept more risky ideas and projects, knowing that a large proportion of these will not eventually succeed.

Source(s), concrete implemented examples and originating industry:

Software industry. Incubators for drug and med-tech development (e.g. Karolinska Institute Science Park/Karolinska Development, Sweden).

Descriptive title of the solution	Solution number: 7

Standardization Bodies: pre-competitive R&D coordination for common challenges

Problem(s) or challenge(s) in antibiotics that is being addressed:

Need for constant product innovation. Complicated nature of antibiotics development and lack of common technical platforms. Need for several complementary competencies to conduct R&D. Lengthy and costly R&D processes. Lack of global equitable access to resulting antibiotics.

Description of how the solution will operate:

A large-scale international 'standardization body' for R&D in antibiotics is created gathering small and large pharmaceutical companies, CROs, research institutes and regulators (e.g., FDA), as well as developers of complementary technologies such as diagnostics. These organizations (many of which are competing against each other) bring their R&D talents into discussions and joint decisions about common R&D and other technological procedures, ranging from basic discoveries to clinical trials and diagnostics. The goal is agreeing on standards applicable in the various phases of antibiotic R&D: more specifically these standards can concern common, platform-like, knowledge and technologies such as libraries of molecules, animal models, clinical trials procedures and, importantly, diagnostic technologies or components thereof.

The goal of this form of R&D coordination is facilitating and speeding up drug R&D by avoiding that every single actor needs to "re-invent the wheel" for every new project. Further, while every standardized piece is proprietarily owned by the originator, access to the various knowledge, models, molecules and other procedures and technologies is granted to all members of the standardization body via licenses applying "reasonable and non-discriminatory" (RAND) rules. Such regulation favouring access allows that progress in the entire field is not blocked in future by exclusive control on key pieces of science and technology.

Optional features or variants of the solution:

Different variants of the antibiotics standardization body focus on different types of knowledge, science and artefacts: only molecules, animal models, diagnostics, or clinical testing procedures.

Effect on fundamental economic, organizational or legal variables:

Division of innovative labour (and associated revenues) among several actors and subsequent creation of standardized pieces of knowledge easy to assemble by anyone across the drug R&D pipeline. Expansion of the pre-competitive collaboration space. Reduction of R&D costs for single developers. Fair-terms access legally granted to core knowledge.

Critical factors to make solution viable, risks, or (potential) disadvantages:

The 'standardization body' requires the willingness to share knowledge among actual or potential competitors. Specific mechanisms will need to be devised to make collective decisions on which pieces of knowledge will eventually become standard and to assess the monetary value of each associated IP: defining and operating such mechanisms can entail conflicts between the various members of the body.

Compared to other industries, pharmaceuticals have very little R&D viewed as "pre-competitive" and hence done jointly: every new molecule is viewed as a source of competitive advantage and therefore must be covered by exclusive IP immediately. Thus, while this solution can more easily work for laboratory and testing procedures or diagnostics, applying it to molecules is problematic: is it possible that firms open for standard RAND use their original/early molecules (or libraries) and focus instead on reaping profits on further developed products? Even sharing only results on failed molecules would be helpful to the entire field as standards of "what does not work".

Source(s), concrete implemented examples and originating industry:

Telecom Equipment Industry; standards-setting organizations.

Descriptive title of the solution	Solution number: 8

Joint, multilateral, non-pooled financing and coordination of R&D targets

Problem(s) or challenge(s) in antibiotics that is being addressed:

High R&D costs. Limited coordination in priority-setting. Reluctance of governments to commit to long-term, binding international agreements, especially tied to financial outlays.

Description of how the solution will operate:

A group of willing countries would form a coalition. This coalition would agree to a specific list of R&D priorities (e.g., a novel antibiotic class or mechanism against CRE, a vaccine against C. diff, a diagnostic for the different strains of gonorrhoea). These priorities would be ranked in terms of the severity of threat. An analysis of the state of existing R&D would be performed to avoid selecting priorities that have a potential solution already near completion.

Target product profiles would be developed for the top 10 or so priorities. Countries would then select one or more priorities in which they commit to finance R&D. Smaller countries may choose to consolidate their financing. For example, Scandinavia could agree to finance the vaccine against C. diff. Commitments and "ownership" would be pledged publicly for accountability. Countries could then internally determine the best route of financing the R&D for the targets they have selected. One country may pair with industry. Another may work with non-profit research institutes. However, countries would ensure that their financing is tied to standard responsible use and access provisions. Countries would report progress annually and discuss any new potential, new priorities. New countries could join at any time. Countries could also leave at any time, although they (and those not meeting their commitments) would be subject to public shaming through media.

Optional features or variants of the solution:

WHO could be empowered to set the priorities, perform the landscape analysis and provide the target product profiles.

Alternatively countries could decide to finance areas already identified by BARDA & IMI.

Effect on fundamental economic, organizational or legal variables:

The political advantages of voluntary membership; no pooled funds (which are difficult to get long-term commitments); each donor can determine how best to engage R&D actors. Burden-sharing between countries on key research needs where the market is not providing solutions. Resulting alignment of public financing with the greatest public health threats.

Critical factors to make solution viable, risks, or (potential) disadvantages:

A critical factor for success of this solution is that at least three countries are willing to initiate it, preferably covering a geographic spread. It would be best to have 5 to 10 countries in the coalition at the time of implementation in order to gain public attention and pressure on other countries' to join. It is important that countries maintain their financing to their committed priority over several years to give predictability to the R&D actors performing the work.

A risk is that individual government priorities will change due to a natural disaster, armed conflict or economic reasons, thereby making the coalition short-lived.

Source(s), concrete implemented examples and originating industry:

International Space Station

Descriptive title of the solution	Solution number: 9

Public procurement, single-buyer scheme for antibiotic R&D

Problem(s) or challenge(s) in antibiotics that is being addressed:

Lack of R&D in a high-risk and uncertain setting. Need of delinking revenues from sold quantities.

Description of how the solution will operate:

A "central public body", either a national state or a transnational organization, procures R&D activities from a range of actors. Specifications of the R&D results to be achieved are made as clear as possible (e.g., antibiotic target profiles) and various actors are invited to tender via open public procurement procedures allowing for competitive bids.

A contract is then signed with the actor, or consortium of actors, behind the winning bid. The R&D delivery contract specifies the deadlines for the various R&D stages and milestones covered by the agreement, with rigorous requirements on quality, reliability, and safety. When the contracted actors deliver the specified R&D results they will be paid as by contract agreement, either on a stage-wise fashion (upon reaching each milestone) or at the moment of final delivery. Ownership of the R&D results is retained by the central public body commissioning the R&D activities, including patents over end-product antibiotics.

Several types of actors (Academia/Research centers/SMEs/Big pharma) can all be contracted for the needed R&D activities.

Optional features or variants of the solution:

-The solution can operate either at national level (single government), or as a transnational body (to be identified) procuring antibiotic R&D for needs shared and agreed upon by several states.

-The procured R&D results can concern only certain stages of antibiotic R&D or stretch all the way to a final product.

-Possible anticipated payments to R&D contractors, i.e., at the start of the contracted R&D activities.

-Multiple-sourcing contracts can be granted to several actors/consortia conducting parallel projects.

-The price paid for R&D results can either be "cost plus" (with attractive margins for contractors over their R&D costs) or be a proportion of the societal, public health value of the antibiotics.

Effect on fundamental economic, organizational or legal variables:

Public IP ownership delinks revenues from sold quantities. Reduced uncertainty for antibiotic developers (especially with anticipated payments). Developers' competition in tendering and collaboration in R&D performance can reduce R&D costs. R&D goals centrally specified reduce duplication of efforts, increase coordination and can speed up R&D times.

Critical factors to make solution viable, risks, or (potential) disadvantages:

A top-down control system needs to carefully devised so to avoid problems of lack of competition and poor productivity/efficiency in resource use. The involvement of multiple actors needs careful coordination to bring projects to next stage efficiently, and risk of delays is high.

It is unclear how drug developers can react to public tendering as competition in the antibiotic field may be either too much competition (generics) or too little (few actors, patents etc.).

Handling and assigning the IPs resulting from these R&D activities is a critical factor. IP applications different than those specified by the tender need to be considered and, if valuable to contracted actors, the related IPRs may be released to them.

Source(s), concrete implemented examples and originating industry:

Aerospace industry, public procurement of R&D in major high-risk projects such as the Space Program at NASA and ESA.

Descriptive title of the solution	Solution number: 10

Upfront payment of R&D by public global consortium/supranational organization

Problem(s) or challenge(s) in antibiotics that is being addressed:

Small or uncertain market size hinders investment in R&D. Limited access due to high costs of end product.

Description of how the solution will operate:

A public global consortium or a supranational organization provides an upfront payment to a drug developer in order to cover entirely or partly the R&D costs for a new antibiotic: this payment, made well before the drug's approval, reduces or eliminates the developer's financial risk (entirely or partly assumed by the consortium), and thus improves the project's NPV.

In return for the investment made and the risk assumed, the consortium/supranational organization retains the rights to price and distribute the new antibiotic globally. The developer, in return for successfully developing the drug, might obtain the rights to sell the antibiotic in some restricted markets or in niche applications as "premium products", as long as the "basic version" is still available globally at equitable conditions (e.g., priced at production costs).

Ideally it is the high-income countries that should finance the consortium/supranational organization fully or in part.

Optional features or variants of the solution:

-Rather than automatic availability to countries that invested in the consortium to fund a given antibiotic's development, the consortium could get revenue from selling the new antibiotics with a profit margin to wealthier countries (possibly granting discounts to countries which help finance R&D). These revenues can then be invested for the next R&D project.

Effect on fundamental economic, organizational or legal variables:

Reduced financial risk for the developer. Improved NPV. Reduced entry barriers: introduction of new types of developers. Delinking revenues from volumes. New pricing scheme. Different competition not based on marketing expenditures but on scientific competence.

Critical factors to make solution viable, risks, or (potential) disadvantages:

There are three critical factors for this solution: the governance of the consortium/supranational organization (who will have influence over the organization?), portfolio management (which antibiotics to invest in?) and financing (where does the money come from?). Other risks are (1) that the developer/producer will push the antibiotic excessively within the allowed application, (2) that non-members of the consortium/supranational organization are treated unfairly regarding access or pricing, (3) that the investments will turn out to be ineffective (e.g., for projects that fail), (4) that some antibiotics not fitting the consortium's mechanisms will be hindered, (5) that the funding runs out during development, making additional payments necessary before its completion.

Source(s), concrete implemented examples and originating industry:

Chatham House/BIC Report 2015. Academic monograph publishing, Knowledge Unlatched (UK). BARDA with strings attached.

Descriptive title of the solution	Solution number: 11

Fully refundable R&D tax credit

Problem(s) or challenge(s) in antibiotics that is being addressed:

Lack of funding for SMEs working in early stage development. SMEs do not have taxable profits to enable them to benefit from ordinary tax credit schemes.

Description of how the solution will operate:

Under a fully refundable tax credit, start-up companies and SMEs can report their investments in antibiotics R&D the same year they are made, and the tax value of those investments (i.e. the amount that would have been deducted from the future profits) is paid out in cash. In other words, the tax return is anticipated, generating a positive cash flow for antibiotics R&D projects, which consequently improves the Net Present Value (NPV) of those investments.

Example: A start-up company invests €10 million for early stage development (for instance toxicity studies etc.) in 2015. Under a standard tax credit regime the company would carry those expenses forward and report them whenever it would start reporting taxable profits, say, 10 years later. In other words, with a hypothetical 25% tax rate theoretically the company could deduct €10 million from their taxable profits in 2025, resulting in a tax credit of €2.5 million. In contrast, under a Tax Cash Refund scheme the tax authorities would pay out that €2.5 million in cash in 2016 instead, thereby making a significant contribution to the company's cash flow.

Optional features or variants of the solution:

-The percentage of the refund can vary in relation to taxation levels on revenues or profits.

-The credit could be tradable as opposed to fully refundable (but that introduces complexity and transaction costs).

Effect on fundamental economic, organizational or legal variables:

Improved cash-flow of start-ups and SMEs that do not have taxable profits. *Risk sharing* with the government (i.e., that a company terminates its operations if their drug candidates or lead molecules fail on a later stage in the R&D process).

Critical factors to make solution viable, risks, or (potential) disadvantages:

As already stated, the government runs a risk of losing the cash refund in case of a close-down of the company.

Such a scheme would have to include provisions for acquisition of the company receiving the refund. Moreover, one would have to avoid creating loopholes, such as allowing a company to receive the tax cash refund and then moving the company abroad and report the R&D costs for profit tax deduction in its new host country at a later stage. Also, criteria for eligibility of R&D costs would have to be carefully elaborated (for instance in order to determine how to elect the R&D costs for an immunology based project whose output results in both antibiotics and non-antibiotic drugs).

Source(s), concrete implemented examples and originating industry:

Source: The Oslo Panel. Industry: The Norwegian Petroleum Industry (the Tax Cash Refund scheme for oil field exploration costs); legislative proposals in USA

Descriptive title of the solution	Solution number: 12
Public or Public-Private Antibiotics Investment Fund for early-stage R&D	
Problem(s) or challenge(s) in antibiotics that is being addressed:	
Lack of venture capital for early-phase antibiotics development. Risk for start-up founders of too quickly losing control of their venture.	
Description of how the solution will operate:	
The lack of venture capital (VC) for early-phase antibiotics R&D puts start-up company founders at the mercy of VC investors. In such cases, the VC intentionally imposes a financing scheme that dilutes equity too quickly, eventually putting the founder in a minority position and the VC takes over the company. To address this problem, a publicly funded antibiotics investment fund would operate as an ordinary private VC fund, and investments would be made on commercial terms, save for the following provisions: - in addition to commercial viability, clinical need would guide investment decisions; - explicit guidelines for 'protecting' the company founders; and - explicit mandate for supporting start-up companies in their early phase. Exit is done by selling individual shares, or by transferring entire portfolios to other investment funds. The Fund board and investment review committee would be composed of business and biomedical competencies, i.e. not politicians. Initially, the Fund would need public funding, but private capital could be invited to participate from an early stage. Later on, exits and gains from previous investments could possibly make the Fund self-sustaining and profitable. The Fund would complement The European Investment Bank's InnovFin funding facility for clinical development of vaccines, drugs, medical and diagnostic devices, and research infrastructures for combatting infectious diseases.	
Optional features or variants of the solution:	
Antibiotic Investment Funds could be created nationally or regionally.	
Effect on fundamental economic, organizational or legal variables:	
Introduction of a new actor/organization which *improves the cash-flows of* and *reduces uncertainty for* early stage start-ups and SMEs. *Risk sharing* between the public fund and private investors.	
Critical factors to make solution viable, risks, or (potential) disadvantages:	
Political interference in investment decisions could potentially reduce the efficiency and, ultimately, the impact of the Fund. It would be potentially challenging to recruit the appropriate competencies to fill the governing bodies of such a Fund.	
Source(s), concrete implemented examples and originating industry:	
Source: The Oslo Panel; BARDA; IMI.	

Descriptive title of the solution	Solution number: 13

Public soft loans for late-stage R&D

Problem(s) or challenge(s) in antibiotics that is being addressed:

Lack of investment for expensive, late stage clinical trials.

Description of how the solution will operate:

The European Investment Bank, World Bank or another already established bank would provide loans with particularly favourable terms for antibiotic developers, such as lower-than-market or no interest rates, limited collateral, longer and flexible payment terms. Known as “soft loans”, these loans would be backed by government commitments to ensure AAA credit rating. These loans would be secured by companies and non-profit developers for specified development activities, such as costly Phase III clinical trials. Applications for support would include detailed descriptions of the trials and a definition of success. This solution would apply to antibiotic-related R&D that has market potential but still entail high uncertainty, e.g., diagnostics, vaccines, narrow-spectrum antibiotics.

If the desired endpoints are achieved, the bank would be repaid over time from the sales of the new antibiotic or technology. If the desired endpoints are not achieved, the loan may be written off partially or completely. The financing facility needs to receive an initial seed fund that is self-replenished based upon repayment and revenues from loans.

Optional features or variants of the solution:

-Loans could be replaced with several types of debt instruments (bonds, mezzanine capital, etc.)

Effect on fundamental economic, organizational or legal variables:

Risk-sharing between the public and private sectors for common goals. Reducing entry barriers or enabling smaller players to take a product through commercialization.

Critical factors to make solution viable, risks, or (potential) disadvantages:

The lending bank must maintain a balanced risk portfolio, including lower risk projects, otherwise the fund will not be self-replenishing. The disadvantage here is that these projects might otherwise have been financed through private markets (or even directly by industry), i.e., the mechanism is shifting resources rather than creating new financing opportunities.

The bank must have access to scientific experts to give feedback on applications regarding risk as well as credibility of design and expected results. Otherwise, it may be possible to game the system by setting the expected endpoints too high and thereby defaulting on the loan.

This mechanism is difficult to pair with responsible use. EIB’s IDFF makes no stipulations on the price of the resulting products. Doing so would impact the ability of the company to repay the loan.

The interlinkages between this mechanism and other mechanisms in earlier stages as well as commercialization need to be addressed. This may pair well with lump sum payments, which could be used to repay the loan and promote responsible use. However, if all early-phase R&D costs are covered by public funding (e.g., through an R&D fund) and Phase III clinical trials are secured through publicly-backed soft loans, there needs to be stipulations on the price of the resulting product in line with the amount of private investment incurred.

Source(s), concrete implemented examples and originating industry:

European Investment Bank’s InnovFin Infectious Diseases Financing Facility

Descriptive title of the solution	Solution number: 14

Antibiotic research bond and auctioning of patent extension certificate

Problem(s) or challenge(s) in antibiotics that is being addressed:

Lack of investment in R&D due to negative return on investment for antibiotics preserved for future resistant bacterial strains. Need of delinking revenues from volumes sold.

Description of how the solution will operate:

This solution includes both a public financing for drug developers (via a governmental bond) and a mechanism to re-finance the public financing facility (an auction of patent extension certificate). In details, governments issue bonds to raise funds for investment into antibiotic R&D (grants or non-dilutive capital for SMEs and larger developers). Once a company has developed a novel antibiotic (passing regulatory approval and meeting target product profile), a patent extension certificate (PEC) is issued and offered for auction to any drug manufacturer to apply to any of its products to extend its market exclusivity for a maximum of three years. The proceeds of the auction will be split between antibiotic developer and bond-issuing government, so that the latter can finance new antibiotic R&D projects.

Effect on fundamental economic, organizational or legal variables:

Redistribution of pharmaceutical revenues (from other therapy areas) to provide investment funding for antibiotic R&D. Legal and regulatory cooperation for patent extensions and national healthcare approval for extended high costs in other therapy areas.

Critical factors to make solution viable, risks, or (potential) disadvantages:

Necessitates close collaboration and multi-national agreement between industry, government, regulatory agencies, patent law and national healthcare systems.

Disadvantage in that non-antiinfectives manufacturers benefit from the scheme if they buy PEC to apply to high-sales products from other areas (e.g. oncology). Risk that richest and already most successful big pharmas benefit by extending exclusivity of their products without supporting research and innovation into antibiotics. Skewed and perverse effect, prolonging high prices in other areas of healthcare system to support investment in antibiotics field; anti-competitive – preventing generic entry in non-antibiotic space.

Prolonged sales of the patented drug covered by the PEC will have to be matched by higher expenses of the (public) healthcare providers paid to pharma holding the PEC: in a public system this can be a zero-sum game at best and negative considering transaction costs.

Post-approval revenues of the antibiotic innovator company (i.e., its share of the auction price) implicitly determined as a percentage of the expected sales of a completely different drug: unpredictable financial effects for all parties and concern with the fairness of such revenues.

Source(s), concrete implemented examples and originating industry:

Chatham House/Big Innovation Centre Report, 2015; J&J testimony to US Congress.

Descriptive title of the solution:	Solution number: 15
Antibiotic Mitigation Bank: compensation fees for causing resistance finance R&D	
Problem(s) or challenge(s) in antibiotics that is being addressed:	
Lack of funding for antibiotics R&D. Need of conservation of antibiotics.	
Description of how the solution will operate:	
This solution makes explicit and visible to users the societal cost of their use of the common resource of antibiotics. Certain actions will be classified as misuse and will demand a compensation fee. The antibiotic users can therefore decide if they want to avoid paying the compensation by undertaking conservatory action themselves or to pay a compensatory fee to an entity called 'Antibiotic Mitigation Bank'. Under this scheme, users such as hospitals or entire healthcare systems pay compensation fees for causing resistance due to their excessive use of antibiotics. This measure can directly reduce the inappropriate use of antibiotics via the economic disincentive of the fee. Further, the payments by the (mis)users to the Antibiotic Mitigation Bank, in turn, can be directed towards financing R&D of new antibiotics or to other stewardship measures.	
Optional features or variants of the solution:	
-Users who use antibiotics in a rational and conservative way (i.e., do not cause resistance) can be financially compensated by the Mitigation Bank for not reaching certain levels of consumption of antibiotics. In this way the Antibiotic Mitigation Bank would act not only as a disincentive to misuse antibiotics but also as a positive incentive for responsible use.	
Effect on fundamental economic, organizational or legal variables:	
The "compensatory fee" (corresponding to a Pigouvian tax) makes visible to users the negative externality of excessive antibiotic use: disincentives to irresponsible use, and optionally incentives to stewardship. Creates a stable source of sustainable financing for new antibiotics R&D and/or stewardship measures.	
Critical factors to make solution viable, risks, or (potential) disadvantages:	
It is problematic and costly to create a reliable and efficient monitoring system (Mitigation Bank) to oversee both locally and globally the use and abuse of antibiotics. Allowed levels of antibiotic consumptions for single organizational users are not easy to set. Hence it is challenging to define what misuse is. Further, arbitration may be needed in cases where the user and the administrative system disagree on classification. High penalties for antibiotics "abusers" may induce them to hide their actual consumption.	
Source(s), concrete implemented examples and originating industry:	
Uppsala Panel. Banking Industry / Environmental Protection. Pigouvian taxes.	

Descriptive title of the solution	Solution number: 16

Reducing the need for antibiotics and increasing awareness of misuse

Problem(s) or challenge(s) in antibiotics that is being addressed:

Lack of stewardship in antibiotics use. Barriers to technology substituting antibiotics. Need of changing end-consumers behaviour in antibiotic consumption.

Description of how the solution will operate:

Governments centrally coordinate and stimulate investments, including the introduction of new technologies, in areas that will reduce the need of antibiotics: better hygiene, improved and diffused diagnostic, other preventive measures. Obsolete and infection-prone equipment/facilities in healthcare will be replaced. Thus, a starting point is improving the infrastructure at the most aware users of antibiotics, such as healthcare organizations like hospitals or community centers. Further, governments also will involve pharmacies and other drug dispensers in stewardship programs for delimiting unnecessary use of antibiotics.

Additionally, public health authorities launch widespread information campaigns showing the actual societal cost of (mis)using antibiotics so to raise awareness of individual consumers: this includes both mass-media coverage and personalized information such as showing to individuals their own level of antibiotics consumption. This form of "smart metering" for patients would require the involvement of doctors or healthcare-based IT systems.

The solution requires either a state agency or an independent body to coordinate efforts, and the building of longer-term relationships to improve cooperation between different stakeholders (including patients and their organizations). For each specific information campaign or round of implementation of new infection-safe technologies, it will be pivotal to identify an organization acting as promoter of that initiative, helping its implementation.

Optional features or variants of the solution:

-Next to human health, this solution may well be applied to animal and agricultural use of antibiotics.

-It could be driven at country level or as part of a transnational program.

Effect on fundamental economic, organizational or legal variables:

Infrastructural and technology investments to reduce infections and hence actual need of antibiotics. Information campaigns to reduce consumers' perceived need and antibiotic use behaviour.

Critical factors to make solution viable, risks, or (potential) disadvantages:

The solution requires interventions at the level of the entire society and the broader social context of the users of antibiotics. Still, it is relevant to act on the more engaged and knowledgeable level of user, i.e., healthcare organizations and drug distributors. Due to difficulty in engaging individual consumers, groups representing patients need to be involved: however, such groups are difficult to find for antibiotics because the use of antibiotics cuts across many different disease areas.

Pharmaceutical companies may pull out of antibiotics development if "too much" conservation reduces the financial attractiveness of the antibiotic field.

High impact of the various conservation initiatives above requires coordinated efforts, which may be difficult to achieve as many stakeholders may want to engage independently from each other or have diverging views on which programs/devices should be implemented or replaced.

A hindrance may concern how and who should finance these initiatives: see the "Insurance/Fire Protection Platform" (No. 4) solution as a possible financing scheme.

Source(s), concrete implemented examples and originating industry:

Energy sector in UK (Chatham House, Big Innovation Center report, 2015)

Descriptive title of the solution	Solution number: 17
Resistance-adjusted variable antibiotic prices	
Problem(s) or challenge(s) in antibiotics that is being addressed:	
Lack of conservation. Difficulty in changing antibiotic users' behaviours.	
Description of how the solution will operate:	
Healthcare authorities monitor the emergence of resistance to specific antibiotics, in terms of both the places where and the time when it is occurring or is expected to occur. Based on this monitoring data and on outbreak forecasting algorithms, the healthcare authorities and reimbursement agencies increase the price of a specific antibiotic in certain specific places/areas or at certain specific times, those closer to the risk of outbreaks. These price increases would constrain the use of an antibiotic only to cases where it is strictly necessary, delimiting unmotivated "trial and error" usage, especially for antibiotics approaching the "risk-of-outbreak" zone or period.	
Optional features of the solution:	
-The solution can operate either as a national system of price adjustments within the boundaries of a country (e.g., specific regions or even hospitals) or as a transnational system, if a common mechanism for pricing is established between several countries (especially relevant with patent buyouts by several states over a given antibiotic). -Price adjustments can follow the geographical spread of resistance only, its temporal spread only, or follow both types of spread (geographical and temporal).	
Effect on fundamental economic, organizational or legal variables:	
Negative externality of consuming an antibiotic is made clear via increased prices. Higher prices when resistance grows discourage use and hence help slow growth of resistance.	
Critical factors to make solution viable, risks, or (potential) disadvantages:	
An antibiotic which is currently far from approaching the risk of resistance outbreak (in terms of time and of few geographical areas with resistance) will have a relatively lower price, which may push overusing it thereby accelerating the pace of development of resistance against it. Therefore, this solution is not optimal for truly innovative antibiotics which are to be used very sparingly and preserved from the risk of resistance. Applying this variable price solution can become relevant after an antibiotic has been utilized for some time (i.e., is not entirely new), and resistance patterns become more known and hence predictable. It is difficult to forecast the patterns of antibiotic resistance development so well to pinpoint when and where an antibiotic is approaching various levels of "risk zones". Further, it is challenging to define which would be the various levels of price increase associated with the various risk zones. A detailed study of demand elasticity for the specific antibiotic will be necessary to set optimal prices; and a very inelastic demand would not diminish even with very high price increases, thereby making these increases ineffective in reducing use.	
Source(s), concrete implemented examples and originating industry:	
Energy markets, time-based electricity tariffs to reduce risk of black-outs, network congestion charges (road tolls for city centre congestion)	

Descriptive title of the solution:	Solution number: 18

Value chain separation of antibiotic R&D from sales

Problem(s) or challenge(s) in antibiotics that is being addressed:

Need of delinking pharmaceutical companies' revenues from sold volumes. Sales push undermines antibiotics conservation.

Description of how the solution will operate:

Drug companies vertically integrated in both R&D and sales earn revenues from sold volumes of antibiotics, which undermines incentives for such companies to conserve them. This solution separates the R&D and sales functions, similarly to the separation between energy generation companies (producers) and energy distribution companies (sales) in some countries and US states.

Separating the ownership of substantial parts of the antibiotic value chain, i.e. reducing the degree of vertical integration, allows for different economic incentives driving different parts of the value chain. While antibiotics developers/producers can be hardly motivated to willingly accept cuts of their revenues by reducing production, antibiotics distributors can be stimulated to focus on other sources of revenues than just pushing unit sales (e.g., subscription fees bundling also antibiotics conservation services). This solution re-organizes the supply market by creating different organizations, open to react to different incentives, not only maximizing unit sales, but also working towards conservation by means of other services provided to the healthcare system.

A fully delinked model would separate both antibiotics production and distribution from antibiotics R&D, or sales can either be at marginal cost or come from a third party generic producer. In other models short of full delinkage, the R&D company still sells for something more than marginal cost and receives a "topping off" contractual payment from payers on a basis that does not relate to volume: e.g., healthcare systems could pay distributors for finding ways to actively decrease the need for antibiotics at hospitals – possibly to an extent that it is a more attractive doing this than selling antibiotics. In order to regulate such payments to "drug" distributors, this solution can be combined with the other solutions above "Value-based subscription" and "Service/supply contracts."

Optional features or variants of the solution:

-In a fully delinked model (separating drug development from production), contractual payments would be made to the generic producers, to support both conservation and adequate access.

-In hybrid models (not fully delinked), these payments could be combined with almost any other incentive system, to support conservation and access.

-Could be implemented as a regulation (binding on all drug suppliers) or contract (voluntary).

Effect on fundamental economic, organizational or legal variables:

Reduction of degree of vertical integration in the antibiotic industry. Incentives addressed to independent companies along the value chain are more fine-tuned to reduce volumes of sales.

Critical factors to make solution viable, risks, or (potential) disadvantages:

Hybrid models (short of full delinkage) make it difficult to find simple and clear incentives and KPIs for distributors to act upon and be rewarded against.

Enforcing a regulatory vertical de-integration of pharmaceutical companies may encounter massive opposition from industry, especially if it should have consequences on other therapeutic areas.

This solution targets conservation and disincentivises wasteful use, but it might have unexpected consequences for producers, including negative ones on their R&D efforts unless other measures are taken to compensate for their loss of unit sales revenues.

Source(s), concrete implemented examples and originating industry:

Big Innovation Centre. Energy generation companies and energy distributors in the US.

Descriptive title of the solution	Solution number: 19
Not-for-profit and controlled retailing of antibiotics	
Problem(s) or challenge(s) in antibiotics that is being addressed:	
Excessive use when sales are pushed by drug developers/manufacturers. Lack of conservation.	
Description of how the solution will operate:	
Pharmacies (or any other retailer selling antibiotics) are by law not allowed to apply any margin on the antibiotics they sell nor to advertise, give discounts or rebates on these products. While only marginally influencing sales in countries which strictly apply prescriptions, this solution would be relevant for countries where antibiotics are sold over the counter. As the retailer has no incentives to sell a product with no margin, it would do it only as a service paid, via a yearly lump-sum fee (i.e., volume independent), by the national healthcare system. The discounts, sales campaigns and pressures by drug suppliers would also be met by a lack of interest as retailers would not be able to add any margin irrespective of the purchase price. Since some pharmacies may opt to exclude entirely antibiotics from their assortment due to zero or even negative margins, national healthcare systems may attach the requirement to carry antibiotics to the assignment of licenses for selling drugs in general.	
Optional features of the solution:	
-Pharmacies under regulation can be either private companies or publicly owned organizations, the latter being more likely to apply this regulation. -Instead of being equal to zero, the margin on antibiotics can be so low to allow just covering the internal goods handling costs of the pharmacy.	
Effect on fundamental economic, organizational or legal variables:	
Legal control on retail margins to reduce incentives to sell. Retailers operating as barriers to drug suppliers' sales push. Pharmacies' profits (if any) on antibiotics delinked from sold volumes.	
Critical factors to make solution viable, or (potential) disadvantages:	
Requiring a zero profit margin on antibiotics retailing entails legislation/regulation which not all countries may be willing to introduce for several reasons (political aversion to regulated markets, strong lobbying groups etc.). The opposition by pharmacies may be strong unless they are compensated in some way. Even if formally approved, the regulation needs to be enforced, entailing considerable costs for monitoring and punishing misconduct. Some countries will face more problems than others in enforcing this type of control on retailer margins. It is important to avoid that pharmaceutical firms or drug wholesalers "cross-sell" antibiotics by giving higher discounts on *other products* in exchange of the retailer's promise to push antibiotics even if they generate no profit for the pharmacy (the profit would be recuperated from the other discounted products). The solution focuses on community overuse of antibiotics, not in the hospital setting.	
Source(s), concrete implemented examples and originating industry:	
Nordic public monopolies on alcoholic beverages and, previously, on pharmacies.	

3.3 Salient differences between similar solutions

Among the 19 solutions reviewed above there are some which bear several similarities, in terms of the variables they influence, the actors involved and their mechanisms of action, especially if they belong to the same grouping among the five above. For instance, solution No. 1 ("Service or supply contract…") is similar to No. 3 ("Value-based subscription…") in that they both include annual subscription fees. However, No. 1 is a solution steered from the healthcare system via its own drug wholesaler, while No. 3 is based on the initiative of the drug developer. Moreover, outsourcing of activities from hospitals to drug providers and integration in healthcare processes between these two actors is much greater in No. 3 than in No. 1. Finally, performance-based payments and innovative and precise KPIs are more relevant in No. 3 than in No. 1.

There is also a similarity between solution No. 1 ("Service or supply contract…") and N. 2 ("Shared risk model"), as both solutions entail an annual fee. However, while in solution No. 1 this fee is fixed, in No. 2 the yearly payment to pharma can vary based on actual volumes of drug usage in healthcare: therefore, solution No. 2 may be viewed as a specific application of No. 1 (which is a more general category of solutions).

Solution No. 5 ("Jointly financed R&D infrastructure…") and No. 8 ("Joint, multilateral, non-pooled financing…") are both solutions that support R&D. However, while solution No. 5 provides such support by creating a joint R&D infrastructure/platform, No. 8 does not create necessarily a common R&D platform, as financing can go to actors who already have their own and will not necessarily collaborate with others. On a more precise level, there are two solutions which both create a R&D platform: the aforementioned solution No. 5 and No. 6 ("Antibiotic innovation platforms"). The difference between these two solutions is that No. 6 is specifically addressed to small actors with limited resources for performing R&D, such as SMEs and individual scientists.

Solution No. 9 ("Public procurement, single buyer scheme…") and No. 10 ("Upfront payment of R&D by global consortium…") bear some resemblance as both are mechanisms for procuring antibiotic R&D. However, No. 9 can procure specific stages of R&D, while No. 10 aims at a final drug. The payments of solution No. 9 can be before or after R&D completion, whereas those in No. 10 are upfront. Another difference is that while solution No. 9 operates only via open public tendering, No. 10 can cherry pick without open tendering or even intervene upon request of a drug developer. Finally, while No. 9 can operate nationally, No. 10 is by nature a global/transnational model.

There are close connections also between solution No. 4 ("Insurance & Fire protection…") and No. 16 ("Reducing the need of antibiotics…"), as both solutions propose preventive measures/investments that reduce the actual use of antibiotics. The difference, and the complementarity between the two solutions, is that No. 4 states how some of the measures/investments can be financed, while No. 16 delves into which these specific measures/investments can be.

4. Conclusions

The approach followed by Task 4 in the search of new business and reward models was explicitly chosen to maximize the number and breadth of novel solutions from other industries. This implied an open and less structured process of identification and selection. Applying a more structured and fully exhaustive process, such as a structured evaluation of all known business models in relation to the antibiotics field would be unfeasible, due to time constraints in identifying all such models and the low level of codification of many business models. Given this limitation, an exploratory approach has the drawback of not ensuring that all possibly relevant industry solutions are identified and evaluated. While some such solutions have been most likely missed, Task 4 has nonetheless identified several novel solutions from other industries not previously identified in similar efforts, for example in the Chatham House/Big Innovation Centre report.

Considering that the 19 solutions will be further vetted in Task 7 and, if selected, ultimately tested in Task 9, the benefits of the exploratory approach of Task 4 remain, while other drawbacks such as overlapping or poorly specified solutions can be compensated for in these later tasks. In particular, since all the solutions eventually selected by Task 7 will need to be testable via computerized models in Task 9 (or at least be viable to be included in very specific recommendations for implementation), it will be pivotal to make very clear for all solutions reaching Task 9 and 10 the following key dimensions: (1) *challenge addressed*, (2) *mechanisms of actions*, (3) *key variables influenced*, (4) *involved/affected actors*, (5) *expected outputs* (at which level in the antibiotics value chain) and (6) *required inputs* (including the *financial* resources required). The template used in this report can be a starting point for this work of systematizing and categorizing the solutions according to these dimensions, but further work needs to be done in that direction.

For future analysis, the 19 solutions presented in this report (along with those emerging from Task 7) can be grouped and categorized in several ways, different from the five groupings used in this report. For instance, the solutions vary in terms of level of abstraction from *operational*, specific solutions to specific challenges (e.g., solutions No. 15 and 19), to more *strategic*, higher level approaches (e.g., solutions No. 4, 5, 6 and 16). Strategic and operational solutions are not only different, but also complementary categories, indicating that they can be used in concert.

Another relevant categorization is *who finances* the specific solution, in the sense of providing the funds necessary to run it. The financing actor can be *governments* (e.g., solutions No. 4, 5, 8, 9, 10, 11 and 13), *healthcare providers and patients* (e.g., solution No. 14), *healthcare providers alone* (e.g., solutions No. 15 and 17), *drug providers or distributors* (e.g., solutions No. 18 and 19); or the solutions might have a neutral, minimal or even positive economic impact requiring *no actor* to provide additional financing (e.g., solutions No. 1, 2 and 3, where the annual fees should not be much higher than the payments currently made by national healthcare systems).

Solutions also differ and can be categorized based on the *level of the value chain* where they intervene, starting from basic science, via the various R&D phases, and all the way to final use by patients. Such a specification of the value chain level addressed would be more precise than simply indicating the challenge addressed: for instance, lack of conservation can be tackled by intervening at least at three different levels, that of drug distributors, that of intermediate users, such as hospitals, and that of final users such as patients. As shown in the table below the 19 solutions reviewed in this report intervene at several different level of the antibiotics value chain.

Given the importance of delinking pharmaceutical firms' revenues from volumes of antibiotics sales, the issue of *delinkage* can be per se a relevant criterion for categorizing the various solutions. The same goes for the *geographic spread* of each solution, classifiable into *national*, *international* or *global*, depending on the need for or the possibility of involving one or several states to implement the solution. Finally, solutions differ in terms of the role of government as opposed to market forces, with at least three possible groupings: *interventionist* (with governments operating directly the solution), *regulatory* (with governments setting sophisticated and detailed rules on how other actors can operate), and *free market* (with governments keeping to a minimum the level of regulations of the behavior of private actors).

Based on the above discussion, we propose a matrix over the 19 reviewed solutions, indicating their categorization in terms of the six following dimensions:

1- Level of abstraction: strategic-operational.
2- Level of the value chain in which they operate: from basic science to patients.
3- Delinkage: Yes, No or Not Relevant (NR).
4- Who finances: global agency, national governments, healthcare providers, patients, providers/distributors, no actor needed.
5- Government role: interventionist, regulatory, or free market
6- Geographic spread: national, international or global.

Solution	Abstraction	Value chain	Delinkage	Financiers	Govern-ment role	Geography
1. Supply contracts	Operations	Producer/ healthcare use	Yes	Not needed	Market	National
2. Risk sharing model	Operations	Producer/ healthcare use	Yes	Not needed	Market	National
3. KPI subscription	Strategy	Producer/ healthcare use	Yes	Not needed	Market	National
4. Insurance/protection	Strategy	Healthcare use/ producer	NR	Government	Interventio-nist	National/ international
5. R&D infrastructure	Strategy	R&D	No	Government	Interventio-nist	International
6. Innovation platform	Strategy	Basic science/ R&D (early)	No	Government /private	Interventio-nist/market	National/ international
7. Standard bodies	Strategy	R&D	NR	Not needed	Market	Global
8. Non-pooled finance	Strategy	R&D	NR	Government	Interventio-nist	International
9. Single buyer scheme	Strategy	R&D/ healthcare use	Yes	Government	Interventio-nist	National
10. Upfront payment	Strategy	R&D/ healthcare use	Yes	Government /global actor	Interventio-nist	Global
11. Full refund tax	Operations	R&D	No	Government	Regulatory	National
12. Early R&D fund	Operations	R&D (early)	No	Government /private	Interventio-nist/market	National
13. Late R&D finance	Operations	R&D (late)	No	Government /global actor	Regulatory	International
14. Antibiotic bond	Operations	R&D (late)	Yes	Healthcare/ patients	Market	International
15. Mitigation bank	Operations	Healthcare use	NR	Healthcare alone	Regulatory	National/ international
16. Reducing need	Strategy	Healthcare use /patients	NR	Government	Interventio-nist	Global
17. Variable prices	Operations	Healthcare use	No	Healthcare alone	Market	National
18. Chain separation	Strategy	Producer /distributor	Yes	Producers/ distributors	Regulatory	National
19. No-profit retailing	Operations	Distributor	Yes	Producers/ distributors	Regulatory	National

Categorizing each solution along the six dimensions is clearly partly subjective and open to diverging interpretation of the content of each solution. However, the attempt in the table above helps to see clearly the differences between the various solutions (and indeed no two solutions present exactly the same values), as well as their complementarities, including how two or more solutions can combined. At first glance, the solutions appear mostly complementary, rather than mutually exclusive, even if the column “Financiers” can reveal those who compete for the same funding. Finally, working with the dimensions such as in the above table can help further modify the suggested solutions: for instance can we take a solution and make it more market-based as opposed to regulated, or change the financiers behind it? What does it take in order to make a solution operate at a global level?

References

1. Jaczynska E, Outterson K, Mestre-Ferrandiz J. Business Model Options for Antibiotics. Learning from Other Industries. London: Chatham House & Big Innovation Centre, 2015.
2. Kitzinger J. The methodology of Focus Groups: the importance of interaction between research participants. Sociology of Health & Illness. 1994;16(7):103 - 21.
3. Hoffman RR, Shadbolt NR, Burton MA, Klein G. Eliciting Knowledge from Experts: A Methodological Analysis. Organizational Behavior and Human Decision Processes. 1995;62(2):129 - 58.

Definitions of key terms

Business model: A description or definition of how an enterprise creates and delivers value to customers, by describing the firm's value proposition, revenue model, market segment, cost structure, profit potential, value network and competitive strategy. Each company may have its unique business model.
Reward mechanism: A reward mechanism is an incentive or regulation that interacts with a firm's business model to induce that firm to work towards a specific policy goal (i.e., greater antibiotic-related R&D investment). Examples include R&D tax credits, advance market commitments, and prizes.
***Reward bundle*:** A reward set-up is a package or bundle of simultaneously implemented reward mechanisms.
Economic model: A description of the entire antibiotic landscape, including business models, the value chain with the R&D process and existing reward mechanisms.
Value chain: A description of the activities that either a single firm or a set of interrelated firms perform in order to bring a product or service, both old and new, to final users.
***R&D process*:** Represents either the sequence of activities conducted repetitively to devise and develop new offerings (according to a predefined template applied to every offering) or the particular sequence of events that characterized the journey from idea to adoption (or premature termination) of a specific new offering. *Example: the rigid template for drug R&D stating which specific activities a new product must go though.*

Appendices

Annex 1: Briefing material for the panelists

Dear n,

Thank you for accepting our invitation to join the panel brainstorming sessions about reward mechanisms and business models for antibiotics development. In this letter we wish to provide you with some basic background material that will guide your efforts, hoping it will inspire your creativity and imagination.

General introduction
Antimicrobial resistance (AMR) is widespread. Its global human and economic burden is tremendous and constantly increasing. Yet today only four among scores of pharmaceutical companies retain active antibacterial drug discovery programmes; a mere two of these have a novel antibiotic in Phase II development. While the elaboration of antibiotics with novel mechanisms of action is scientifically complex, the chief challenge is diminishing incentives. Pre-market regulatory requirements and increased control on post-market access, use, and pricing of new antibiotics are strong deterrents to new drug development. One result of these challenges is that major companies to a large degree have left the field while SMEs are still too few and small to compensate, partly because risky and unattractive end markets limit venture financing. Meanwhile, healthcare payers are not currently prepared to reimburse antibiotics at prices that would directly support the cost of development.

Applied to antibiotics, a simple sales-based economic model contradicts the public health mandate to reduce their consumption in order to preserve their efficacy. Alternative models that can create incentives for the discovery of novel antibiotics and yet reconcile these incentives with responsible antibiotic use are long overdue. We wish to address challenges both from a policy and an industry perspective.

The assignment
Specifically, we are requesting that, based on your experience of several sectors and fields, could you please suggest:
a) sectors/fields that face one or more of the challenges listed below and that have successfully addressed them?
b) which specific solutions have different actors introduced to tackle the challenges you have selected? Solutions include incentives, contracts, regulations, new business models or parts of them, but also creation of new entities and introduction of new forms of collaboration or division of labour. The different actors include companies such as suppliers or customers, as well as regulators and other private or public organizations.

The overarching challenge
In the antibiotic field policy makers aim to achieve simultaneously three partly conflicting goals, namely

- equitable **access** to products, including in low-income countries;
- **conservation** of existing antibiotics by stewardship policies and rational use;
- product **innovation** to keep ahead of antibiotics resistance development in pathogenic bacteria.

This overarching challenge entails further challenges that we group into four major areas, all of which will be expanded on in the following.

A. Conservation and market-related challenges;
B. R&D and product innovation challenges
C. Profitability and industry structure challenges
D. Universal access to essential antibiotics.

A. Conservation and market-related challenges

Antibiotics are a rather peculiar public good that implies not only short-term positive externalities in the form of treated patients, but also more distant negative externalities in the form of "pollutant" resistant bacteria (Challenge 1 in summary table). Thus, industry is facing stewardship and conservation measures: health authority guidelines demand that any new products be used with great parsimony, that is, only when really necessary, which reduces market size and profitability for manufacturers and distributors (Challenge 2).

Moreover, as antibiotics entail short treatments curing acute illnesses the markets will be inherently small, in contrast to chronic illnesses, making antibiotics markets small and uncertain (Challenge 3).

Despite required proof of effectiveness, antibiotics, especially for out-patient use, are procured at prices comparatively much lower than other drug categories (Challenge 4). Finally, new, patented products can often be substituted with low-cost generic versions of pre-existing products, and the resulting downwards price spirals further reduce profitability (Challenge 5).

B. R&D and product innovation challenges

Antibiotic resistance creates a negative feedback loop in the sense that the utilization of any new products will result in development of resistant bacteria, thereby requiring constant product innovation (Challenge 6). Nevertheless, no truly novel products have entered the market in the last 30 years (Challenge 7).

A major problem is that in antibiotics R&D there are complicated technical and biological challenges and probably, since the “low hanging fruits” have already been harvested, making new discoveries is becoming increasingly demanding, despite recent developments in basic biomedical sciences (Challenge 8). The technical risk is of a different kind than in many other industries. For instance, a flawed computer program can be improved by investing more resources, while a promising molecule that suddenly turns out to be toxic represents a dead end with ensuing loss of the invested R&D efforts.

The difficulties in antibiotic R&D are compounded by the fact that it requires several complementary competences that need to be mobilized and coordinated (Challenge 9). Moreover, the field suffers from reduced availability of innovation sources and of R&D competences in both academia and industry (Challenge 10) due to downscaling of several public and private research programs in recent years.

C. Profitability and industry structure challenges

Antibiotics entail lengthy and costly R&D processes, causing major sunk costs, without any guarantee that those costs will be recouped by sufficient sales (see challenges under point B), which reduces profitability (Challenge 11). Large multi-product pharmaceutical companies face high opportunity costs, and have diverted away resources from antibiotics R&D into drugs perceived to have higher ROI (Challenge 12). An extreme result of this internal competition for resources has been that in the last 20 years almost all major companies left antibiotic R&D, while SMEs are still too few and small to compensate (Challenge 13). This problem is aggravated by the fact that only limited (venture) capital is available to finance SMEs due to risky and unattractive end markets (Challenge 14).

D. Universal access to essential antibiotics:

There is an ethical case to provide equitable access to the product globally, also in low-income countries: hence high prices are not a solution and conservation in use is harder to enforce in countries with weak public health systems (Challenge 15).

Final remarks

We would like to emphasize that we do not expect any proposed solution to address *all* these challenges. We would be highly interested in proposed solutions that deal with a few or even only one

of the above challenges. As previously stated, you will be given a ten minute time slot to present your main ideas, and there will be ample time to discuss proposals and to add prepared proposals as well as spontaneously emerging ideas.

Final remarks
We would like to emphasize that we do not expect any proposed solution to address *all* these challenges. We would be highly interested in proposed solutions that deal with a few or even only one of the above challenges. As previously stated, you will be given a ten minute time slot to present your main ideas, and there will be ample time to discuss proposals and to add prepared proposals as well as spontaneously emerging ideas.

Further reading and input
In case you wish to seek out further input to this process, we would like to suggest the following sources (enclosed to our email message):

Jaczynska, E., Outterson, K. & Mestre-Ferrandiz J., 2015, *Business Model Options for Antibiotics. Learning from Other Industries*, Chatham House – BIG Innovation Center report.

Kinch, M.S., Patridge, E., Plummer, M. and Hoyer, D., 2014, An analysis of FDA-approved drugs for infectious disease: antibacterial agents, *Drug Discovery Today*, 19/9: 1283-1287.

Nathan, C., & Cars, O., 2014, Antibiotic Resistance — Problems, Progress, and Prospects, *New England Journal of Medicine*, 371:1761-1763.

Ramanan Laxminaryan's TED talk at:
http://www.ted.com/talks/ramanan_laxminarayan_the_coming_crisis_in_antibiotics
and the following website:
http://www.reactgroup.org/

Many thanks for your help
Sincerely

Practical information
[Venue, time, access, lunch, reimbursement practicalities

Annex 2. Summary table over challenges in the antibiotic field

Overarching challenge: Simultaneous policy objectives of access, innovation and conservation
A- Conservation and market-related challenges: 1- A public good but also a distant "polluter" 2- Stewardship/conservation measures: parsimony in product use results in reduced market size 3- Small and uncertain markets (non-chronic diseases) 4- A low-price category of drugs (despite requirement of demonstrated efficacy) 5- Substitutability by generics causes downwards price pressure and reduces profitability
B- R&D and product innovation challenges: 6- Vicious circle: resistance development requires constant product innovation 7- No truly novel products in the last 30 years 8- Complicated technology and biology; new discoveries more and more demanding 9- Need of several complementary competences to conduct R&D. 10- Reduced innovation sources and R&D competences in both academia and industry
C- Profitability and industry structure challenges: 11- Lengthy and costly R&D → major sunk costs and reduced profitability 12- Opportunity costs at large Pharmas → resources diverted away from antibiotic R&D 13- Exit by major companies, but hard to fill the void by SMEs 14- Limited (venture) financing to SMEs (due to risky and unattractive end markets)
D- Ensuring universal access to essential antibiotics: 15- Global access collides with high prices, and conservation is more difficult in low-income countries