Economic considerations to strengthen the development of antibiotics

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1 Content

2 Abstract

The increasing bacterial resistance to antibiotics is one of the greatest medical challenges of our century. Antibiotics are of utmost importance for the treatment of bacterial infectious diseases, but the effect of approved antibiotics is constantly decreasing due to the increasing development of resistance. At the same time, hardly any new classes of antibiotics are being developed, although there is an urgent need from a social point of view. The lack of development of new products is mainly due to economic reasons and market failure.

The state has various possibilities of intervention at its disposal to correct this market failure. By coordinating the right push and pull incentives, within an international setting, the state can get the development of new urgently needed antibiotic classes back on track. As a country with an outstanding research and development ecosystem, Switzerland must play a leading role in the international debate. This first requires a consensus within Switzerland between politics, research institutions, society, and industry on the incentive mechanisms to be set and their financing options.

To create the legal basis to advance the topic of antimicrobial resistance and the development of innovative antibiotics, this should be included in the new edition of the "Master Plan to Strengthen Biomedical Research and Technology". This would allow the Federal Council, which has recognised the importance and urgency of the issue, to initiate an intensive dialogue between representatives of industry, the authorities, politics, society and science. In addition to developing sustainable alternative R&D models, the aim of this dialogue could be to reach agreement between the various groups with a binding agreement on the incentive mechanisms to be used for financing. A clear commitment by the Federal Council to strengthening development incentives could also encourage investors, in particular venture capital, to press ahead with the development of new antibiotics classes.

3 Background

The increasing antimicrobial resistance is one of the greatest medical challenges of our century. Antibiotics are of utmost importance for the treatment of bacterial infectious diseases, but the effect of approved antibiotics is steadily decreasing due to the increasing development of resistance (see Figure 1). In Switzerland, the Swiss Centre for Antimicrobial Resistance "anresis.ch" has been collecting data since 2004 and publishes it monthly in the FOPH bulletin. The effectiveness of conventional empirical antibiotic therapies can no longer be relied upon in both the hospital and outpatient sector. The situation is worsened by the fact that fewer and fewer innovative antibiotics are being approved, while the number of substances that have become obsolete due to increasing resistance is steadily increasing (Kinch et al. 2014). It has been proven that a rapid, resistance-oriented therapy reduces mortality and health costs by decreasing the length of hospitalization and the rate of side effects. Furthermore, targeted therapy can reduce the use of unnecessary broad-spectrum antibiotics and thus also counteract the increasing development of resistance. In the US, the total annual cost of antimicrobial resistance is estimated at US$ 26 billion and mortality from antimicrobial resistance infections at 23,000 deaths per year (Brogan and Mossialos 2013).

To maintain the effectiveness against bacterial infectious diseases, the development of new antibiotic classes would have to be substantially increased. However, only three new classes have been developed since the 1980s (Coates, Halls, and Hu 2011; Laxminarayan 2014). The constellation of an increasing number of antimicrobial resistance combined with the slow development of new antimicrobial agents represents one of the greatest medical challenges of our time. A similar problem to antibiotics exists with antifungals, i.e. antimicrobial substances that are used for the therapy of diseases caused by fungi for which no new class has been approved since 2006 (Denning and Bromley 2015). Although this area faces similar challenges and is also very important, the focus of this paper is on antibiotics.

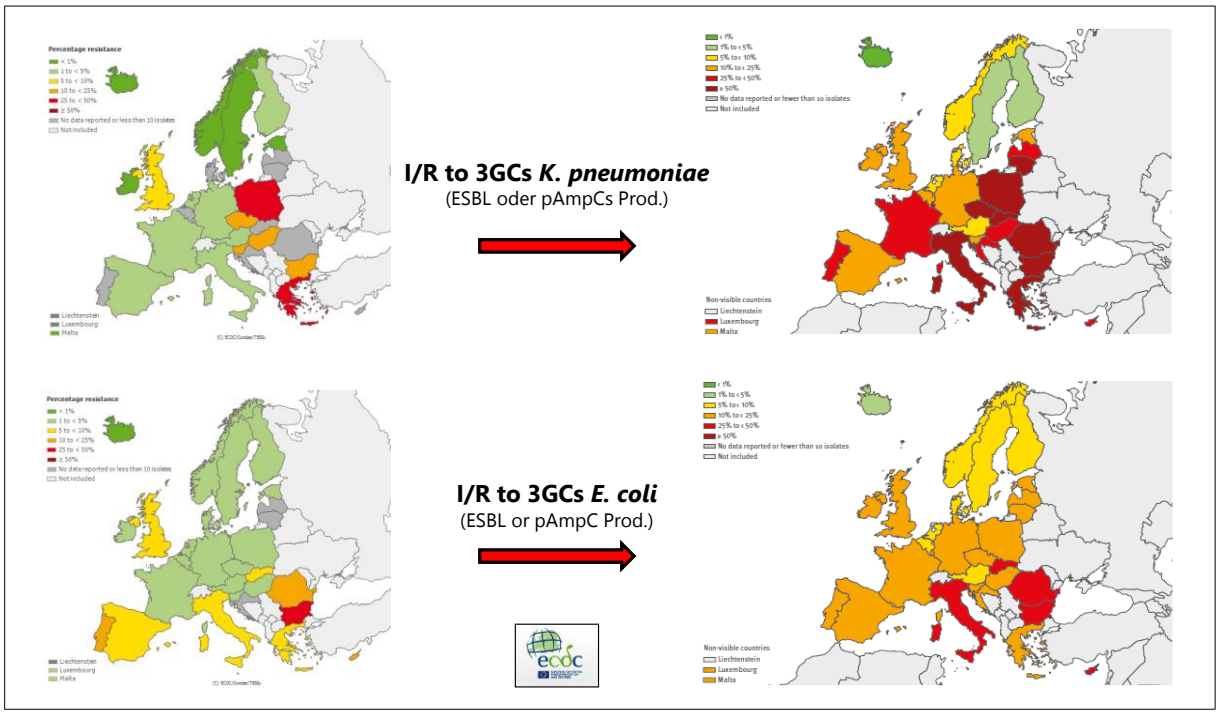

Figure 1: Development of antibiotic resistance in Europe 2005-15 (European Centre for Disease Prevention and Control 2016)

The causes of insufficient development of new effective products are not only a biomedical challenge. Various promising antimicrobial substances are known in basic research today (Hamad 2010). The lack of development of new products is mainly due to economic reasons and market failure, i.e. no new

classes of antibiotics are being developed due to insufficient economic incentives, although there is an urgent need from a social point of view (Renwick, Brogan, and Mossialos 2015).

3.1 Market incentives for the development of new drugs (non-antibiotics)

In the following, the development incentives for companies for pharmaceuticals in general are presented first. The following chapter explains why these incentives do not work in the case of antibiotics.

The research and development process for a new drug is lengthy, resource-intensive and expensive. Normally the participating companies and institutions accept the high initial investments because the very high sales and profits after successful approval cover the research and development costs. The life cycle of a new drug is divided into different phases (see Figure 2).

- **Basic research** to find a target for the treatment of a disease, identification of drug candidates and for initial tests in the laboratory to prove the postulated mechanism of action. Basic research takes place primarily at universities and ETHs, which are financed by the Confederation, the cantons and foundations. In addition, there is the possibility of project-based financing, e.g. via SNF funds. Most donors have no direct economic interests and do not expect a target return on the invested funds.

- **Preclinical testing** for evaluation and documentation of effects and tolerability using cell cultures and targeted investigations of the entire organism in animals to guarantee safety. Depending on the scope of the study, this phase is financed differently. While smaller studies are often still carried out by universities, ETHs and hospitals, larger studies can only be financed with the involvement of an external investor, especially venture capital. However, external investors only finance studies that promise a competitive return. The return is normally realized by selling the shares at a later date.

- Before a new drug can be **approved**, a potential active ingredient must be developed into a ready-to-use product. To this end, the dosage form (tablet, syrup, injection, etc.) is developed and studies are carried out on patients to investigate efficacy, tolerability, dosage and side effects. After positive completion of the **clinical phases**, the drug is approved by the competent authority, e.g. Swissmedic. In particular, clinical studies in humans are very expensive and are usually not financed by universities or hospitals. Rather, venture capital or private equity must be used. These investors often sell their company or their results to large pharmaceutical companies after the successful completion of the first or second clinical phase, which strengthen the large companies' portfolio.

- In the vast majority of cases, a fully developed drug is **sold** by established pharmaceutical companies. These have a sales team to establish the product in use as quickly as possible. Fast increases in sales and turnover are important, as high prices combined with high sales can only be achieved during the comparatively short phase of patent protection.

- **After patent expiry**, usually 8-12 years after approval, generic manufacturers enter the market that leads to competition that reduces the original manufacturer's earnings.

In the phases described, all parties involved have an interest in obtaining marketing approval as quickly as possible, as the high costs invested are offset by a high sales and profit potential, which quickly decreases as patent protection expires. During the patent term, manufacturers have a high interest in maximizing sales of the product. This is because the production costs of an additional package (mar-

ginal costs) are minimal and represent only a fraction of the realized sales price. This incentive structure means that patients have very fast and efficient access to new innovative products. The following chapter shows why this mechanism has no effect on antibiotics.

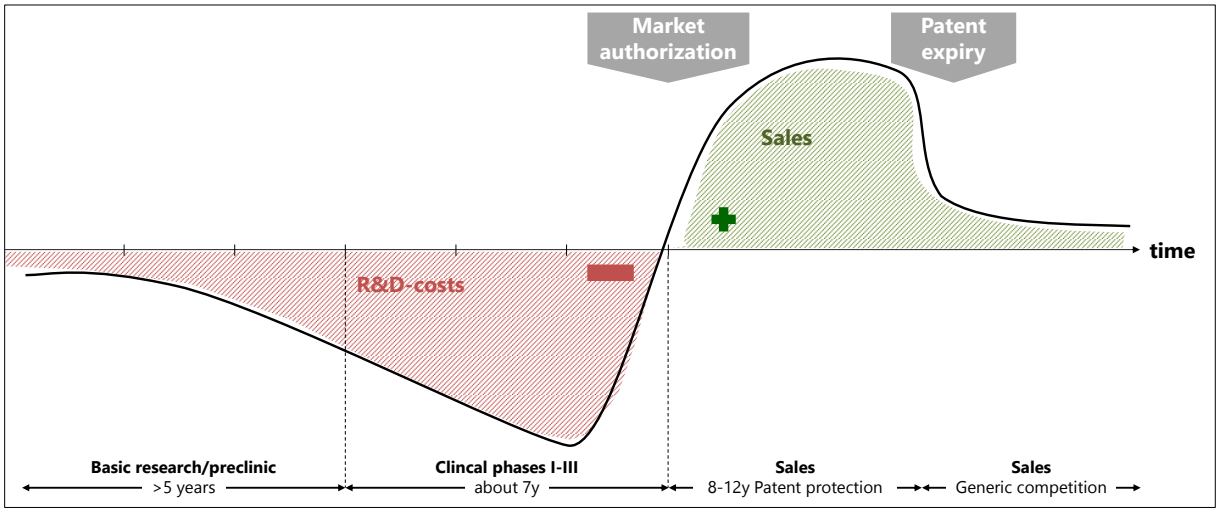

Figure 2: Expense and earnings structure over the life cycle of a normal drug (non-antibiotics)

3.2 Market failure in the development of new antibiotics

The incentive structures described above have no effect in the development of new antibiotic active substances, which explains the sluggish development. From an economic perspective, various interwoven effects play a role here (Towse and Sharma 2011):

- **The link between the use of antibiotics and the development of resistance**
  The broad use of antibiotics in medicine and agriculture leads to an increased incidence of resistant bacteria that cannot be treated with the available antibiotics (Alanis 2005). In particular, the use of antibiotics for viral diseases, the lack of adherence to therapy (Nugent, Pickett, and Back 2008) and the widespread use in animal husbandry favor the development of resistant pathogens. The development of resistance reduces the therapeutic and monetary value of an antibiotic.

- **Low incentives for research and development**
  The cost of developing a new drug are in the billion USD range (DiMasi, Grabowski, and Hansen 2016). For the investing companies not only the resources and costs involved are of importance, but the high opportunity costs are the much stronger factor influencing the investment decision. Opportunity costs are revenues lost because existing development opportunities are not exploited, e.g. if a company uses its drug developers for an antibiotics project and not for higher yielding oncology projects. The time and effort required for development to obtain marketing authorization is equally high for all drugs, irrespective of the field of expertise. However, the yield is usually higher in non-antibiotic projects. An examination of the net present value then shows relatively quickly that an investment in oncology or neurology projects promises higher returns on investment than an investment in antibiotics development (Projan 2003).
- **Responsible use of antibiotics (Stewardship)**
  Due to the risk of resistance formation when antibiotics are released and used without restriction in humans, animals and the environment, there are various formal and informal prescription guidelines that limit the release (Allerberger et al. 2009). From the point of view of society as a whole, the cautious prescription and use of antibiotics should be aimed for, but

from a manufacturer's point of view, the narrowing of the market reduces the incentive to develop new products. However, this would not be desirable from a social perspective.

- **Low market prices for existing antibiotics**
  With a few exceptions, the antibiotics on the market were developed over 30 years ago. Due to the expiration of the patent term, these products are exposed to strong generic competition, which leads to lower prices. High prices can only be achieved for the few newly developed products. However, due to the higher costs, the still high efficacy of older antibiotics, and to maintain efficacy, the new products will only be used if the older products do not achieve the therapeutic goal. As second- or third-line therapy, sales of the new products are correspondingly small. In addition, newly developed antibiotics will continue to be priced low in most countries due to stronger Health Technology Assessment activities (Kesselheim and Outterson 2010). Furthermore, although the entire antibiotics market is large in volume, it is fragmented into numerous markets according to speciality and resistance patterns. For example, the individual markets for antibiotics may be relatively small (Årdal et al. 2018).

The market incentives that work in the traditional drug market and guarantee patients access to new drugs time and again therefore do not work in the development of new therapies to combat antimicrobial infections (Stern et al. 2017). The expected turnover after approval of a new antibiotic is too low to cover the high research and development costs (see Figure 3). Without additional incentives from third parties, companies will not take the high risk of developing antibiotics at a low return on investment.

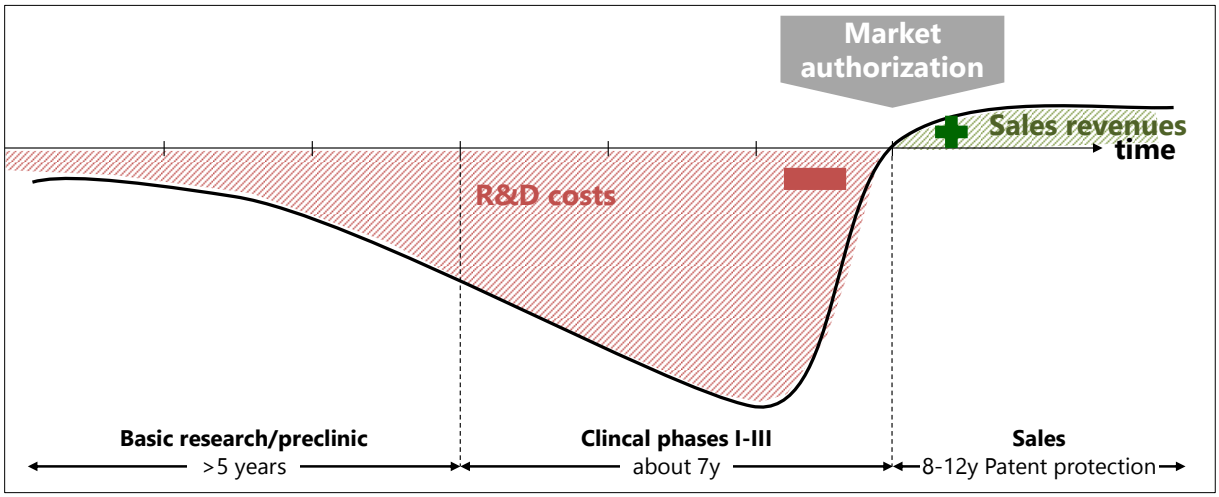

Figure 3: Expense and earnings structure over the life cycle of an antibiotic

4 Incentive mechanisms

According to the prevailing economic opinion, it is appropriate for the government to take regulatory actions in the event of a market failure in order to achieve a socially desirable result. It should be noted that it is basically the responsibility of companies to finance the development of new active ingredients. Any government intervention should only be carried out to the smallest possible extent because government intervention unnecessarily burdens market activity and disrupts the self-regulating principles of the markets. In particular, care must be taken to ensure that private development activities are not replaced by governmental activities (crowding-out), as the government is in most cases less efficient in achieving objectives than the private industry.

The government has various so-called push and pull instruments at its disposal. Push instruments include all incentives that relieve the industry of high costs in research and development, while pull instruments reward the actors by creating a demand market (Mossialos et al. 2010). The incentives to be set are intended to motivate the companies involved to (i) invest in R&D and bring new products to market, (ii) protect valuable resources from excessive dumping and premature development of resistance, and (iii) establish global access to life-saving antibiotics (Outterson 2014). Existing programs worldwide to promote research and development of new antimicrobial agents are outlined in Figure 4. Although the figure shows support in all areas from basic research and development to post-approval, this does not mean that all companies with all antibiotic agents are eligible, as many programmes are linked to requirements. For example, JPIAMR funding requires cooperation between at least three countries and GARD-P funding is only granted for specific antibiotic classes (e.g. neonatal sepsis). In particular, there are only a few financing options for phase III studies. The funding opportunities provided by the Biomedical Advanced Research and Development Authority (BARDA), which is responsible for the procurement and development of countermeasures against bioterrorism, chemical, nuclear and radiological threats, pandemic influenza and new diseases, were also limited to biological threats with the political change in the US government in 2017.

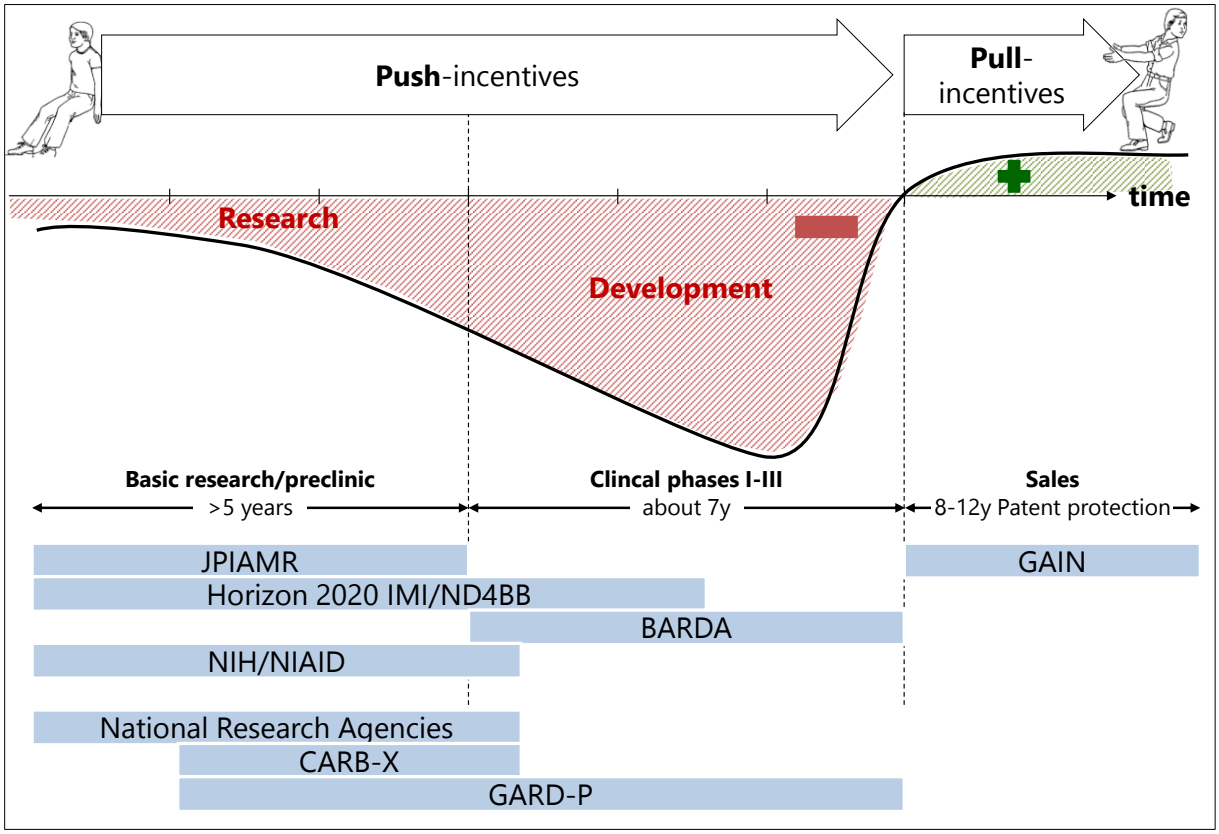

Figure 4: Overview of existing push and pull incentives for the development of new antibiotics

Companies have a choice of financing options for basic and preclinical research. New drug candidates are also constantly being developed. Substantially fewer financing options exist for the development of new active ingredients, i.e. for the expensive clinical phases I-III. In connection with the fact that many active substances from basic research and preclinical studies do not always meet the requirements for modern and safe active substances for clinical trials, the result is that potential active substances are often not further developed (see Figure 5).

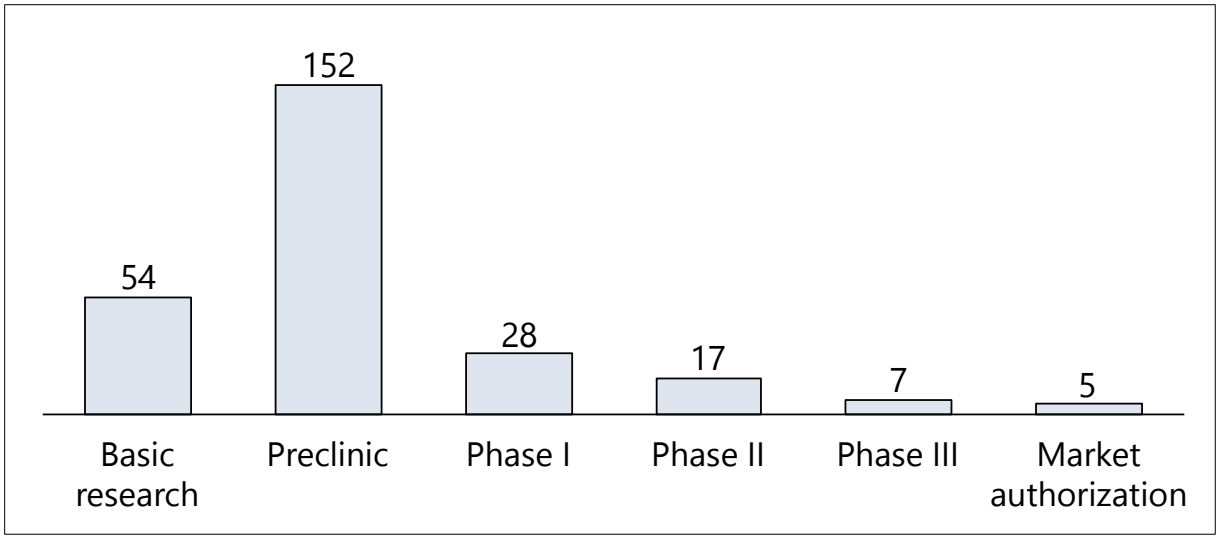

Figure 5: Number of existing drug candidates by stage in 2009 (Hamad 2010)

Especially with pull incentives, but also with push incentives, there is the difficulty of defining the milestones to be achieved in advance. Three criteria should be met by new drug projects: firstly, research and development should focus on compounds that tackle resistant targets, secondly, the drug projects should have a narrow spectrum of activity to reduce the likelihood of development of a resistance in other bacterial species, and thirdly, the projects should address relevant and urgent challenges to public health care (Laxminarayan and Powers 2011). The WHO priority list, which identifies a total of twelve priority pathogens to be controlled, can be used for the latter criterion (Tacconelli et al. 2018). However, even if the above criteria are precisely defined, the question of the amount of funds to be awarded remains challenging. The funds used should not exceed the amount of social benefits, but should nevertheless provide sufficient incentives for the development of new active substances.

The final report of the DRIVE-AB project of the New Drugs for Bad Bugs Program (ND4BB) of the Innovative Medicine Initiative (IMI) (Årdal et al. 2018) provides a detailed current overview of the possible incentive mechanisms. The report by Jaczynska, Outterson, and Mestre-Ferrandiz (2015) also presents several innovative business models that could drive the development of new antibiotics.

4.1 Push incentives

Push incentives include research funding through project-linked or project-independent grants, support for drug development through public-private partnerships (PPP) and regulatory simplifications (see Figure 6). In all push mechanisms, the development risk is shifted from industry to the payer, usually the public sector. From a company perspective, lower research and development costs will increase market attractiveness and attract additional market participants (Towse and Sharma 2011). Push instruments are often used at both national and international level, particularly because of the results that can be produced quickly and the low costs compared to pull instruments.

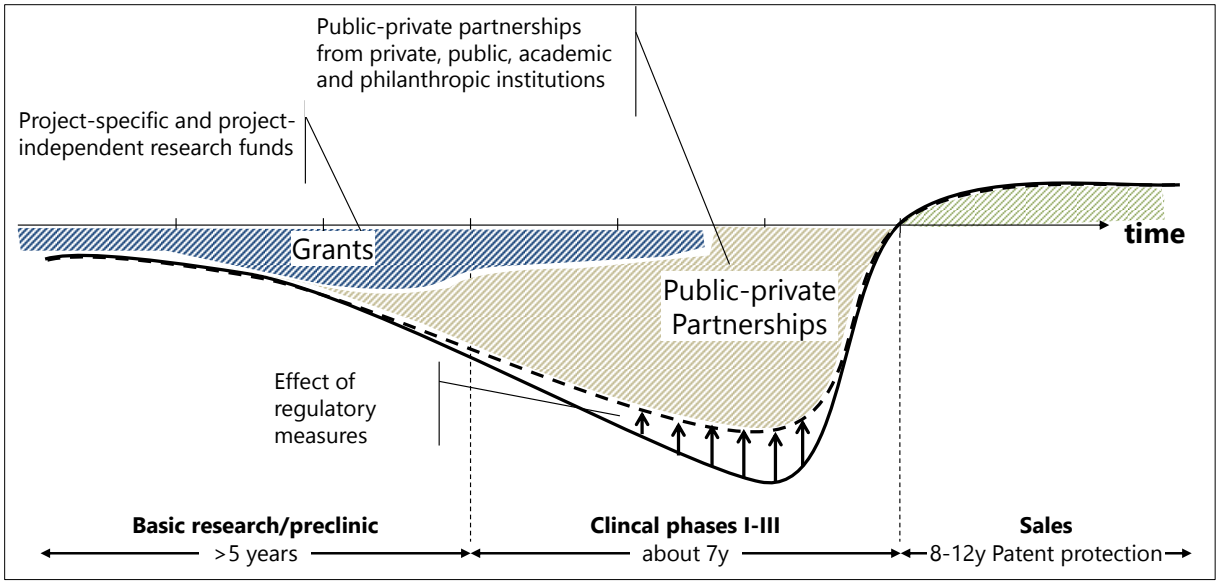

Figure 6: Effects of push instruments

The (cost) risk of development shifted by the push incentives from industry to the donor reduces the financial pressure on industry. In particular, the asymmetric distribution of information between industry and payers creates a principal-agent problem that can be exploited by industry (Morris 2003). The funding body, usually the government, has few opportunities to monitor the research and development activities of companies. In the worst case, due to a misinterpretation by the funding provider, unpromising projects are supported and resources are wasted.

In the following, various basic forms of instruments belonging to the push incentives are presented.

4.1.1 Project-related and -unrelated grants

In principle, a distinction can be made between project-related and project-independent grants. One of the classic project-independent push incentives is the basic financing of universities and ETHs. During their general work in basic research, these institutions repeatedly come across new mechanisms of action, which are then published scientifically in a further step. Furthermore, project-related funds for projects in the field of antimicrobial resistance formation are often also awarded. In particular, they promote monitoring, prevention, understanding of the development of resistance and the spread of resistant pathogens, screening, diagnostics and research into new active substances and mechanisms of action. Table I provides an incomplete overview of existing and past project-related funding programs and their exploitable results in which Swiss institutions have been, or still can participate. In the area of development (phase III studies) in particular, the funding possibilities are very limited.

4.1.2 Public-private partnerships

Public-private partnerships (PPP), which promote or carry out the development of new antibiotics themselves, have established themselves as effective push instruments in recent years. These institutions, often endowed with several US$ 100 million, have no intention of making a profit and can therefore carry out the development of drug candidates more cheaply and take higher risks in the projects than profit-oriented companies. PPPs include the New Drugs for Bad Bugs (ND4BB) program of the Innovative Medicine Initiative (IMI), the WHO Global Antibiotic Research & Development Partnership (GARDP), the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB X) in the USA and other national initiatives.

4.1.3 Regulatory push measures

Regulatory measures and simplifications in the push area include efforts to accelerate the approval of new products, to simplify the remuneration process or to reduce approval costs. One measure in this area would be the granting of a special status, similar to orphan drug status with the EMA, which provides submitting companies with a package of free administrative and scientific advice, tax relief, research support and fee waivers.

Table I: Overview of basic research programs and push incentives for the development of new antibiotics that can be used in Switzerland

	Basic research, prevention, preclinical						Clinical Phases I-III
	Monitoring	**Prevention**	**Development of resistances**	**Spread of resistant pathogens**	**Screening & Diagnostics**	**Research into new chemical agents**	**Development of new Antibiotics (push incentives)**
Scientific question	– Where and when do resistant pathogens spread? – How many antibiotics are consumed?	– How can the development of resistant pathogens be prevented? – How can nosocomial infections and antimicrobial resistance be combated?	– How do resistant pathogens develop?	– How do resistant pathogens spread in the ecosystem?	– How can the type of pathogen be determined?	– Which new active ingredients are promising?	– What development of antibiotics is financed by public funds?
Funding Programs	– NFP49, StAR – ND4BB, EU AMR Actions plans (2011, 2017) – WHO AMR Action plans (2001, 2015)	– FOPH – NFP49, NFP72, StAR – EU AMR Action plans (2011, 2017) – WHO AMR Action plans (2001, 2015)	– NFP49, NFP72 – ND4BB (Translocation)	– NFP49, NFP72, StAR – EU AMR plan (2017) – WHO AMR Action plan (2015)	– NFP49, NFP72, StAR – EU AMR Action plans (2011, 2017) – WHO action plans (2001, 2015)	– NFP49, NFP72	– ND4BB (COMBACTE)
Results	– ANRESIS – EARS-Net – ESAC-Net	– Guidelines for the correct use of antibiotics – information campaigns – National Centre for Infection Prevention Swissnoso	– understanding of the development of resistance: – E. coli (ST131) – S. aureus – P. aeruginosa – A. fumigatus – Enterokokken	– understanding the spread of resistant pathogens through: – livestock – tourism – agriculture – waste water – foods	– PCR analysis for P. aeruginosa – Classification method for MRSA – DNA chip technology for the detection of resistant genes in gram positive bacteria	– whiB7 Regulatory gene and PknG (tuberculosis) – Further development of the class of aminoglycoside antibiotics	– MEDI4893 (p. aureus) – MINOCIN against Acinobacter infections – MEDI3902 (P. aeruginosa) – DAV132 for the prevention of Clostridium difficile

4.2 Pull incentives

The pull instruments are result-oriented instruments that are only paid out once milestones have been successfully reached, e.g. when a new antibiotic has been approved. In contrast to the push instruments, the development risk here lies with a private company and thus these instruments have a positive influence on the efficiency of the development process (Morel and Mossialos 2010). Due to the shifting of risk, pull mechanisms are usually more expensive than push mechanisms. To date, almost no pull mechanisms have been adopted or implemented (see Figure 4), although there is a scientific consensus that a combination of push and pull incentives is essential for the effective development of new active substances.

Pull incentives are outcome-oriented, i.e. the drug developer only receives a remuneration or premium if a predefined result, in the best case the approval of a new antibiotic, has been achieved. The cost of an expensive aberration, which is only terminated in a late phase, is borne by the drug developer. The fixed premium in the event of success provides incentives for high technical efficiency on the part of the active ingredient developer. He will make every effort to get to the new product as quickly and efficiently as possible, as he can record the difference between the costs incurred and the premium as a profit.

4.2.1 Delinking sales from volume

Profit-oriented pharmaceutical companies have a high incentive to maximize their sales and volumes in the first years due to the threat of patent expiry. However, this behaviour leads to a rapid development of resistance and to a decrease in the therapeutic and monetary value of the product. This disincentive can be avoided by decoupling sales and volume. Pull incentives must be set in such a way that the volume has no or at least reduced influence on the company's profits. This can be done, for example, by paying time-dependent premiums. In this case, a company receives a premium from the payer independent of sales and must make the newly developed antibiotic available to patients at marginal costs or completely free of charge. (Outterson et al. 2016; Rex and Outterson 2016).

4.2.2 Market entry premiums

Market entry premiums are individual or a series of payments to a company that are linked to the achievement of certain milestones. This could be, for example, the achievement of marketing approval for a pre-defined antibiotic or the achievement of marketing approval for children. Market entry premiums can be structured in different ways. The following can be preset

a) Premiums fully decoupled from volume, providing guaranteed fixed payments to the producer. In this case, the delivery of the newly developed product will not be reimbursed additionally. Thus, the manufacturer has no incentive to over-sell the antibiotic. This reduces the risk of resistance formation. For investors, a premium that is decoupled from sales has the effect of a revenue cap and is therefore only conditionally attractive (see Figure 7a).
b) Fixed premiums paid in addition to sales generated are significantly more attractive to investors as there is no revenue cap for investors. In this way, however, manufacturers have no incentives for a sustainable release of antibiotics (stewardship). This tends to promote the development of resistance (see Figure 7b).
c) a one-off premium for the transfer of intellectual property rights in a new antibiotic to a public body (payer or medicines agency). This position subsequently assumes full responsibility for production, sales and regulatory issues. This enables the control of stewardship and access.
d) Their hybrid forms, such as sales-adjusted premium payments, which decrease with stronger sales of the new antibiotic.

Another special form of market entry premium is the agreement of insurance cover against payment of an annual premium. In this model, a manufacturer assumes the risk that effective treatment for a particular pathogen is available at all times.

Regardless of the design of the market entry premiums, they must be sufficient to cover the development costs and the risk incurred by the manufacturers. This means that with a fully delinked premium, the premium will be higher than with a non-delinked model. One of the biggest challenges of market entry premiums is the definition of the antibiotics to be developed.

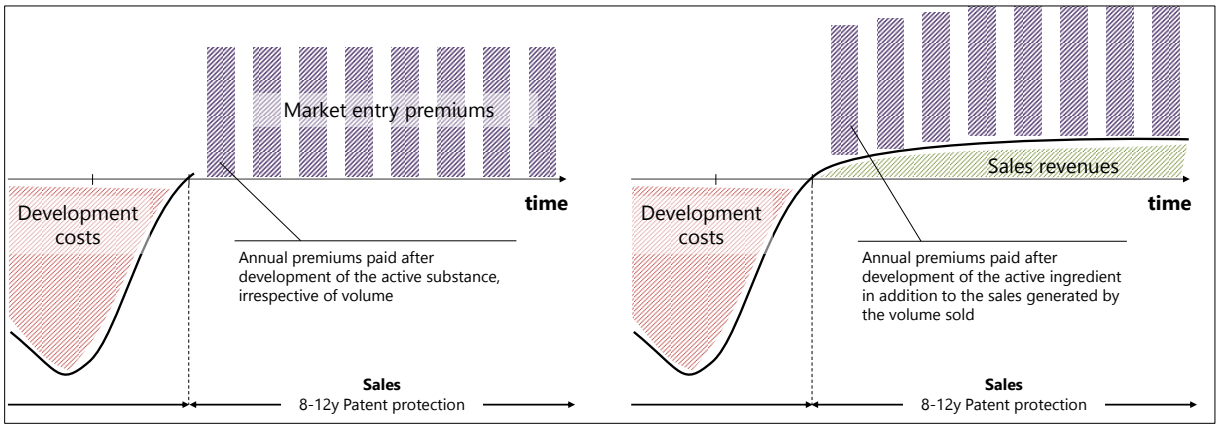

Figure 7: Possibilities for the design of market entry premiums

4.2.3 Advanced market committments

Advanced market committments can also have a pull effect for the development of new antibiotics. In this case, the payer, e.g., the state or a group of health insurers, undertakes to purchase a certain quantity of a newly developed product at a predetermined price for a certain period of time. Depending on the agreed purchase quantity and price, purchase guarantees exercise a similar pull incentive as market entry premiums. In combination with an exclusivity agreement, i.e. a ban on the sale of the product on the open market, volume is de-linked from sales and thus the incentive for excessive sales of antibiotics is eliminated. Accordingly, the distribution is controlled by the single buyer.

4.2.4 Market exclusivity

The granting of market exclusivity is one of the regulatory pull incentives (Figure 8). Here, a company is assured for a predetermined period of time that no alternative product, in particular no counterfeit product, will be permitted for sale. This means that manufacturers without generic competition can skim off a monopoly yield over a longer period of time, generate profits and thus refinance their investments. Such regulations were awarded, for example, for the development of so-called "orphan drugs", i.e. drugs for the treatment of rare diseases in the USA and in Europe. This regulation has also substantially improved the availability and access to treatment for these population groups (Blankart, Stargardt, and Schreyogg 2011).

To stimulate the development of antibiotics and antifungals, the Generating Antibiotics Incentives Now (GAIN) law was enacted in the USA in 2012. This legislation extends the exclusivity period of antibiotics for the treatment of serious or life-threatening infections by five years.

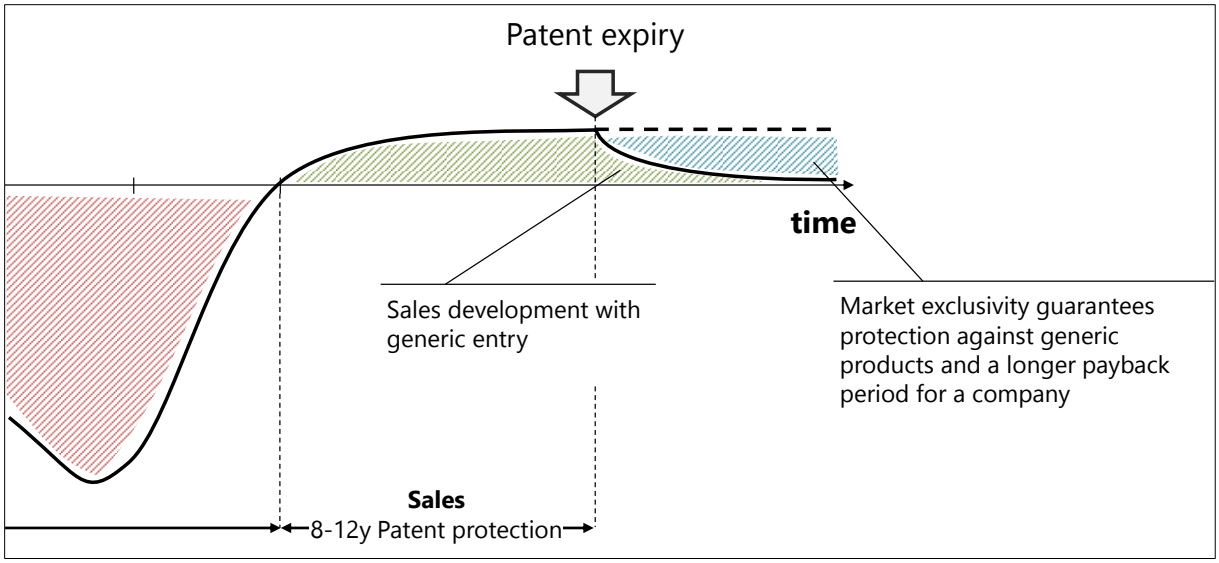

Figure 8: The effect of market exclusivity

4.2.5 Transferable Exclusivity Extensions and Priority Review Vouchers

Transferable Exclusivity Extensions (TEE) are a special form of market exclusivity. TEEs are awarded to companies after successful marketing approval and guarantee market exclusivity for a defined period for any product. They may be applied to any of the company's own products, but they are also tradable and can be sold to other manufacturers. The transferability of market exclusivity makes the TEE very valuable. Exercising a TEE for a blockbuster (> $1 billion in annual revenue) threatened by patent expiry and generic competition guarantees the manufacturer continued monopoly returns. A one-year TEE that would have been used to protect a blockbuster like Pfizer's Lipitor could have been worth up to US$7.3 billion. After patent expiry, sales to Lipitor fell from US$ 9.6 billion in 2011 to US$ 2.3 billion in 2013 (Pfizer 2013) due to the onset of generic competition. The advantage of TEEs is that they are relatively easy to implement. To limit costs, TEEs could be limited in advance to a short term or a certain sales volume.

Like TEEs, priority review vouchers (PRVs) are issued to drug companies when they have achieved a predefined goal, e.g. the development of a new antibiotic. The use of a PRV leads to accelerated testing of a new active substance by the authorities. The shortening of the approval process thus extends the time in which an active ingredient is subject to patent protection and also enables the realization of a first mover advantage if necessary. PRVs can be traded similar to TEEs.

4.3 Characteristics of push and pull incentives

The effective development of new antibiotics requires both push and pull incentives. While push incentives are a very effective instrument for promotion in the early stages, pull incentives are particularly effective in the later development phases. Table 2 gives an overview of the different characteristics of push and pull incentives.

Table 2: Overview of the characteristics of push and pull incentives

Push incentives	Pull incentives
Incentive effect	
• Effective instruments to promote basic research and preclinical research.	• Effective toolbox to promote the transition from preclinical to commercially approved products.

• Incentive effects in later phases (drug development: Phase II&III) relatively low, as manufacturers tend to use their development team for more profitable programmes, e.g. oncology programmes, as these promise higher profits, as opportunity costs are not replaced by push incentives.	• Incentive effect for basic research and preclinical research low, as incentives are too far in the future.
Distribution of development risk	
Development risk is with grant sponsor • Development tends to be technically inefficient[1], as development costs are borne by the grant sponsor who does not fully oversee the development process. • Problem of financing expensive undesirable developments due to information asymmetry between developer and grant sponsor.	Development risk is with developer • Tends towards technically efficient development[1], as the risk is borne by the developer who is owner of the whole development process.
Effect on antimicrobial resistance	
• Delinking of volume and sales is not possible. After successful development, the incentive for the manufacturer remains to maximize the sales of the newly developed product. This increases the probability of the development of antimicrobial resistance.	• Delinking of volume and sales possible and intended for many pull incentives. This reduces the incentives for the manufacturer to maximize sales of the newly developed product and therefore reduces the chance of the development of antimicrobial resistance.
Implementation challenges	
• Straightforward implementation possible, as existing programs, e.g. NRPs, are established and already available. • National implementation without international alignment possible.	• Politics, industry and research must come to an agreement on programs and develop them in detail. • Due to the high costs involved, implementation must take place in international coordination. • Determination of the financial amount of the pull incentive and, if applicable, challenges in offsetting pull against push incentives. • Agreement on possible targets (e.g., prior description of the product to be developed) is a challenge. • Prioritization of antibiotics to be developed differs by country/region • Politically difficult to raise the high amount of funding required to grant an adequate premium. • Countries have different preferences for pull incentives: in the US, transferable exclusivity extensions are more conceivable due to the fragmentation of healthcare

[1] The development of a new product is said to be technically efficient if a new product is developed with the minimum quantity of inputs, i.e., without waste.

	payers while Europe favors market entry premiums due to the more centrally organized health care systems.
Status quo • Many funding opportunities for basic research and preclinical research. Very limited funding opportunities exist for phase II and III studies.	• No programs implemented apart from GAIN (extension of market exclusivity, USA).

5 Procurement of funds

From a global perspective, the researchers of the DRIVE AB consortium estimate the funding requirement for incentive mechanisms in antibiotics research and development to be approximately US$ 1.2 billion per year. Providing these annual funds over a period of 30 years would lead to 18 drugs developed to market maturity (Årdal et al. 2018).

Regulatory intervention to develop new antibiotics is always accompanied by a redistribution of resources. With the introduction of a new regulation, the question of the origin of funds must therefore also be clarified. The question of who has to raise the necessary funds is primarily a political decision, not an economic one. Various basic models for financing antibiotic development funds are presented below. These can also be used in mixed forms.

5.1 General taxes

General cantonal or federal taxes could be used to finance the development of antibiotics. In this case, development costs would be borne by the entire population according to the performance principle, i.e. depending on the tax rate, more efficient taxpayers would pay more to finance development than weaker taxpayers. Financing from general taxes makes sense inasmuch as sufficient funds are certainly procured and the performance principle is adhered to. Especially against the background that none of the dangers of antimicrobial resistance can protect itself and thus the protection of the general public is guaranteed, speaks for this kind of fundraising.

5.2 Packing and usage fees

The development of antibiotics could be financed through an earmarked levy on each drug package supplied. This fee would be invoiced to the patient at the place of delivery, i.e. at the pharmacy or at the dispensing physician. The patient would submit this to his health insurance company for reimbursement once his deductible rate has been exhausted.

As a special form of package delivery, a restriction on antibiotic packs or a usage fee for antibiotics is conceivable. The resulting higher price would also curb the excessive prescription of antibiotics. This regulatory effect is basically positive, but must not complicate access for patients dependent on the antibiotic. Furthermore, it is questionable whether the full amount of the funds can be generated via a levy on only one product class.

Due to the structure of the health system, the additional costs are expected to be passed on in full to the recipient of the drug, i.e. the patient. Only after reaching the individually selected deductible rate will the additional costs are borne by the insurance company. Since the insurances are not profit-oriented in the obligatory part, they have few possibilities to bear these additional costs themselves. In all probability, they will charge the increased costs of the insured community through higher premiums. In both cases, the performance principle is violated, as the costs of developing antibiotics are initially borne by only a part of the population, the patients. The increased costs of the health insurance

company are also passed on evenly to the insured persons via increasing premium payments and not according to capacity.

5.3 Market exclusivity and transferable exclusivity extensions

Regulatory interventions such as the guarantee of market exclusivity, the award of TEEs or PRVs are also redistributed. These regulatory interventions prevent generic manufacturers from entering the market after patent expiry or extend the patent term and thus prevent price competition from arising. Generic competition is an important cost-containment factor in healthcare, as it also enables doctors to prescribe cheaper drugs with the same effect. In this respect, as with a package levy, patients and, in the further course of the treatment, the insured community is primarily affected by the lack of a discount on drug therapy. As in the case of the package levy, such financing does not comply with the performance principle.

5.4 Funds of the pharmaceutical industry

The necessary funds could continue to be raised through an industry-fund for the development of new antibiotics. This could, for example, be a sales-related contribution from any pharmaceutical company operating in Switzerland. It would also be conceivable for health insurers to participate in the fund, as they could benefit from lower costs, especially due to less severe and expensive infections in hospitals. With the establishment of such a fund, companies could also fulfil their corporate social responsibility. However, two things remain challenging: on the one hand, voluntariness will not allow sufficient funds to be generated and companies will continue to find it difficult to co-finance promising projects of their competitors using such an instrument.

5.5 AMR impact funds

The idea behind Impact Funds is the creation of an investment vehicle with which not just purely economic goals but also social goals are pursued. In the case of the AMR Impact Fund, a fund with a volume of USD 250-500 million could be envisioned, which would invest in new development projects in the field of antibiotics. The funds could be used for push incentives, in particular for financing promising projects in clinical phase III, but also for pull incentives.

The fund is not intended for purely yield-driven investors, but in particular for investors who wish to achieve not only a return of 2-4% but also social goals. Furthermore, such a fund offers reinsurance companies the opportunity to reduce the risks inherent in their industry. Elementary risks, such as the spread of a pandemic, can be reduced by the timely development of the appropriate drugs. Further alternative financing options are outlined in the (World Health Organization 2016).

6 Conclusion and further action

The risk of the spread of resistant pathogens is an international economic challenge that is not limited to developing countries where hygiene regulations are less stringent. In particular, the international integration of the economy, agriculture, and tourism promote the worldwide spread of resistant pathogens. The spread and control of antimicrobial resistance is therefore not only a national problem, but requires international coordination to tackle the problem.

In contrast to the traditional pharmaceutical market, the traditional innovation mechanisms do not work due to the special features of resistance formation and the resulting small market size for newly developed antibiotics. For this reason, innovative push and pull mechanisms are needed to create in-

centives for innovation and a legal basis for its long-term financing. In order to develop the new innovative financing mechanisms, public authorities, industry, investors and society must work together and test the models in pilot studies (United Nations 2016).

The financing of the new models can only be implemented on an international level, because from the perspective of large multinational companies, the measures taken in a small country such as Switzerland are of little relevance for their decision-making. The envisaged incentive models must be implemented at international level because the pharmaceutical industry gears its development pipeline to the needs and willingness to pay of the world market. However, Switzerland has an excellent research and development location, which it can strengthen by playing an active role in international discussions on the implementation of new programmes. In order to play a credible leading role, a consensus must be reached in Switzerland on the framework conditions for the development of new active substances and their financing. In coordination with Switzerland's other activities, such as participation in the Global Antimicrobial Resistance Research and Development Hub (AMR R&D Hub[2]), the topic of antimicrobial resistance and the development of innovative antibiotics could therefore be included in the new edition of the "Master Plan for the Promotion of Biomedical Research and Technology". This would give the Federal Council, which has recognised the importance and urgency of the issue, the opportunity to actively contribute to the antibiotics strategy at national and international level.

The inclusion of this topic in the "Master Plan for the Promotion of Biomedical Research and Technology" to be redefined in 2019 would allow the Federal Council as a first measure to initiate an intensive dialogue between representatives of industry, authorities, politics, society and science. In addition to developing sustainable alternative R&D models, the aim of this dialogue could be to reach agreement between the various groups with a binding agreement on the incentive mechanisms to be used and financing. A clear commitment by the Federal Council to strengthening development incentives could also encourage investors, in particular venture capital, to press ahead with the development of new antibiotics classes. In order to create an evidence-based basis for decision-making, this dialogue will be accompanied by research projects in the field of incentive mechanisms.

[2] G-20 leaders agreed to form the research hub at their summit in Hamburg 2017. Switzerland joined the activities of the Global AMR R&D Hub in 2018.

7 Further literature

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