Effective antibiotics for the Swiss health care system: today and in the future

WHITE PAPER

Swiss Round Table on Antibiotics

Effective antibiotics for the Swiss health care system: today and in the future

a Swiss Round Table on Antibiotics white paper

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This white paper represents solely the views of the Swiss Round Table on Antibiotics and the involved authors. These views do not necessarily reflect those of the stakeholders who contributed information and comments.

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Preface

This white paper represents the culmination of collaborative efforts by members and staff of the Swiss Round Table on Antibiotics, as well as numerous individuals and organisations in Switzerland and abroad – all working together to address the "silent pandemic" of antimicrobial resistance. Through this joint endeavour, national and international organisations, authorities, individuals, and associations have generously shared their expertise, experience, and advice, transforming years of discussions about remedial measures into tangible action in Switzerland.

This publication has greatly benefited from the constructive feedback provided by reviewers representing a wide range of national and international stakeholder groups. We sought input from nearly 100 representatives of the Federal Administration, Parliament, cantons, and political parties spanning the entire political spectrum, as well as from opinion leaders, researchers, health care professionals and organisations, industry stakeholders, investors, and accelerators.

On behalf of the Swiss Round Table on Antibiotics' board, its members, and staff, I extend my heartfelt gratitude to the community of contributors and authors for their invaluable support.

Prof. Dr. Rudolf Blankart

President

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Management summary

Antibiotics have played an indispensable role in clinical medicine, public health, animal husbandry, and veterinary medicine since the early decades of the 20th century. Their remarkable effectiveness in treating bacterial infections and reducing the risks of surgery, chemotherapy, and other medical procedures has established them as the cornerstone of modern medicine. However, their widespread success and affordability have also led to their overuse, often exceeding clinical necessity. This has accelerated the natural development of what is known as «antibiotic resistance» in bacteria as they adapt to their environment.

As resistance continuously erodes the effectiveness of antibiotics, bacterial infections can become challenging or even impossible to treat, particularly when bacteria develop resistance to multiple antibiotics. The growing number of fatalities underscores the gravity of this trend.

Despite the pressing need for new antibiotics and for a dependable supply of existing ones, the stark reality both in Switzerland and globally is a troubling stagnation in the renewal of the antibiotic arsenal. This is a consequence of (i) low research and development (R&D) activity, (ii) manufacturers' reluctance to launch antibiotics in more than just a few high-income countries, (iii) shortages due to neglected supply chains and, (iv) in Switzerland, the frequent withdrawal of antibiotics from its relatively small market.

To address these multiple challenges, the Swiss national action plan Strategy on Antibiotic Resistance Switzerland (StAR), has outlined initiatives across eight fields of action, including one that calls for government and stakeholders «to promote the availability of first-choice antibiotics and the development of new antibiotics» (**Chapter 2**).

In this white paper, the Swiss Round Table on Antibiotics presents a proposal for increasing the availability of new antibiotics in Switzerland, particularly those needed to treat multidrug-resistant infections. To achieve this goal, it is imperative that the remuneration of antibiotics in Switzerland represents a fair share of the income manufacturers need to generate globally to cover the costs of research, development, manufacturing, and market maintenance, while also allowing for a reasonable profit. This financial viability is essential for encouraging industry investment in antibiotics, a field that many larger companies have abandoned in recent decades due to the higher risk of financial losses.

To reinvigorate antibiotic innovation, it is essential to implement economic and regulatory incentives throughout the entire pharmaceutical lifecycle **(Chapter 3)**. Our proposal focuses on so-called pull incentives, which take effect after a new antibiotic has been granted marketing authorisation. **Chapter 4** outlines our approach to developing this proposal. **Chapter 5** provides a detailed description of four pull-incentive models, followed by their evaluation in **Chapter 6,** which helped us identify the subscription model as the most suitable for implementation in Switzerland. Lastly, in **Chapter 7**, we propose a remedy for a key limitation of the transferable exclusivity extension voucher (TEEV) model and explore the prevalence model as a potential interim solution if the implementation of the subscription model takes longer than expected.

Throughout our efforts, we have consistently maintained our focus on the StAR mandate "to promote the availability of first-choice antibiotics". The troubling rise in antibiotic shortages and market withdrawals has compelled us to evaluate the potential of pull-incentive models to mitigate these problems. While acknowledging that a range of measures will be necessary, our analysis indicates that the subscription model we propose can play a significant role in achieving this goal.

Abbreviations

Abbreviation	Explanation
DRG	Diagnosis-related group
EMA	European Medicines Agency
EpidA	Federal Act on the Control of Communicable Diseases in Humans (Epidemics Act)
EU	European Union
FDA	Food and Drug Administration
FOPH	Federal Office of Public Health
G7	Canada, France, Germany, Italy, Japan, United Kingdom, United States
GDP	Gross domestic product
HERA	European Health Emergency Response Authority
IPI	The Swiss Federal Institute of Intellectual Property
KVG	Federal Health Insurance Act
KVV	Ordinance on Health Insurance
MER	Market entry rewards
NESA	Federal Act on National Economic Supply
NHS	National Health Service for England
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
PatA	Federal Act on Patents for Inventions (Patents Act)
R&D	Research and Development
RDP	Regulatory data protection
SME	Small and medium-sized enterprise
SNSF	Swiss National Science Foundation
StAR	Strategy on Antibiotic Resistance Switzerland
STEDI	Characteristics of an antibiotic based on its spectrum of use (**s**pectrum), its role in reducing spread (**t**ransmission), its ability to enable access to medical treatment (**e**nablement), its role in increasing treatment options (**d**iversity), and its ability to function as a last-resort treatment (**i**nsurance)
TEEV	Transferable exclusivity extension voucher
WHO	World Health Organization

1 Introduction

Since their advent in the early decades of the 20th century, antibiotics have saved countless lives. However, bacteria are continually adapting to their environment, naturally evolving resistance to these critical drugs. The situation is exacerbated by human actions, particularly the overuse and misuse of antibiotics, which accelerates the development of resistant strains and diminishes the effectiveness of existing treatments. As a result, antibiotic resistance has escalated into a global crisis, now recognised as one of the top 10 public health threats worldwide [1].

Effective antibiotics are the foundation of modern medicine. Their absence would make treatments excessively risky or even impossible in fields such as surgery, oncology, and general infection management, posing a grave threat to society. Research indicates that each year, infections caused by resistant bacteria claim the lives of approximately 300 people in Switzerland [2], 35,800 in Europe [1], 35,000 in the United States [3], and a staggering 1.27 million globally [4]. However, these statistics only scratch the surface of this **"silent pandemic"**. Managing antibiotic-resistant infections often requires multiple treatment attempts, each with its own set of potential adverse effects, as well as prolonged stays in hospitals and intensive care units, and longer recovery times. The consequences are many: diminished patient health and well-being, high health care costs, and socioeconomic losses due to sick leave and incapacity to work [5].

There is therefore an urgent need for effective new antibiotics [6]. However, there is a lack of innovation in Switzerland and worldwide, and the supply of existing antibiotics is characterised by bottlenecks and market withdrawals of existing products, both in Switzerland [7] and globally. This puts health care systems around the world at risk of not being able to cope with the increasing number and severity of difficult-to-treat multidrug-resistant infections.

This innovation shortfall does not stem from a lack of ideas or insurmountable technological barriers, but rather from a lack of incentives. The prevailing economic and regulatory environment of the infectious disease area is daunting and makes it far more lucrative for researchers, clinicians, and industry to channel their expertise, workforce, and financial resources into other medical fields, such as immunology, oncology, or gene therapies.

The objective of this white paper is to propose **solutions** aimed at counteracting this silent pandemic and ensuring that there will be a sufficient supply of effective antibiotics in the Swiss market for the successful treatment of infectious diseases. To achieve this, we introduce so-called **pull-incentive models** for potential implementation in Switzerland. These models are designed to stimulate the development and availability of antibiotics by ensuring appropriate remuneration *after* the successful market entry of a new antibiotic.

The conventional and most common pull incentive relies on generating revenue through the sale of products at a per-unit price. However, this approach inherently encourages higher product volumes. In the case of antibiotics, this is counterproductive because increased use of these drugs can lead to a loss of effectiveness. To prevent or slow down this self-defeating cycle, healthcare professionals, including doctors and pharmacists, should only prescribe or dispense antibiotics, and patients should only use them, when there is clear clinical justification, in line with the motto of the Federal Office of Public Health (FOPH), "antibiotics: use wisely, take precisely". In international terminology, measures that promote the appropriate use of antibiotics are referred to using the English term **"stewardship"**.

Stewardship measures are intentionally designed to reduce the use of antibiotics. However, when these are combined with the relatively modest prices that can be achieved even for new antibiotics, the result is lower revenue and profit. The conventional revenue model, based on "price times quantity", cannot simultaneously promote the preservation of antibiotic efficacy (through stewardship) and increased investment in the development and availability of antibiotics (by ensuring a reasonable return for manufacturers).

As a result, there is a great need for alternative remuneration mechanisms, especially for new and innovative antibiotics, to ensure their development and availability. Ideally, these mechanisms should decouple revenue from product volume.

2 Short- and long-term availability of effective antibiotics is at risk

2.1 Signals of the global antibiotic markets

Signs that the antibiotic market can no longer effectively meet current and future needs are evident across the entire value chain, from R&D to the launch of products and the maintenance of marketing authorisation.

R&D activities are insufficient: There is a conspicuous shortfall in the development of new antibiotic technologies, both in Switzerland and globally. The last new chemical classes, oxazolidinones and lipopeptides, were discovered in 1978 and 1987 respectively and launched in 2000 and 2003. Hence there have been no marketing authorisations for new chemical classes of antibiotics in the last 20 years [8]. Major international pharmaceutical companies have shuttered their antibiotic research programmes [9], and even developers who have recently launched new products have had to file for bankruptcy [10]. The World Health Organization (WHO) has concluded that "overall, the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antibiotic resistance" [11].

Launch rates of new antibiotics remain low[1]: Among the 18 antibiotics authorised by the medicines agencies of the United States, European Union (EU), Japan, or Canada from 2010 to 2020, the majority were introduced in just three out of 14 markets (United States, United Kingdom, and Sweden), as demonstrated by a recent international study. In 11 high-income countries, fewer than half of these antibiotics were accessible. The median annual sales for these 18 antibiotics in the first launched market, typically the United States, were very low, amounting to only USD 16.2 million [12].

In Switzerland, only nine systemic antibiotics and drugs for the treatment of tuberculosis were registered from 2010 to 2022, accounting for a mere 39% of the total registered in the EU during the same period (according to our own analysis).

***Shortages and market withdrawals affecting essential antibiotics*:** Antibiotics that have reached the market have become increasingly susceptible to supply disruptions, both in Switzerland [13] and globally. As of autumn 2023, supply disruptions in Switzerland have extended beyond hospitals to the community sector, with troubling shortages observed for oral antibiotics and vaccines [14]. This long-standing problem stems mainly from the complexity of global supply chains and the lack of, or inappropriate investment in, their resilience. The last remaining fully integrated production chain for antibiotics in Western Europe, Sandoz's Kundl facility, only narrowly avoided closure thanks to substantial subsidies from the Austrian government in 2020 [15].

In 2021 and 2022, the highest numbers of withdrawals from the Swiss market were recorded for antibiotics in a list of seven product categories [7]. The most frequent reason for market withdrawals is the inability to generate sufficient revenue to cover the costs of maintaining marketing authorisation, including pharmacovigilance and related reporting.

The inadequate renewal of our antibiotic arsenal can be attributed to several factors, including low R&D activity, manufacturer reluctance to pursue marketing authorisation and antibiotic launches in more than just a handful of high-income countries, supply chain neglect (especially for antibiotics used in primary care), and frequent withdrawals of antibiotics from the Swiss market. Together, these factors paint a picture of what is sometimes called a "broken market". Despite the evident need, this market fails to respond by increasing investments in new product development or enhancing the resilience of product supply chains.

[1] Note that a single chemical class can serve as the basis for the development of multiple drugs. This can be achieved by modifying a molecule, combining molecules from different classes (including older classes of drugs) or by providing the drug in different dosage forms (syrups, tablets capsules, injections, creams, and more) to meet the needs of different patient groups, including children.

While the underlying reasons for this situation are manifold, they share a common economic denominator: a lack of proper financial incentives and adequate methodologies to determine the reimbursement value for antibiotics. Left unaddressed, this situation poses a significant threat to health care globally and at the national health level, including in Switzerland, affecting both community and hospital settings, and endangering the lives and wellbeing of patients, both now and in the future.

2.2 Swiss national action plan: Strategy on Antibiotic Resistance Switzerland (StAR)

In response to this challenge, the Swiss Federal Council approved the national action plan StAR in 2015 [16]. StAR is a comprehensive plan of action encompassing the human, animal, agricultural, and environmental domains (One Health) to address the challenge of antibiotic resistance. The plan outlines initiatives in eight key areas:

1. Monitoring of resistance trends and antibiotic use
2. Infection prevention
3. Prescription guidelines for appropriate use of antibiotics
4. Combatting the transmission of infections
5. Research and Development
6. Cooperation between the One Health sectors, across various scientific disciplines, and internationally
7. Information and education
8. Creation of an appropriate political and legislative framework to support the development of new antibiotics, their appropriate use, and the reduction of antibiotic use in animal production.

This white paper describes the Round Table on Antibiotics' proposal for **designing and implementing measure 3.8.3 in action field 8**: the promotion of "the availability of first-choice antibiotics and the development of new antibiotics".

First-choice antibiotics are routinely used both in the community and hospital environments. In contrast, newly developed antibiotics are often classified as reserve antibiotics[2] which are intended for use as a last-resort option to treat severe infections caused by bacteria that have developed resistance to several common antibiotics [17], [18]. Reserve antibiotics are usually deployed in hospitals and represent slightly less than 1% of total antibiotic use [19].

While the minimal use of reserve antibiotics in Switzerland might appear reassuring, there is no room for complacency. The patterns of infections and antibiotic resistance seen in Switzerland are consistent with global trends. Switzerland's location at the heart of Europe, coupled with its open economy and affluence, encourages extensive travel, which in turn facilitates the cross-border spread of infections and resistance. Genetic analyses of resistant pathogens in Switzerland have identified similarities between resistance genes found in Switzerland and in neighbouring countries, as well as in countries beyond the Swiss neighbourhood [20]. These findings suggest that resistance patterns in Switzerland are not detached from those in other countries with which it has regular contact.

Among the member states of the Organisation for Economic Co-operation and Development (OECD), approximately three out of four deaths attributed to resistant infections are caused annually by only

[2] WHO Model List of Essential Medicines, 22nd edition, 2021: "This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. (…) These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable."

three groups of bacteria [5][3]. In Switzerland, two of these three groups pose a particular threat to public health. As a result, infections with these pathogens have been subject to mandatory reporting to the FOPH since 2016. Since then, the number of reported infections and associated deaths has risen steadily. The authors stated that "while the figures may appear relatively low compared to neighbouring countries, it is important to recognise that cases of multidrug-resistant bacteria are exceptionally difficult to treat" [20]. As the number of such cases continues to grow, it would be wise to ensure that our health care system is adequately prepared to manage them.

The observed similarity in infection patterns between Switzerland and foreign countries is not surprising. The ease with which microorganisms spread globally was most recently demonstrated during the COVID-19 pandemic.

[3] *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*) and *Staphylococcus aureus* (*S. aureus*)

3 Measures to promote the development of new antibiotics and secure their availability

When companies make decisions about drug supply chains and drug development, they adopt a global perspective. Industry decision-makers allocate their expertise, along with human and financial resources, to projects that are lucrative on a global scale. When considering investments, they take into account R&D risks, costs, subsidy availability, administrative and regulatory burdens, and, ultimately, the potential for financial gain in the market. Companies naturally prioritise projects that offer the highest profit potential, and they avoid unprofitable ventures. Given that investments in antibiotics are associated with low profit margins, losses, and even bankruptcies, entrepreneurial decision-makers often give precedence to investments in other areas, whether developing new drugs or strengthening product supply chains [21].

The conventional perception of the pharmaceutical sector as a free market driven by customer preference and willingness to pay is not entirely accurate, particularly in high-income countries like Switzerland with their tightly regulated health care systems. In these countries, drug pricing, reimbursement policies, and procedures for monitoring the continued justifiability of drug prices are shaped by health care regulations and are thus influenced by political priorities and budgetary constraints. Given this environment, the pharmaceutical industry's reluctance to invest in antibiotics is a logical response to policy frameworks that often fail to recognise the life-saving potential of antibiotics and their critical contribution to the effectiveness and safety of modern health care systems.

In the remainder of this chapter, we use the following broad definitions of "push" and "pull" incentives and regulatory ease:

Push incentives refer to all forms of funding that advance a project or drug candidate from the initial stages of basic research to marketing authorisation, regardless of the funding source. This includes all investments from public and private sources that support a product up to the point of marketing authorisation.

Pull incentives include any form of payment made to manufacturers after marketing authorisation, such as proceeds from sales, tax benefits, subscription payments, or transferable (tradable) vouchers that extend exclusivity.

Regulatory ease refers to any actions or measures that reduce the regulatory burden at any stage of the marketing authorisation process and in reimbursement procedures. This can include scientific advice provided by regulatory bodies, fee waivers, fast-track procedures, and measures that simplify the requirements for demonstrating the efficacy or cost-benefit ratio for certain medicinal products.

3.1 Push and pull incentives

Numerous countries and jurisdictions, including all G7 nations,[4] the EU and its member states, and Australia, are actively exploring ways to encourage the development of novel antibiotics and improve supply security. They aim to achieve this by lowering regulatory hurdles or ensuring that the rewards for these antibiotics reflect their true value to society or secure their supply to national health care systems. These initiatives are at various stages of planning and implementation, with **Sweden** and **the United Kingdom (UK)** leading the way through their pilot programmes for innovative reimbursement models. These illustrate that the specific measures taken at the national level can vary widely without jeopardising their overall effectiveness. Indeed, national diversity in reimbursement has long been common in the pharmaceutical business and poses no significant challenges when implementing innovative reimbursement approaches for antibiotics.

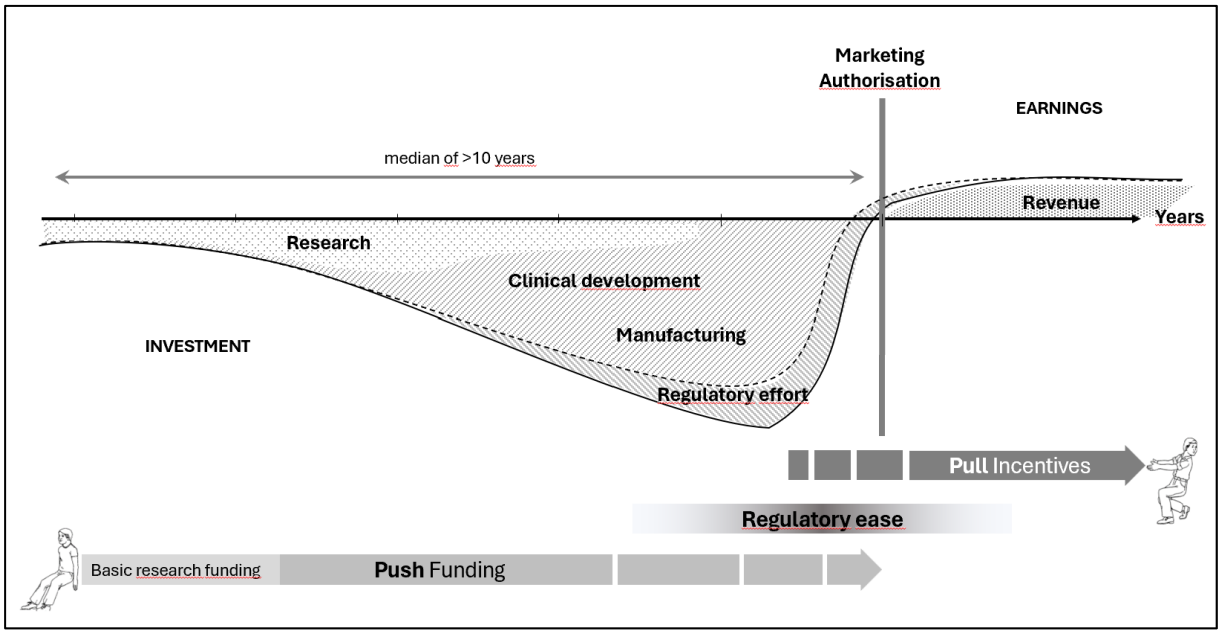
[4] Canada, France, Germany, Italy, Japan, United Kingdom, United States

Figure 1 shows the three core challenges of bringing antibiotics to the market and keeping them there: high development costs, administrative efforts to achieve marketing authorisation and remuneration, and insufficient market returns. To stimulate investments in new antibiotics and ensure a reliable supply, we need to reshape the economic and regulatory environment to improve the profitability of investments. Broadly speaking, there are three approaches to achieving this objective:

1. Reducing development costs through subsidies for basic research and drug development **(push incentives)**
2. Streamlining regulatory processes to simplify administrative procedures and expedite the marketing authorisation and reimbursement processes **(regulatory ease)**
3. Improving market prospects by improving the commercial viability of a product **(pull incentives)**

Importantly, a mix of push and pull incentives is needed. Without a viable business outlook in the market, private investors, including pharmaceutical companies, will not be willing to finance push incentives. Currently, small and medium-sized enterprises (SMEs) are responsible for approximately 80% of global antibiotic development [11]. Since many large pharmaceutical companies have withdrawn from the antibiotics business, SMEs face significant challenges in securing financing for their projects.

Figure 1: Challenges along the pathway of bringing antibiotics to the market



The three core challenges of bringing antibiotics to the market and keeping them there: high development costs, administrative efforts to achieve marketing authorisation and remuneration, and insufficient market revenue.

3.1.1 Push incentives

Push incentives are designed to facilitate the discovery of new drug candidates and support their progression through non-clinical and clinical development stages. A large proportion of these incentives is funded through national and international public and private investments, primarily via research programmes, grants, and private equity companies. These programmes focus mostly on basic academic

and pre-clinical research, with some allocation towards first-in-human studies. In Switzerland and internationally, companies can benefit from programmes like

- Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)
- Global Antibiotic Research and Development Partnership (GARDP)
- Horizon Europe Programme of the European Commission
- Horizon framework programmes of the Innovative Health Initiative (IHI) financed by the European Federation of Pharmaceutical Industries Associations (efpia) and the European Commission
- Incubator for Antibacterial Therapies in Europe (INCATE)
- National Center of Competence in Research
- Innosuisse and specific instruments and programmes of the Swiss National Science Foundation (SNSF), e.g. Bridge as a joint programme of Innosuisse and SNSF

3.1.2 Regulatory ease

Regulatory bodies like the Swiss Agency for Therapeutic Products (Swissmedic), the European Medicines Agency (EMA), and the US Food and Drug Administration (FDA), offer various measures to streamline regulatory processes, including

- scientific advice
- fast-track procedures
- participation in international work-sharing initiatives, such as the Access Consortium
- information-sharing systems like the US FDA's "Orbis" project or the EU's OPEN initiative
- waiving fees associated with pre- or post-market registration
- permitting the submission of additional clinical study data after marketing authorisation, such as under a temporary authorisation procedure

Health care payers also contribute to regulatory ease by

- introducing innovation surcharges for drugs meeting certain criteria
- exempting certain medications in Switzerland, like life-saving treatments, from regular price reviews
- coordinating parallel reviews of the marketing authorisation application dossier by Swissmedic and the reimbursement application to the FOPH, facilitating early access to drugs (e.g., the early-access programme for life-saving drugs that came into force in Switzerland at the beginning of 2024)
- simplifying or streamlining processes to demonstrate drug effectiveness or cost-effectiveness (e.g., Germany's AMNOG process allows exceptions to the usual evidence requirements)

3.1.3 Pull incentives

Whereas push incentives carry the risk of investment loss due to project failure, pull incentives are awarded only after a drug successfully obtains approval and enters the market. Importantly, pull incentives have an impact well before a new drug enters the market, influencing the investment decisions made by researchers, developers, and the industry [22].

Pull incentives also offer the opportunity to decouple revenues from sales volumes, making them a powerful stewardship measure by not incentivising overuse or misuse. In addition, they can be designed to guarantee continuous product availability in the market. Lastly, they create predictability in costs and revenues for payers and manufacturers, mitigating the costs of uncertainty [23].

The mechanisms by which pull incentives operate include:

- Market entry rewards (MERs), a one-off payment upon marketing authorisation or distributed over a limited timeframe
- TEEVs
- Subscription agreements with an annual guaranteed remuneration to compensate manufacturers for ensuring the availability and accessibility of certain antibiotics as and when needed.

4 Our approach

To develop our recommendations for the Federal Council of Switzerland, we employed a three-step approach.

In the first step, we gathered evidence from scientific and grey literature exploring solutions to the problem of inadequate antibiotic availability and the underlying incentive challenges. We also obtained feedback from representatives of the Federal Administration and cantonal administrations, as well as from health insurers, the industry, and further stakeholders from Switzerland and other countries pursuing measures similar to our Swiss initiative.

Based on this review and feedback, we shortlisted four pull-incentive models. Among these, two have gained international recognition for their capability to specifically address the low investment in antibiotics: the **subscription model** and **TEEVs**. The remaining two models follow the classical approach of revenue generation by multiplying product volume sold by pack price: the **high price model** and the **prevalence model**.

In the second step, we developed a framework for evaluating these models. This framework consists of three main criteria:

- Effectiveness
- Speed of implementation
- Societal acceptance in Switzerland

For a detailed breakdown of our evaluation criteria, please refer to section 6.5, **Table 1**: Evaluation of pull incentives for implementation in Switzerland.

- The *effectiveness* of an incentive is measured by its ability either to encourage the introduction of innovative new antibiotics into the Swiss market or to ensure a dependable supply of the essential antibiotics already authorised and launched in Switzerland.
- The *speed of implementation* is a critical factor given the low number of new antibiotics launched in the Swiss market and the lengthy process of antibiotic development and approval. The speed with which a model can be implemented depends primarily on the extent of the legislative changes needed.
- *Societal acceptance in Switzerland*, which will likely depend on the sources of funding and the transparency of funding and payment arrangements.

Ensuring the availability of effective and appropriate antibiotics is key to addressing the Swiss public's concerns about mounting healthcare costs and annual increases in health insurance premiums. Such availability contributes to controlling infection spread and avoiding lengthy treatments and their side effects, thereby reducing the disease burden on patients, lowering the risk of death, and lessening the strain on health care facilities. A recent study by the OECD [5] estimated that with further investments in robust hygiene and stewardship practices in hospitals, Switzerland could prevent more than 25,000 infections, save 270 lives, and reduce hospital stays by 200,000 days each year with its population of approximately 9 million. The ability of a pull incentive to promote stewardship is therefore a vital component in our evaluation of the various pull-incentive models.

In the third step, we used this framework to evaluate the suitability of the shortlisted models specifically for Switzerland. To accomplish this, we conducted a stakeholder workshop and additionally engaged in extensive discussions outside the workshop with a diverse range of stakeholders, including representatives from the Federal and cantonal Administrations, health care payers, patient associations, clinicians, scientists, industry representatives, investors, and accelerators. Lastly, we sought insights from international organisations, foreign initiatives, and governments that have developed plans or already implemented pull-incentive models in their countries. In particular, we drew upon the experiences and lessons learned from pilot programmes carried out in Sweden and the UK, which were instrumental in helping us identify key design elements for a subscription model in

Switzerland. The stakeholder discussions took place between November 2022 and September 2023, and the workshop was held in March 2023 at the University of Basel.

5 Description of shortlisted pull incentives from a Swiss perspective

This white paper discusses remuneration strategies designed to bring more new and innovative antibiotics to the Swiss market and to motivate manufacturers to continue supplying their older but essential antibiotics in Switzerland. Given that pharmaceutical development and marketing decisions are made with the world market in mind, Switzerland's remuneration strategies will always be evaluated in terms of their viability in the wider global context. Indeed, unless the remuneration offered by Switzerland and other nations together allows manufacturers to achieve reasonable global revenue targets, we will not obtain the antibiotics we need.

This reality binds the wealthier nations together in a shared responsibility, with each expected to contribute its fair share to a globally viable remuneration amount. It is important to recognise that a pull incentive can achieve an appropriate impact at the global level without the need to adopt an internationally harmonised model. Country-specific reimbursement procedures are the norm for pharmaceuticals, even in the EU. What counts is having a reward whose magnitude encourages manufacturers to invest in research, development, and product availability in many markets. Nevertheless, even a modest contribution from a single country's pull incentive can shift the dialogue within pharmaceutical companies, potentially expediting access to innovations or alleviating shortages, as the Swedish pilot has demonstrated.

Tasked by the G7 group of countries, the Berlin-based global AMR R&D Hub monitors global initiatives aimed at revitalising commitment and investment in the antibiotic sector. The Swiss Round Table on Antibiotics engages in the exchange of information, ideas, and experience with counterparts in other countries. Special attention is given to pilot projects in Sweden and the UK, which are described in section 5.5. Insights from these interactions enriched this white paper.

5.1 Subscription model

How the model works: The subscription model entails an annual guaranteed remuneration that is decoupled from sales volume and grants the manufacturer a fixed annual revenue agreed in advance [24]. The model thus offers financial planning security to the healthcare system and the manufacturer alike. This **"guaranteed revenue"** is intended to help amortise the costs of R&D, market entry, ongoing market presence, and to yield a fair profit. In return, the manufacturer commits to ensuring the availability of the new antibiotic to meet health care demands [25]. Additionally, by decoupling revenue from product volume, the guaranteed revenue eliminates the manufacturer's incentive to increase sales beyond a clinically justified level. This helps slow down the development of resistance and preserves the effectiveness of antibiotics for longer.

In this respect, subscription payments pursue a goal similar to the "direct payments" *(Direktzahlungen)* made by the Swiss government to farmers. The direct payments, which are decoupled from product volume, intend to recognise the contributions of farmers to preserving natural resources and biodiversity, and to securing a reliable food supply for the population [26].

Another relevant example is the Swiss government's provision of a retention premium to operators of hydroelectric power plants. This premium is given in exchange for retaining an agreed-upon amount of water in reservoirs for a specified period to secure Switzerland's electricity supply during times of shortage [27]. The amount of the premium is based on revenue that plant operators forego during the retention period. In return, the electricity suppliers contribute to the security of the energy supply in the country.

In all three sectors – healthcare, agriculture, and the energy industry – an agreed level of income is granted that is independent of product volume, with the aim of preserving natural resources. This approach helps ensure a sustainable supply of essential goods.

***Implementation*:** Insights from expert advice commissioned by the Swiss Round Table on Antibiotics indicate that the introduction of a subscription model is feasible under the current framework of the Federal Health Insurance Act (KVG), supported by the Federal Act on the Control of Communicable Diseases in Humans (Epidemics Act, EpidA).

New innovative antibiotics, which are often classified as reserve antibiotics, serve the public health interest by being effective in cases where other antibiotics cannot (or can no longer) guarantee successful treatment. Furthermore, their use should be minimised to prevent the development of resistance. Therefore, there explicitly should not be a conventional market for such antibiotics. In the discussion about the appropriate legal basis for reimbursing new innovative antibiotics under a subscription model, the Federal Act on National Economic Supply (National Supply Act, NESA) was deemed less relevant, as it assumes the presence of a functioning market.

On the other hand, the KVG is relevant when the marketing authorisation holder applies for reimbursement of a medicinal product authorised in Switzerland. According to the KVG, the efficacy, appropriateness, and cost-effectiveness of the medicinal product must then be assessed. Pricing is primarily established by the Federal Council in the Ordinance on Health Insurance (KVV).

The EpG strengthens the legal basis of the KVG by more effectively supporting the proactive actions of the federal authorities than the KVG does. Article 44 of the EpidA stipulates that the Federal Council is responsible for ensuring a sufficient supply of the most important medicinal products for the prevention and treatment of communicable diseases for the population. This obligation is not restricted to epidemic situations or severe shortages.

As new innovative antibiotics also contribute to preventing the transmission of resistant pathogens from one person to another, Art. 44 of the EpG also provides the appropriate legal basis from an epidemiological perspective. In addition, this allows the federal government to act as a purchaser of new innovative antibiotics and to enter into subscription agreements with manufacturers.

Article 73 of the EpidA assigns the funding responsibility to the compulsory health, accident, and military insurance funds. The Federation is responsible for financing any remaining expenses not absorbed by the insurance funds. The Federation is also obliged to cover the costs of drugs that cannot be dispensed.

***Flexible design*:** Subscription models offer a high degree of design flexibility and can be tailored to fit national contexts, meeting legislative requirements and adapting to existing health system structures [28]. This flexibility can be applied in various ways:

- ***Adjusting the level of guaranteed income depending on the overarching aim of the model:*** To incentivise the registration and availability of innovative antibiotics in Switzerland, higher levels of guaranteed income will be required. In contrast, lower levels of guaranteed income may suffice to secure a dependable supply of essential older antibiotics. The pilots conducted in Sweden and England illustrate the flexibility to vary the level of remuneration depending on whether a model aims to encourage innovation (England) or secure the supply of specific antibiotics (Sweden) (refer to sections 5.5.1 and 5.5.2). Both versions of the model can be implemented for different antibiotics in a country simultaneously.
- ***Adjusting the level of guaranteed income depending on product characteristics*:** Not all antibiotics should receive equal remuneration. Instead, the guaranteed income level should reflect the extent to which an antibiotic fulfils predefined criteria. Regulators in the UK have proposed a tiered system with annual payments of GBP 5, 10, 15, and 20 million in England, depending on the percentage of pre-defined criteria met by a specific antibiotic.
- ***Funding*:** The subscription model can be funded in various ways, such as through general taxation, health insurance, fees, surcharges, or special funding sources [23], as foreseen by the relevant national legislation.
- ***Additional conditions*:** Details regarding the timeline and level of the guaranteed income are specified in the contractual agreement between the public authority/payer of the scheme and the marketing authorisation holder. The fulfilment of particular obligations, such as ensuring the

availability of a drug in Switzerland and adhering to stewardship measures, can be set as prerequisites for receiving subscription payments, thereby aligning the actions of the company with public health goals.

It is not surprising that a large majority of international pull initiatives favour the subscription model [29]. In the EU, alongside efforts to establish a legislative basis for a TEEV model by the European Commission, discussions are underway to explore the participation of member states in subscription models under the coordination of the Health Response Emergency Authority (HERA) [30].

***Performance monitoring and contract adjustment*:** The performance of the scheme and the manufacturer's adherence to the terms of the contract must be subject to continuous monitoring. Regular reviews based on this monitoring may lead to necessary contract adjustments.

5.2 Transferable Exclusivity Extension Vouchers

***How the model works*:** The TEEV model introduces a mechanism that rewards developers of new antibiotics with tradable vouchers, which confer an extended term of intellectual property rights (patent) or regulatory data protection (RDP) for any chosen medicinal product, not limited to antibiotics. This approach generates funding through the sale of these vouchers, thereby rewarding the development of new antibiotics. Assuming that the buyer will apply the voucher to a blockbuster drug, the voucher sales proceeds may be quite attractive to the seller.

***Minimal public sector involvement*:** It is likely that the vouchers will be issued by a government agency, such as the licensing authority. After that, however, the Federation is not involved in selecting the drug to which the voucher will be applied. The negotiation process typically involves direct interaction between two private actors, the antibiotic developer (seller) and another pharmaceutical company (buyer), minimising the involvement of public sector administrators. This streamlined process arguably improves the efficiency of the model.

***Impact on implementation timelines*:** The practical application of the TEEV model varies considerably depending on the type of extension applied – patent or RDP – as this not only has technical but also legal and administrative implications. Patent extensions follow the directives of the Federal Act on Patents for Inventions (Patents Act, PatA), placing the onus on the Swiss Federal Institute of Intellectual Property (IPI), whereas RDP extensions are subject to the medicinal products legislation, with Swissmedic bearing the responsibility for their governance. The final draft of the revised EU pharmaceutical legislation provides for an extension of RDP [31].

***Timing of public funding*:** Initially, the reward for antibiotic developers is funded through the sale of the voucher to other companies rather than relying on public money. However, ultimately the costs are shouldered by the patients (often through co-payments) who require the drug associated with the voucher, as well as by their insurance providers and the generics industry. The generics industry incurs losses because it is temporarily prevented from competing with the buyer's originator product. Typically, none of these ultimate payers are involved in the initial voucher sale.

***Determinant of the voucher value*:** The price at which the voucher is sold is determined mainly by three factors: (i) the length of the exclusivity extension (determined by the issuing authority in consideration of product characteristics), (ii) the extended sales and profitability potential of the medicinal product to which the buyer intends to apply the voucher, and (iii) the level of competition on the buyer side.

5.3 High price model

***Pricing to reflect societal benefits*:** The high price model generates turnover according to the classic "price times quantity" mechanism. The term "high price model" alludes to the potential for achieving a higher turnover through higher pricing. The standard process determines the price of a new product by referencing prices of the same product in a basket of foreign countries and by referencing prices of comparable products in Switzerland. The possibility of a mark-up of up to 20% on the referenced prices

of comparable products in Switzerland may not do justice to very innovative antibiotics. Prices higher than the marked-up prices would have to be justified by the special benefits of innovative antibiotics.

Innovative antibiotics offer substantial medical benefits not only to individual patients but also to society and the healthcare system as a whole. This broad impact can justify a significantly higher price. To place a value on the societal benefits, Rothery *et al.* (2018) propose applying STEDI criteria [32]. These criteria can be used to assess the characteristics of an antibiotic based on its spectrum of use (**s**pectrum), its role in reducing spread to other individuals through effective treatment (**t**ransmission), its ability to enable access to medical treatment by preventing infections during surgery and other medical interventions (**e**nablement), its role in increasing the variety of treatment options available (**d**iversity), and its ability to function as a last-resort treatment (**i**nsurance) within the healthcare system and society. As part of the pilot project in England, National Institute for Health and Care Excellence (NICE) developed different methods for evaluating STEDI criteria and gained initial experience with them.

***Implementation for reserve antibiotics*:** Currently, higher package prices for innovative medicinal products are possible under the existing pricing models agreed upon between manufacturers and the FOPH for certain high-price drugs. It seems reasonable to assume that these models could also be applied to reserve antibiotics. We thus anticipate that implementing the high price model for reserve antibiotics will require minimal or no adjustment to the legal basis.

***Financing*:** The treatment costs are borne by patients (often through co-payments), their health insurance providers, and cantonal taxpayers, as per the standard processes.

***Swiss Diagnosis Related Groups (DRG) carve-out*:** Reserve antibiotics are dispensed in hospitals and reimbursed using flat-rate fee schemes such as the Swiss DRGs. However, high prices in DRGs can create perverse incentives: hospitals may be reluctant to use reserve antibiotics with high prices if lower-priced treatments with similar effectiveness are included in the DRG. To promote the appropriate use of high-price antibiotics where they are most needed clinically, they should be considered for add-on payments *(Zusatzentgelt*), an approach known as DRG carve-out.

5.4 Prevalence model

***Background*:** The prevalence model was developed in response to procedural request nr. 19.3703 submitted by MP Dittli ("Setting up new marketing authorisation and pricing rules") and is presently under review. The model aims to set the price per pack of an innovative medicinal product such that the manufacturer can generate viable revenue even if patient numbers are initially low. Initial trials have been conducted with medicinal products that received marketing authorisation via the fast-track pathway. The primary determinant of the initial price is the expected patient prevalence. The standard price-setting procedure is not applied. If the actual patient prevalence exceeds the initial estimates, the pack price will be adjusted downwards to manage the budget impact of the product.

***Applicability for reserve antibiotics*:** The prevalence model was not designed with antibiotics in mind. However, innovative reserve antibiotics that are typically set aside for use in cases in which all other treatment options have proven ineffective might benefit from such a model. Because these cases are still relatively rare in Switzerland, this characteristic might allow reserve antibiotics to achieve pack prices in the 5-6-digit CHF range.

***Implementation*:** Individuals involved in the development of the prevalence model have indicated that its implementation would not require major legislative adaptation.

***Financing*:** The treatment costs are borne by patients (often through co-payments), their health insurance providers, and cantonal taxpayers, as per the standard processes.

***DRG carve-out*:** Similar to the high price model and for analogous reasons, reserve antibiotics reimbursed under the prevalence model should be considered for add-on payments (*Zusatzentgelt*), an approach known as DRG carve-out.

***Stewardship*:** Analogous to the high price model, the prevalence model generates revenue according to the classic "price times quantity" mechanism and therefore does not decouple revenues from prescribed product volume. However, it does incorporate a mechanism whereby the pack price would be reduced as the prevalence of treated patients increases. This feature may act as a form of stewardship, potentially making the overuse and misuse of the antibiotics less attractive.

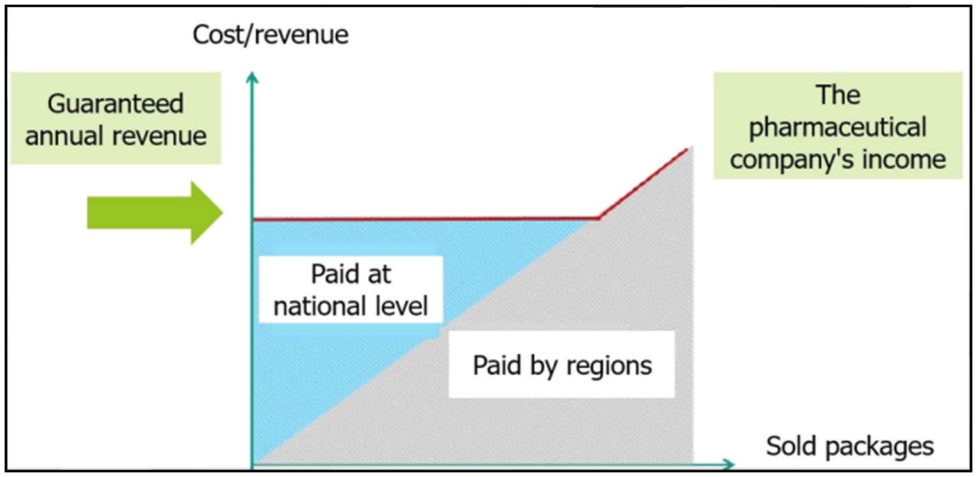
5.5 Learnings from pilots in Sweden and in England

Contacts in Sweden and the UK from the private and public sectors have expressed their willingness to engage in dialogue regarding the implementation of a pull incentive for antibiotics in Switzerland. They are committed to contributing their insights and experiences to interested individuals in Switzerland.

5.5.1 Earlier availability of selected antibiotics in Sweden

The Swedish government initiated a pilot programme with the aim of ensuring the earlier availability of certain antibiotics in the Swedish market, while also evaluating the efficiency and effectiveness of an alternative reimbursement scheme. The programme ran from mid-2020 to the end of 2022. The scheme established a guaranteed *minimum annual income* per product, set at SEK 4 million (approximately CHF 320,000). This revenue consisted of two components: (i) the regular sales revenue from product packs sold at the pack price determined using standard Swedish pricing methods and (ii) subsidiary payments made at the national level to cover any difference between the actual sales revenue and the guaranteed minimum income. Refer to the infographic in **Figure 2**.

Figure 2: Remuneration concept of the Swedish pilot project



A partially decoupled subscription model with the aim of gaining earlier access to selected antibiotics [33].

To incentivise sales beyond the minimum revenue in case of higher clinically justified demand, a fixed annual logistics fee was provided to cover stock-keeping costs. The Swedish pilot thus incorporates a partially decoupled design.

All antibiotics meeting the following medical and logistics eligibility requirements were accepted to participate in the pilot programme:

- Demonstrated activity against carbapenem-resistant pathogens[5]
- Maintenance of defined stock levels in the country and ability to supply the products to hospitals within 24 hours

[5] Specifically: *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*

Participating products included new antibiotics and a generic: MSD's ceftolozane-tazobactam (Zerbaxa) and imipenem-cilastatin-relebactam (Recarbrio), Shionogi's cefiderocol (Fetcroja), and Meropenem-vaborbactam (Vaborem) and Fosfomycin (Fosfomycin), which were marketed by the local distributors Pharmaprim and Unimedic Pharma.

5.5.2 NICE-NHS England subscription pilot for innovation

The ongoing pilot run by NHS England aims to compensate for antibiotics' broader value to the NHS, focusing on their impact on population health rather than the volume of products sold. The scheme, which commenced in mid-2022, is supported by NICE, which is the world's first health technology assessment agency to quantify the drugs' contribution to the health of the population rather than the individual patient [34]. The pilot is scheduled to run for a duration of 3 to 10 years.

Eligibility criteria for participation in the pilot encompassed:

- Demonstrated activity against priority pathogens as defined by the WHO
- Evidence of previous commitment to antibiotic availability and stewardship, high manufacturing standards, and high environmental standards

The model sets an *annual flat fee per product* at a level significantly above the minimum annual flat fee per product in the Swedish model. Specifically, the guarantee stands at GBP 10 million annually per product (about CHF 11.1 million). The latest proposal by NHS England and NICE is to introduce a tiered remuneration scheme with rewards ranging from GBP 5 and 20 million per product annually (refer to section 5.1), indicating that the GBP 10 million guarantee was an important first step towards establishing an appropriate reward size.

The two products included in the pilot are Pfizer's ceftazidime-avibactam (Zavicefta), which had been on the market for several years and already had real-world data regarding its performance beyond clinical trials, and Shionogi's newly launched cefiderocol (Fecroja), which lacked real-world data specific to the UK at the start of the pilot.

Transactions involving the purchase and sale of these products occur at a confidential "nominal price", which guides the use of the products in accordance with stewardship requirements – in other words, it is set in such a way that it is neither too low compared to the prices of possible alternative drugs, nor too high. The price is intended to promote the effective use of the antibiotic in clinically indicated situations. Any sales at the nominal price have to be refunded, reflecting a fully decoupled model design.

5.5.3 Drawing conclusions from the international pilots

***Local and international success*:** The pilots performed in Sweden and England have proved to be successful, not only in achieving their stated aims within local healthcare systems, but also in serving as role models for similar initiatives worldwide, including Switzerland [33], [34].

The Swedish pilot successfully facilitated Swedish residents' access to all four newly authorised antibiotics, even earlier than in comparable European countries. However, two of the five drugs met with very low demand. During the evaluation of the pilot project, the question was raised about whether their inclusion in the program was justified. At the same time, the assessors acknowledged that the broader product range with overlapping indication areas contributed to securing the availability of treatment options in the event of extended supply disruptions of any one drug. In their final report on the pilot, the Swedish Public Health Agency confirmed that the model was not intended nor financially powered to be used as an incentive to develop new antibiotics. The minimum income per product and year guaranteed in the pilot would have been far from sufficient, as a comparison with the fixed guaranteed annual revenue in the English pilot suggests [33].

The English pilot was subjected to a lessons-learned assessment shortly after its launch. The feedback from the participating companies and further assessors was positive and provided well-informed suggestions on how to make the design of the scheme even more efficient and attractive.

***Open cooperation and contract adjustment*:** Participating manufacturers appreciated the open cooperation with the authorities in both countries during the design and implementation of the pilot projects. This collaborative approach allowed for timely resolution of issues and adjustments to contracts, benefitting both the health authorities and the manufacturers.

- In the Swedish pilot, one of the manufacturers successfully advocated for a decrease in the mandated target stock levels in the country.
- Feedback received from the consultation in England led to NHS England and NICE reconsidering and redesigning the method by which the size of the fixed annual guaranteed income for a product is determined (refer to section 5.1) [35].

***Risk sharing*:** Both pilots highlighted the need to reconsider the balance of financial risk related to supply security. It became evident that estimating the requested stock levels more accurately and sharing the risk associated with accommodating varying demand sizes and fluctuation would be essential for the sustainability of the schemes.

***Eligibility*:** The new model put up for consultation in England would make on-market, on-patent products eligible for participation in a subscription scheme in addition to new antibiotics. Feedback from industry representatives on both pilot programmes indicated a desire to broaden the eligibility criteria so that antibiotics with activity against WHO priority pathogens other than those prioritised as "critical" and other antimicrobials, such as antifungals, would qualify for remuneration under a subscription model.

***Reward size*:** Initially, both pilots adopted a uniform (minimum or fixed) reward size per product, mainly due to administrative limitations. However, industry feedback advocated for a more flexible approach, with the reward size adjusted based on the products meeting specific criteria. NHS England and NICE have embraced this feedback. The extent to which the antibiotic in question fulfils the criteria determines its annual guaranteed income level in a four-tier remuneration system, which covers a range of GBP 5-20 million (refer to section 5.1).

***Learnings for Switzerland*:** Should Switzerland adopt a subscription model, it could benefit greatly from insights from the English and Swedish pilot programmes, as well as from related initiatives in countries like Canada and Australia. Critical areas for learning include information about methods for establishing eligibility criteria for an antibiotic's remuneration under a subscription model, calculating guaranteed income levels (with the tiered payment scheme developed by NHS England and NICE potentially serving as an inspiration for Switzerland), structuring agreements between health authorities and manufacturers, and monitoring processes. These international experiences offer valuable precedents for Switzerland and demonstrate that such models can be implemented in a pragmatic manner.

6 Evaluation of pull incentives for implementation in Switzerland

To gain acceptance in Switzerland, a pull-incentive scheme must demonstrate through its design that it can achieve the desired effect of bringing more new antibiotics to the Swiss market. We assessed the shortlisted pull-incentive models according to the criteria outlined in our framework (refer to **Table 1**).

6.1 Subscription model

The subscription model, as demonstrated by the pilots in Sweden and England, is flexible and can accommodate different aims, making it potentially suitable for implementation in Switzerland. The FOPH is responsible for securing access to innovative new drugs, including reserve antibiotics, for the Swiss population. In this context, a subscription incentive modelled after the English approach could generate enough revenue for manufacturers to recover the costs of research, development, registration, and post-market obligations while allowing for sustainable profit. This could encourage pharmaceutical companies to include Switzerland in their global launch plans and motivate them to seek marketing authorisation in the country.

The Federal Office of National Economic Supply (FONES) in Switzerland is responsible for ensuring a dependable supply of the essential antibiotics already authorised and launched in Switzerland. In this context, a subscription incentive modelled after the Swedish approach could be effective in preventing manufacturers from withdrawing certain antibiotics from the Swiss market.

Importantly, both innovation-focused and dependable-supply-focused versions of the subscription model can be implemented in parallel for different antibiotics.

The subscription model allows for various degrees of revenue decoupling from product volume. It can also be structured to include a minimum volume guarantee with a set price per pack, offering an effect similar to that of an annual subscription payment while still employing the "price times quantity" mechanism to some degree *(Kapazitätsverträge)*. Additionally, the model is versatile in terms of financing. While funding through compulsory health insurance is a viable option as per article 73 EpidA, alternative funding sources could also be justified at least during a pilot phase.

6.2 Transferable Exclusivity Extension Vouchers

The TEEV model was designed to promote the development of new antibiotics, yet there appears to be no implementation or pilot of this model in any country at present, leaving us without direct evidence of its effectiveness. The model's ability to incentivise antibiotic development depends on its design, including aspects like eligibility criteria, the details of patent or RDP extensions, the length of these extensions, and whether it is possible to accumulate multiple vouchers for a single antibiotic.

The TEEV model requires only minimal involvement from the Federal Administration, and the Administration's role may end as early as when the voucher is assigned to the antibiotic.

Depending on whether intellectual property (the patent), RDP, or both are extended, Switzerland can make these decisions with varying degrees of independence, affecting the implementation timeline.

Once the voucher system has been established, it is operated by private stakeholders, and transparency and control of the use of vouchers are transferred to them. The choice made by the buyer regarding which medicinal product in their portfolio should benefit from the exclusivity extension has significant repercussions for stakeholders who were not involved in the voucher deal. This includes patients who need the drug to which the voucher is applied and their insurers, who will have to pay the higher monopoly price during the extended exclusivity period. Additionally, generic manufacturers will incur losses while they are prevented from competing with the buyer's originator product.

To maintain some level of control, the Federal Administration may require that antibiotic developers (i.e., the initial holders of the vouchers) report details such as the timing of the sale, the identity of the buyers, and the sales price. In cases where patent extensions are implemented, mandatory reporting in compliance with the PatA would be necessary, requiring official applications to register the beneficiary product and the duration of the extension. In addition, a reporting system would need to be established between the IPI and the FOPH to enable the IPI to verify the authenticity and validity of the vouchers.

Importantly, however, enforcing the appropriate use of an antibiotic and its availability in the Swiss market may be challenging once the TEEVs have been granted because the authorities no longer have any leverage to enforce supply, stewardship, or other obligations.

To address the shortcomings of the TEEV model, we propose considering a staggered pay-out of the voucher sale proceeds to the antibiotic manufacturer, with the Federal Administration taking on the role of facilitator or broker in a public-private-partnership setting [36]. Under this adapted design, the Federal Administration would regain some control by making the payments contingent on the antibiotic manufacturer's compliance with availability and stewardship requirements.

6.3 High price model

An approach that justifies a high price, or premium for antibiotics by demonstrating their broader value for public health and societal wellbeing, beyond their value for individual patients (refer to the STEDI value sources in section 5.3) would represent a major shift in the Swiss pricing and reimbursement system to a value-based pricing framework. This in itself would constitute a hurdle to implementation, which would be compounded by the challenge of quantifying these sources of broader value in the Swiss health care context.

Meeting the data requirements of regular pricing and reimbursement procedures, which are ill-suited for innovative products like new antibiotics, would pose another challenge. Established procedures cannot guarantee full implementation of pricing decisions in the short term. In particular, the data required for the standard price-setting process would not be available for innovative antibiotics or other drugs at the outset but would need to be gathered over an initial period that could extend to three years or more. During this period, the drug could be used and reimbursed under special provisions, but only upon pre-approval by the patient's health insurer and on a case-by-case basis. This process would require time, additional administrative effort from health care providers and insurance companies, and regular reporting of purchase prices paid. Consequently, there is a risk that antibiotics might not be available promptly when they are needed as a last resort treatment against multidrug-resistant infections.

Although the high price model does incentivise the availability of antibiotics in the Swiss market, there are three caveats to consider. First, the standard pricing procedure in Switzerland has so far not allowed manufacturers to achieve sufficiently attractive prices for antibiotics. Unless these procedures provide room for more sophisticated health technology assessments that support claims of societal benefits, we have little confidence that the achievable prices would be satisfactory. Second, there is uncertainty about the achievable sales volume if acceptable cheaper treatment alternatives are available. Third, the financial burden of high-priced antibiotics would be shouldered by only a few patients and their insurers.

6.4 Prevalence model

The prevalence model was developed in response to a procedural request supported by the Federal Council and Parliament. The model was created to promote early access to innovative drugs for Swiss patients while mitigating potentially excessive budget impacts. Although a guaranteed annual income is not explicitly agreed upon, it operates on the principle of setting the price per pack of a drug to ensure that the manufacturer generates viable revenue from the outset. If applied to innovative antibiotics, the targeted revenue achieved by the classic "price times quantity" mechanism under the prevalence model would have to be similar to the guaranteed income of a subscription model.

However, the design of the model has not been finalised as of the date of this white paper. When contrasted with the high price model, the prevalence model incorporates a mechanism that reduces pack prices as patient prevalence increases, which can have a stewardship effect on antibiotics usage.

Considering the amount of time potentially required to implement a novel reimbursement model for antibiotics, adopting a prevalence model in the interim could provide a quicker solution. This approach would enable manufacturers to generate sustainable revenue while a subscription model, specifically designed to accommodate the unique aspects of antibiotics, is being developed and put into place.

6.5 Summary

Table 1 provides a summary of the discussion and our findings.

Table 1: Evaluation of pull incentives for implementation in Switzerland

Criteria	Subscription model	TEEV model	High price model	Prevalence model
Effectiveness				
Will society obtain the antibiotics they need?	HIGH	HIGH	MEDIUM	MEDIUM-HIGH
Stewardship	YES	NO*	NO	LOW
Security of supply	YES	NO*	YES	YES
Successful precedents	YES	NO	NO	NO
Speed of implementation				
Extent of legislative changes needed	MEDIUM	MEDIUM – HIGH	LOW	LOW
Effort for model implementation	MEDIUM – HIGH	HIGH	LOW	MEDIUM
Societal acceptance				
Acceptance of assigned payer	DEPENDS ON PAYER**	?	YES	YES
Payer = Beneficiary?	YES	NO	PARTIALLY	PARTIALLY
Transparency	YES	NO	LIMITED	LIMITED
Reimbursement amount depends on product characteristics	YES	DIFFICULT	MEDIUM	MEDIUM

* This disadvantage can be mitigated as suggested in section 6.2.

7 Our recommendation for Switzerland

On the basis of our evaluation of the four pull-incentive models, we present our recommendation as follows:

***Subscription model*:** Based on our systematic and comprehensive analysis, coupled with feedback from a range of stakeholders, we recommend the subscription model for implementation in Switzerland. This model's flexible design can be tailored to achieve different goals for different antibiotics at the same time: it can encourage manufacturers to seek marketing authorisation for their innovative new antibiotics and make them available in the small Swiss market, and it can be tailored to secure a dependable supply of first- and second-choice older antibiotics, for example by preventing manufacturers from withdrawing such products from the Swiss market. By ensuring an annual guaranteed income decoupled from product sales volume, the model promotes the appropriate use of antibiotics and helps to slow the evolution of antibiotic resistance. The design and implementation of a subscription model in Switzerland can draw upon insights obtained through the pilot projects conducted in England and Sweden, as well as from the exchange of experiences with international teams preparing similar models in their respective countries.

***TEEV model*:** While this model has the potential to generate a viable financial reward if adequately designed, it has major shortcomings in terms of transparency and equitable treatment of patients and health insurers. Moreover, it lacks an inherent mechanism to promote the security of supply and stewardship for the antibiotic that gained the reward in the first place. To address these issues, a potential solution could be the involvement of the Federal Administration as a broker in a public-private partnership. This arrangement would be between the Federal Administration and the private contractual relationship of the seller and buyer of the voucher. In this role, the Federal Administration could facilitate staggered payments from the proceeds of voucher sales, making them conditional upon the antibiotic manufacturer's compliance with availability and stewardship requirements.

***Prevalence and high price models*:** Of the two models that generate revenue through the classic "price times quantity" mechanism, we perceive an advantage of the prevalence over the high price model: its price-building mechanism aims to promote innovation and early patient access to medicinal products (here: antibiotics) that meet strict eligibility criteria. It foresees pack price reductions with increasing patient prevalence (a proxy for product volume use), which may have a certain stewardship effect. Its expected low hurdle to implementation could make this model a viable temporary solution while the favoured subscription model is being established.

Eligibility for remuneration under a pull-incentive system: We assume that not every antibiotic with marketing authorisation in Switzerland will be eligible for remuneration under a pull-incentive model. This implies the need for national health authorities to define eligibility criteria. If the focus is on reserve antibiotics, these criteria should include the effectiveness of the antibiotic against priority pathogens as defined by the WHO or a subset thereof, particularly those posing a significant threat to Switzerland. The selection process should prioritise medical needs in Switzerland and globally, rather than only the novelty of the drug. This approach allows for the inclusion of drugs already available in other countries, regardless of their patent status, in a subscription-based remuneration system. It can include on-patent, off-patent, and generic drugs. The possibility of applying the chosen incentive system to drugs targeting other microorganisms, such as fungi, should be maintained as an option.

***Determination of the reward size*:** Standard pricing procedures in Switzerland (and elsewhere) are designed to determine a unit price per product pack. Hence, they are not well suited for determining the size of the guaranteed income under a subscription contract. Various methods have been proposed to tackle this challenge, including the tiered system developed by NHS England and NICE with annual guaranteed income sizes of GBP 5, 10, 15 or 20 million depending on the percentage of pre-defined criteria met by a specific antibiotic.

Global remuneration amounts are crucial in shaping pharmaceutical companies' decisions regarding investments in research, development, and product launches. According to estimates by Outterson *et al.* (2021) a viable global remuneration amount for innovative antibiotics falls within the range of USD 220 – 480 million per product per year [37]. Assuming that a new antibiotic is marketed in all G7 nations, the remaining EU member states, and Switzerland, and assuming that each country contributes a share to this global remuneration amount based on the ratio of its gross domestic product (GDP), Switzerland's "fair share" would amount to approximately CHF 3.1 – 6.9 million per antibiotic and year[6]. This range may serve as a benchmark for determining the size of the local pull incentive designed to attract innovative antibiotics to the Swiss market. Considerably lower price ranges would apply if the main aim is to enhance security of supply of products that may have been on the Swiss market for some time, for example by preventing the withdrawal of products from the market.

***National implementation*:** We propose that the selected pull-incentive model be implemented at the national level in Switzerland, subject to governance and ongoing oversight by the Federal Administration. National-level oversight would reflect the Federation's responsibility for ensuring the supply of the most critical drugs for combatting communicable diseases, as stipulated by article 44 of the EpidA.

To lay the groundwork for implementing a subscription model, several critical design elements must be defined, including the following:

1. Eligibility criteria that new antibiotics must meet to qualify for reimbursement under the subscription model
2. Method for calculating the annual guaranteed income level either to incentivise the introduction of new antibiotics to the Swiss market and/or maintain the availability of antibiotics that have a marketing authorisation in Switzerland
3. Sources and mechanisms for funding of the annual guaranteed income in both scenarios
4. Responsibility for contracting, performance monitoring, and payments within the subscription model framework

If a TEEV model is used, several decisions about the scheme's design need to be made before the first voucher can be issued, including the following:

1. Determination of the nature of the entitlement conferred by the voucher (intellectual property and/or regulatory data protection)
2. Duration of the exclusivity extension
3. Sunset period by when the validity of the voucher expires
4. Whether the number of vouchers issued within a certain timeframe should be limited
5. Whether several vouchers may be accumulated for application to one product
6. Implementation procedures, including the verification of the validity of the vouchers
7. Assignment of responsibility if the administration were to assume a broker's role

Through the publication of this white paper, the Swiss Round Table on Antibiotics hopes to contribute to the design and implementation of a remuneration system in Switzerland that addresses the unique aspects of antibiotics – ensuring the availability of existing antibiotics today and facilitating access to novel antibiotics in the future.

[6] This is based on the assumption that the marketing authorisation holder acquires the drug candidate before the start of phase II clinical trials. Further assuming that the product is launched in the markets of all G7 nations, EU member states, and Switzerland, and they remunerate it according to the relative size of their GDP (Swiss GDP is 1.6% of the total GDP of G7, the EU, and Switzerland.)

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Swiss Round Table on Antibiotics

The Swiss Round Table on Antibiotics is a multidisciplinary non-profit Swiss association which was founded in 2019. We are committed to measures that promote the development of antimicrobial technologies and ensure their availability to safeguard the future functioning of health care systems. Our members are from health care, science, politics, industry and further areas of expertise.

We promote public awareness of the increasing prevalence of antimicrobial resistance and the need to take countermeasures, support policy-making, and facilitate multidisciplinary projects. Our activities are focused on two main areas including

(i) the design and implementation of financial incentive models that facilitate the development and commercialisation of new antimicrobial technologies and
(ii) measures to ensure the supply of new and existing antibiotics to patients in Switzerland and worldwide.

We are committed to Switzerland and are involved in international initiatives.

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