Pull models contributing to the revival of the global antibiotics market and benefiting Swiss patients

Review and assessment of Pull models considered for application in Switzerland

February 7, 2023

Authored by

Samira Marty, Swiss Round Table on Antibiotics

Barbara Polek, Swiss Round Table on Antibiotics

Chantal Morel, Swiss Round Table on Antibiotics and University of Bern

Rudolf Blankart, Swiss Round Table on Antibiotics, University of Bern, and sitem-insel

1. Introduction

The magnitude of the effects of Antimicrobial Resistance (AMR) is undeniably a major global public health challenge for the years to come and is listed as a top 10 health threat by WHO (WHO 2020). As the current market environment does not set consistent incentives to stimulate the innovation, development, and distribution of new antibiotic therapies, the Swiss Round Table on Antibiotics (RTA) advocates for financial pull rewards. Pull incentives create a competitive environment expected to foster the efficient development of new drug therapies. In addition, pull mechanisms can incentivize the reduction of shortages when tied to access conditions. Therefore, they are considered more efficient alternatives compared to push funding and more effective than current pricing mechanisms in incentivizing the development of new antibiotics.

Therefore, the RTA pledges Switzerland's contribution of a fair share to a global reward for successful antibiotic drug development. Piloting and implementing a Swiss pull reward follows the footsteps of the proposed PASTEUR Act (Doyle 2021) in the US, as well as the already piloted subscription model in England (Government of the United Kingdom: Global and Public Health Group 2019; Perkins and Glover 2020). It may also benefit from the insights gained from Sweden's access-geared pilot scheme (Folkhälsomyndigheten 2023).

The RTA understands that the implementation of a stand-alone pull model in Switzerland will not have substantial effects on the investment decisions of multinational pharmaceutical companies or other investors. However, Switzerland, with its thriving research community and prominent pharmaceutical and biotech industry, can make a crucial contribution to easing the AMR crisis. In addition, the pioneering role of Switzerland in antimicrobial innovation will encourage other countries to commit to and offer pull incentives, which increases the overall incentive effect.

This paper aims to inform the discussion and selection of a pull incentive for implementation in Switzerland. It pursues the following structure: In section 2, we will first examine eligibility criteria for participation in a pull model and then present three economic pull model suggestions in section 3.

While our preliminary assessment of the described models suggests the subscription model has the best chances of acceptance in politics, society, and industry, we will also look into implementation options of the high-price model (HPM) due to its proximity to the current standard procedures. The HPM may at least serve as a comparison for the subscription model.

2. Eligibility Criteria

Eligibility criteria, set forth by government-commissioned agencies, play a gatekeeper role in ensuring that rewards from a pull incentive scheme go to drugs that generate the highest value to the healthcare system. The following examples shall serve as an illustration.

For antimicrobial drugs to qualify for funding under the US's debated Pasteur Act need to be "intended to treat an infection for which there is an unmet clinical need, an anticipated clinical need, or drug resistance" (S. 2076 of Bennet and Young S. 20762021; H.R. 3932 of Doyle and Ferguson 2021).

Recently enacted German legislation exempts (reserve) antibacterials from the normal HTA process if they show efficacy in treating multi-drug resistant bacterial infections with limited alternative therapeutic options and whose use is based on a strict diagnosis (Gemeinsamer Bundesausschuss 2021; Gotham et al. 2021).

3. Pull Model Suggestions

The RTA examines the following three models that shall inform further discussion in Switzerland:

- the Subscription Model,
- Transferable Exclusivity Extension Vouchers (TEEVs), and the
- High-Price Model.

Each of these three models will be briefly introduced, oriented along the following questions with regards to a possible implementation to the Swiss healthcare system:

- What are the model's main characteristics, potential payers and beneficiaries?
- Who is involved in the decision-making?
- Where do we see advantages and challenges?

3.1.1 Subscription Model

The main characteristics of the subscription model – also known as the "Netflix-type" model (Årdal et al. 2020:267) – are the provision of a regular amount paid to Marketing Authorization Holders (MAH), independent of the sales volumes (Perkins and Glover 2020). This so-called de-linkage of sales and volumes prevents MAHs from pushing sales beyond a clinically justified level and guarantees a certain revenue. The payers to this scheme are national governments, health insurers, or cantons, who set up a contract with a MAH (Renwick et al. 2016:10). Subscription models cater to design flexibility, the provision of planning security, and expected security of supply.

The decision on how to implement a subscription model depends on each national context, depending on both legislative structures and the public health system structures in place (DRIVE-AB 2018). The contract between the MAH and the scheme's administrative body defines the timeline and magnitude of the financial reward. The funding source for the subscription amount can be chosen independently, i.e., the legislator can decide to fund the subscription through general taxation, fees or surcharges, or special funding sources. Payment of subscription amounts can be made conditional on the company meeting key targets, such as maintaining production and ensuring supply over a certain time period, abiding by stewardship measures, the performance of post-marketing studies, and others.

The Market Entry Reward (MER) is an extreme case of the subscription model. It financially compensates the approval of a novel product as one lump sum or staged over only a few years (Shlaes and Bradford 2018:32). The financial contributor for the MER is equally national governments, cantons, or health insurers. MAHs of novel products are the main beneficiaries of the MER, receiving a high upfront payment without entering long-term contractual obligations.

Summary and RTA Assessment: Subscription Model

Main characteristics:

- Annual flat payment providing incentives to develop innovative antibiotic and granting access to it.
- Special form of subscription is a one-off payment resulting in a market entry reward (MER).
- Size of the reward can be determined in a national context and depending on product characteristics.
- Annuities can be tied to additional conditions such as security of supply and stewardship obligations.
- Option for re-assessment of reward size and eligibility after a pre-defined time period.
- Funding of reward can be freely determined within national context, e.g., tax, premium, levy.

Potential payers and beneficiaries of the model:

- Payers are defined by model characteristics.
- Beneficiaries are developers and MAHs who serve the market.

Decision-making:

- Follows statutory procedures.

Advantages:

- Great flexibility in implementation modalities.
- Financial security supports industry and political ability to plan (therefore lower cost of capital).
- Process provides opportunities for contract re-negotiation after expiration of the contract term.

Challenges:

- Abolishment of scheme, if deemed indicative in light of technological progress, is challenging.
- Frontloaded MER does not guarantee good post-market performance or security of supply.
- Higher international alignment needed due to challenge of free riding.

3.2 Transferable Exclusivity Vouchers (TEEVs)

The transferable exclusivity extension voucher (TEEV) offers the developer of a new antibiotic a tradable voucher, granting its owner an extended term of intellectual property protection (IP) for a medicinal product of their choice for a certain time in a certain jurisdiction. In this sense, the TEEV is a way to generate funding through the sale of vouchers to reward the developer of a new antibiotic. Direct negotiation between the antibiotic developer (seller) and the buyer means that the public sector administrator has minimal involvement, arguably increasing the efficiency of transaction. However, the timing of the transaction is important to consider. The developer is granted the TEEV upon approval of the antibiotic, at which point the sale of the TEEV to the buyer can be finalized. This means that potential developers of new antibiotics do not know the value of the pull reward ahead of time. The reward size remains abstract throughout the development of the drug, because the number of vouchers that will be available and the conditions of the marketplace at the time of the actual sale remain unknown – providing no clear signals to investors at key junctures in the development process (i.e., the value of the voucher has to be discounted due to the high uncertainty). TEEVs also leave significant uncertainty and (potentially disproportionate) overall costs imposed on the patients needing the drug to which the voucher is applied, their insurers, as well as losses to generics industry while they are prevented from competing with the buyer's originator product. Also, crucially, the one-off reward structure of the TEEV implies that the public sector has limited recourse if the antibiotic that is rewarded ultimately does not perform to expectation (similar to MER).

Summary and RTA Assessment: TEEV

Main characteristics:

- Development is rewarded by tradable voucher that extends market exclusivity for a product of industry's choice.
- Reward size is dependent on sale or auction price of the voucher and characterized by uncertainty.

Potential payers and beneficiaries of the model:

- Generics manufacturers and patients/insurers of protected drug carry the burden.
- Developer of antibiotic and buyer of the TEEV share the benefits.

Decision making:

- The decision to award the voucher to the developer, as well as the duration of the extended market exclusivity would likely be taken by the medicines agency or a governmental body.
- The sales price of the voucher is determined via auction or direct sale.

Advantages:

- The TEEV model requires no operational involvement of the public sector beyond the initial awarding and upfront determination of the duration of the extended market exclusivity.
- The TEEV mechanism does not require upfront public funding.

Challenges:

- Due to coverage of development costs by TEEV: Discounted sales prices in operational transactions do not reflect the due value of the drug and therefore set distorted price signals.
- While the model can incentivize antibiotic development it does not foster a transparent antibiotic market, effective stewardship measures (no de-linkage), nor positive effect on security of supply.
- The lack of transparency deprives the public sector of control.
- The impact of the scheme's design on the integrity of IP legislation is uncharted territory.
- The reward is paid as a one-off and cannot be adapted later.
- Abolishment of scheme, if deemed indicative in light of technological progress, is challenging.

3.3 High Price Model (HPM)

The incentive created by the High Price Model (HPM) is the MAH's option to price their products higher than the likely outcome of a standard WZW assessment[1]. The price premium to a standard WZW price would have to reflect additional benefits, such as the antibiotics' value to society and the healthcare system. To value such additional benefit, one could follow Rothery et al.'s (2018) STEDI[2] criteria that consider the values of Spectrum, Transmission, Enablement, Diversity, and Insurance. The higher prices would have to be absorbed by the patients, health insurers, or taxpayers (the latter financing the cantonal share of in-patient treatment costs).

In the case of a DRG-based in-patient setting, the effects of the bundled payments must be considered. In the presence of lower-priced treatments, hospitals will be reluctant to use high-priced novel antibiotics, which might be positive from a stewardship perspective but counteracts the incentivizing effect. To overcome this barrier, the HPM might be combined with the DRG carve-out option of the supplementary charge (also known as "*Zusatzentgelt*") and/or a revenue guarantee.

Summary and RTA Assessment: HPM

Main characteristics:

- High price incentivizes antibiotic drug development and fosters security of supply.

Potential payers and beneficiaries of the model:

- Paid by patient and in second line by health insurer (premium payers) and canton (taxpayers).
- Payers and beneficiaries are congruent (no subsidies).

Decision making:

- Negotiated price by industry and payers (e.g., Federal Office of Public Health (FOPH)/hospitals).

Advantages:

- Close to standard practice and easily implementable.
- Transparent (if no confidential market entry agreement (MEA) is applied).

Challenges:

- Quantifying and translating additional benefits to society, such as STEDI values, in price determination is still novel and would present technical and political challenges.
- High price may jeopardize stewardship if drug's use is not strictly controlled.
- Especially in DRG-based hospital settings and when lower-price alternative treatment options are available, a high price may prohibit usage and therefore jeopardize the incentivizing effect.

[1] *WZW* represent the Federal Office of Public Health's assessment criteria of efficacy (*Wirksamkeit*), appropriateness (*Zweckmässigkeit*) and cost-effectiveness (*Wirtschaftlichkeit*).

[2] This has the purpose to calculate return of investments, i.e., to quantify the health effects of AMR programs. STEDI stands for calculated Spectrum value, Transmission value, Enablement value, Diversity, and Insurance value (Towse and Silverman Bonnifield 2022:5).

References

Årdal, Christine, Manica Balasegaram, Ramanan Laxminarayan, David McAdams, Kevin Outterson, John H. Rex, and Nithima Sumpradit. 'Antibiotic Development — Economic, Regulatory and Societal Challenges'. *Nature Reviews Microbiology* 18, no. 5 (May 2020): 267–74.

Bennet, Michael, and Todd Young. Pioneering Antimicrobial Subscriptions To End Up surging Resistance Act of 2021 (PASTEUR Act of 2021), Pub. L. No. S. 2076 (2021). https://www.congress.gov/bill/117th-congress/senate-bill/2076/text.

Doyle, Michael F., and Drew Ferguson. Pioneering Antimicrobial Subscriptions To End Up surging Resistance Act of 2021" or "PASTEUR Act of 2021", Pub. L. No. H.R.3932 (2021). https://www.congress.gov/bill/117th-congress/house-bill/3932/text.

Drive AB. 'Revitalizing the Antibiotic Pipeline. Stimulating Innovation While Driving Sustainable Use and Global Access', 2018. http://drive-ab.eu/.

European Commission. 'EU Action on Antimicrobial Resistance: Council Recommendation'. *Public Health*, 17 November 2022. https://health.ec.europa.eu/antimicrobial-resistance/eu-action-antimicrobial-resistance/council-recommendation_en.

Folkhälsomyndigheten. 'Availability of Certain Antibiotics: A Pilot Study of an Alternative Reimbursement Model'. Swedish National Board of Health, 2023.

Gotham, Dzintars, Lorenzo Moja, Maarten van der Heijden, Sarah Paulin, Ingrid Smith, and Peter Beyer. 'Reimbursement Models to Tackle Market Failures for Antimicrobials: Approaches Taken in France, Germany, Sweden, the United Kingdom, and the United States'. *Health Policy* 125, no. 3 (March 2021): 296–306.

Government of the United Kingdom: Global and Public Health Group, Emergency Preparedness and Health Protection Policy. 'Tackling Antimicrobial Resistance 2019–2024. The UK's Five-Year National Action Plan'. London: Department of Health and Social Care, UK, 24 January 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1070263/UK_AMR_5_year_national_action_plan.pdf.

Government Offices of Sweden. 'Updated Swedish Strategy to Combat Antibiotic Resistance'. Swedish Ministry of Health, 27 April 2020. https://www.government.se/articles/2020/04/updated-swedish-strategy-to-combat-antibiotic-resistance/.

Juchler, Fabrice, Jan A. Roth, Alexander Schweiger, Marc Dangel, Massimo Gugliotta, Manuel Battegay, Friedrich S. Eckstein, et al. 'Costs versus Earnings in Colon Surgery and Coronary Artery Bypass Grafting under a Prospective Payment System: Sufficient Financial Incentives to Reduce Surgical Site Infections?' *Infection Control & Hospital Epidemiology* 39, no. 10 (2018): 1246–49.

Perkins, Mark, and David Glover. 'How the "NHS Model" to Tackle Antimicrobial Resistance (AMR) Can Set a Global Standard'. *NHS England*, 18 December 2020. https://www.england.nhs.uk/blog/how-the-nhs-model-to-tackle-antimicrobial-resistance-amr-can-set-a-global-standard/.

Renwick, Matthew J, David M Brogan, and Elias Mossialos. 'A Systematic Review and Critical Assessment of Incentive Strategies for Discovery and Development of Novel Antibiotics'. *The Journal of Antibiotics* 69, no. 2 (February 2016): 73–88.

Rothery, Claire, Beth Woods, Laetitia Helene Marie Schmitt, Karl Philip Claxton, Stephen John Palmer, and Mark Sculpher. 'Framework for Value Assessment of New Antimicrobials: Implications of Alternative Funding Arrangements for NICE Appraisal'. Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU), September 2018.

Shlaes, David M., and Patricia A. Bradford. 'Antibiotics—From There to Where?' Pathogens and Immunity 3, no. 1 (22 February 2018)

Silverman Bonnifield, Rachel, and Adrian Towse. 'Estimating the UK's Return on Investment from an Ambitious Program to Incentivize New Antibiotics'. London: Center for Global Development, 22 November 2022.

Towse, Adrian, and Rachel Silverman Bonnifield. 'An Ambitious USG Advanced Commitment for Subscription-Based Purchasing of Novel Antimicrobials and Its Expected Return on Investment'. Center for Global Development, November 2022. https://www.cgdev.org/publication/ ambitious-usg-advanced-commitment-subscription-based-purchasing-novel-antimicrobials.

World Health Organisation (WHO). '10 Global Health Issues to Track in 2021', 24 December 2020. https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021.