Executive Summary (English)

This study on market mechanisms and incentive systems deals with ways to minimize resistance to antibiotics (AB). While most intervention strategies aim to reduce the consumption of ABs in human medicine, others are directed at targeting AB use to where it is most needed. The aim of this study is the prioritization of intervention strategies.

Review of the literature on incentive systems / measures

There are many individuals involved in influencing AB consumption and resistance, and these can be divided into five levels of social organization, beginning with the individual level comprised of patients and healthcare practitioners, and culminating with the broadest level, the societal level.

1. Individual level
2. Organizational level
3. Network level
4. Political level
5. Societal level

At the *individual level*, decision-making behavior of AB-prescribing physicians is examined, as well as the expectations of patients (or patients' parents), both of which contribute to AB consumption. At the organizational *level*, the focus is on healthcare procedures. At the *network level*, the cooperation of different suppliers with regard to AB use or resistance formation is considered. At the *political level*, government regulations or intergovernmental agreements pertaining to AB consumption is based on political decisions. At the highest level, the *societal level*, the most general and difficult one to measure or to influence, relates to general social norms and attitudes about the appropriate use of AB therapies.

For individual decisions of practitioner and patients, psychological theories have been put forth (most prominently, the Theory of Planned Behaviour), but so far these have not received enough attention to be included in intervention strategies. At all other levels, only the broad distinction between empowerment and control (enforcement) is customary and will help in classifying measures. The evidence (i.e., the quantity and quality of studies of the intended influence on a factor influencing AB use or resistance formation) varies widely.

As part of a systematic literature review, 587 journal articles were identified. Of these, only 47% quantified (in the broadest sense) their respective effects (n = 278). Because the topic of AB resistance has garnered substantial scientific and public interest since the adoption of the Global Strategy of the World Health Organization (2001), which is still increasing, the initial literature search done in July 2017 for this review was updated in both April and May of 2018, leading to a substantial increase in the literature included.

At the *level of individual influencing factors*, treating physicians recognized that training and attitudes of physicians could be influenced through education and personalized feedback. The use of activating learning methods for education was particularly effective. For Switzerland, however, there is currently no overview of training requirements. Immediate feedback on the planned prescription of an AB (for example via computer-assisted decision support) has been shown to lower the AB prescription frequency, especially when a high baseline level is present.

The provision of feedback in difficult indications with high uncertainty leads to a consistent approach, but may still not be optimal. The timely availability of "point of care" tests reduces uncertainty and reduces consumption by decreasing the number of indications and shortening treatment duration. In dealing with patients who carry AB-resistant pathogens or suffer from them, hand hygiene by the treating physician is a very important element of infection control, and also indirectly influences the need for AB prescriptions in previously uninfected patients.

Another individual level factor for potentially reducing the risk of developing resistance is patient adherence or compliance to the AB medication strategy (duration, dosage). This has been included in the generally accepted body of medical knowledge but the effect on AB resistance has not been thoroughly empirically researched.

The willingness of parents to wait for an agreed-upon deadline with the doctor ("delayed prescription") also reduces AB use in children (e.g., for upper respiratory tract or otitis media infections). However, such strategies are often not favoured by doctors, as they often doubt the decision-making competence and compliance of patients or parents.

Communication between practitioners and patients can reduce AB consumption by tempering patient expectations for AB prescriptions. Training practitioners to better communicate with patients reduces AB consumption, especially when used in tandem with rapid testing.

At the *organizations level*, the creation and use of guidelines for AB prescribing would standardize the indication for AB treatment. Depending on the actual formulation within the new guidelines, AB consumption could thereby be reduced. Policies are more effective if they have been created specifically for the institution concerned and if they not only formulate targets but also include behavioural proposals for implementation. To optimize guidelines, feedback on the prescribing habits at an aggregate level (time windows, wards, etc.) makes sense, in particular when used as part of stewardship programs.

Modern IT tools for improving the intra-institutional flow of information have also proven to be significant and advantageous in ensuring that guidelines are being followed. Bundling responsibilities in the implementation of AB guidelines with a specialist representative or in a special interdisciplinary team brings with it opportunities for improvement in terms of consumption as well as in the implementation of therapy. However, initial hopes of minimizing the formation of resistance through a unified, simultaneous replacement of the primary AB preparations ("cycling") could not be proven. Availability restrictions for medications (for example, prior authorization for prescriptions or bureaucratic hurdles) are poorly understood in the scope of AB, with conflicting results and rather small effect sizes. The emergence of infections caused by re-

sistant pathogens has shown that theoretically meaningful measures to isolate and control the spread at the behavioural level (of employees and visitors) are reaching their limits, and thus do not bring any particular patient benefit.

If the institution-related information on pathogen epidemiology and resistance is linked as comprehensively as possible with the data of other institutions, then the *level of cooperation within networks* is affected. At the respective organizational level, however, it is incumbent upon hospitals, for example, to derive appropriate recommendations for action from this improved data. The more specific the statements of such "active surveillance" are for the institution in question, the more advantageous it is for AB consumption and drug selection. "Antimicrobial Stewardship Programs" are an empirically well-proven measure also in the area between institutions and networks, and have proven to be particularly effective whenever they are interdisciplinary and not only supported by the medical profession.

At the *political level*, involving legal decisions dealing with AB prescriptions, attempts have been made to achieve a reduction in consumption through regulatory interventions. For example, efforts at changing the dispensing mode of AB tablets to outpatients to deliver precisely counted numbers of pills, are possibly moderately effective, although there is currently rather limited evidence for this. A ban on the self-dispensation of AB by medical practices has proven to be an effective measure to reduce consumption internationally, with some potentially corroborating evidence from Switzerland, that self-dispensing practices had higher AB usage. Increasing out-of-pocket charges for AB as a disincentive cannot be relied upon as a general measure since this measure has been used effectively largely in health systems without sufficient insurance coverage for patients.

State or supranational (WHO, EU, etc.) increased support for research efforts is currently focused on the approval of new ABs, providing incentive mechanisms for pharmaceutical companies. Increased microbiological and/or pathogen epidemiological research and vaccines receive far less attention. However, the success of research efforts cannot be reliably predicted, and therefore not quantified within an attempt to prioritize different measures.

The final level, that of *social norms and attitudes* towards the use of antibiotics, is achieved by strategies aimed at general awareness of the resistance problem (e.g., mass media campaigns). Their efficacy and effectiveness are unknown because interventions have, for the most part, not been used in isolation, but packaged together with institutional-related measures or information. The design of such campaigns has largely been poorly founded theoretically and not geared to known factors for behavioural modification.

Utility judgments by experts

Due to the heterogeneous nature of the various market mechanisms and incentive structures and the widespread nature of their approach at different levels, a traditional assessment of the relative utility of the measures (for example via meta-regressions) is not effective. Therefore, a multi-level Delphi process with judgment by relevant experts (with different knowledge and ex-

perience background) was used. Twenty-one measures or intervention strategies were selected on the basis of the literature analysis as well as for theoretical reasons.

In the first stage, separately and without time pressure, n = 17 experts decided in "ranking tasks" on the basis of 100 randomly assembled intervention quartets on the relative importance of four of 11 frequently described measures / packages (Basket 1). This limitation of comparing 4 measures per judgement was done to avoid bias introduced by fatigue. These data were collected online through a specifically designed survey tool and resulted in 1785 to 1914 judgments in which each measure was judged against the other 10 measures in a paired comparison. At the same time, the experts assessed 10 further intervention strategies (Basket 2) using magnitude scaling (i.e., an estimate of the benefit of the strategy on a visual-analog scale (VAS) from 0 ("no benefit") to 100 ("maximum perceivable benefit")). To avoid positional and ranking effects, these strategies were systematically varied in their performance sequence. Two of these ten VAS tests were retest measurements using Basket 1 strategies. This served to assess the validity of judgment across different methodology and bridge information for later co-scaling of the two baskets.

As a second step in the Delphi process, the results were statistically analyzed and differing judgments discussed in an in-person meeting (workshop January 2018). In plenary discussions and in smaller working groups, conceptual misunderstandings were clarified, differences in the assessment of the effectiveness of these strategies were recorded, and strategies reassessed by all participants in a second appraisal. In addition, supplementary information from the experts on further strategies or the interpretation of external influences were compiled and recorded in a free discussion. The workshop concluded with proposals by the experts to bundle measures into meta-strategies or "policies" they considered useful.

The third stage of the Delphi process was a revised survey (using visual analog scaling as well as a Ranking Task) for the participants to assess which meta-strategies were most useful for the reduction of AB consumption or could provide for the containment of resistance formation. Participants were also asked to assess the feasibility (political feasibility, technical implementation, funding, etc.) with scale ends of 0 (“impossible to implement”) and 100 (“can be implemented fully”). The survey was conducted (to remain identical to the procedure during the Delphi workshop) via a paper-pencil questionnaire. Presumably because the time gap between workshop (end of January) and third-party survey (mid-March 2018) was greater than originally planned due to illness, only one third of the workshop participants responded to this third survey, resulting in some limitations with regard to the empirical basis of results.

In the ranking exercise, Package 1 - "*Clinical Measures in Infection Prevention and Therapy*"[5] was ranked ahead of the other two in terms of both impact and feasibility. The least feasible and least effective was Package 2 - "*Measures in the area of economic and information technology frame-*

[5] Consists of the following measures: rigorous containment, vaccination, shared decision making, active surveillance (for definition, see section 3.4 of this report)

work conditions"[6]. In the middle, Package 3 - "*Measures in Formulating and Implementing Guidelines*"[7], ranked second in terms of both utility and feasibility. Using the Magnitude Scaling method, the guideline-based single-strategy Package 3 outperformed the clinically / therapeutically-oriented Package 1, but only in the expected benefit, but not in the estimated feasibility.

The critical assessment of the methodology used here of a multi-stage Delphi procedure found a very similar approach used recently by WHO to prioritize research on AB-resistant bacteria.

Conclusion and recommendations

Switzerland is already pursuing important strategies with measures taken by SwissNOSO, the ANQ association, the Patient Safety Foundation and the Geneva University Hospital to monitor wound infections, hospital-acquired urinary tract infections and the point prevalence of healthcare-associated infections to reduce the consumption of antibiotics. The formulation of guidelines for AB use by the two specialist societies, the Swiss Society for Infectious Diseases and Swiss Society for Microbiology, is nearing completion, and can then be incorporated into a) the SwissNOSO recommendations on how to deal with resistant pathogens in hospitals, and b) the development of modules for Antimicrobial Stewardship programs also by SwissNOSO.

These steps make sense from the perspective of the study results and should continue to be used. For isolation and containment measures, it can also be concluded from the study results that the inclusion of social and behavioural expertise is useful for increasing the effectiveness of infection control measures.

From a synopsis of the evaluation of intervention strategies in the Delphi process and the effects of the same strategies reported in the scientific literature, three primary strategies for implementation are recommended:

1. **Increased use of "point of care" tests**. The biggest barrier to the increased use of rapid tests (C-reactive protein or procalcitonin test PCT) is the cost. Firstly, the procalcitonin test is not on the list of compulsory health insurance benefits, and secondly, this test is 10 times more expensive in Switzerland than in the EU. To allow greater application of this test, government interventions are recommended to make the test more affordable.
2. **Immediate feedback on prescribing ABs**. To prepare for this effective measure to reduce AB use, IT requirements must be met. This is particularly important in the outpatient sector as difficulties can be expected here because of the heterogeneity of the IT systems used. In the future, cognitive-psychological approaches should be integrated in the feedback provided to practitioners; these measures are currently not included in the two National Research Programs.

6 Consists of the following measures: economic incentives for new ABs, alignment of broadband and specific AB rates, improved IT structure for active surveillance, improved interinstitutional data linkage for patient-level outcomes (see sections 5.1 and 5.2 of this report).

7 Consists of the following measures: further development of prescribing guidelines, point of care tests, post-prescription feedback, specific AB representative per institution (see section 3.4 of this report).

3. **Active surveillance.** A small-scale detection of pathogens was set by BAG with the introduction of a reporting obligation for certain resistant pathogens. However, it is necessary to significantly broaden this reporting database. A significant expansion of the services and authoritative competencies of ANRESIS is recommended.

Two other measures are recommended because they can exert a significant broad impact beyond the supply system and they ensure the sustainability of existing steps.

4. **Vaccinations:** It is recommended for healthcare facility staff to review and, if necessary, extend the obligation to vaccinate against both bacterial and viral agents as it acts both as a health and safety measure for resistant pathogens, and as a control of nosocomial infections in patients. Increased vaccinations are also recommended for the public, but should only be encouraged on a voluntary basis.
5. The fourth recommendation (vaccinations), as well as the acceptance of the above-noted measures, the promotion of patient compliance and the reduction of patient-side demand for AB, call for **increased awareness for the public**. This could be achieved via appropriate mass media campaigns that address clear messages to well-defined audiences through appropriate channels.