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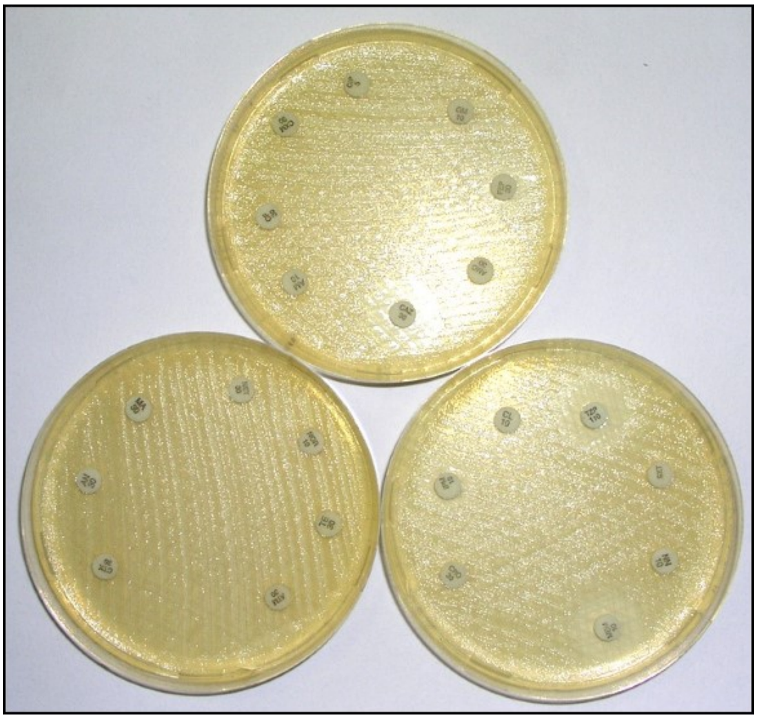
Swiss Expert Committee for Biosafety SECB

Biological Risks in Switzerland

Dossier:

Antibiotic resistances



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1 Introduction and definition

1.1 Introduction

Antimicrobial resistance (AMR) is a major threat to global health and the world economy. Resistant microbes double the probability of developing a complication and triple the risk of death compared to non-resistant forms. Plans must be developed as part of cross-sectoral efforts under the 'One Health' framework, acknowledging that the health of humans, animals and ecosystems are tightly interconnected. Global solutions are needed to promote prudent use of antimicrobials, and to foster effective infection prevention and control. Over 23'000 people currently die each year in the US due to antibiotic resistance, with at least another 25'000 die across Europe, 700'000 people worldwide. Rising antimicrobial resistance in G20 countries is a fact (OECD, 2017). Based on scenarios of rising drug resistance, the burden of deaths from AMR could increase to 10 million lives each year by 2050, at a cumulative cost of global economic output of $100x10^{12}$ USD (O'Neill, 2016).

Global problems need global strategies, but actions are necessary to be taken in each country: "Think globally, act locally". The aim of this risk assessment is the description of scenarios of increases of antibiotic resistance in Switzerland.

In June 1999, in response to the WHO request, the Federal Council approved the launching of the National Research Programme "Antibiotic Resistance" (NRP) 49 (SNSF, 2006). Undoubtedly, the most important operational achievement of NRP 49 was the establishment of SEARCH (Sentinel Surveillance of Antibiotic Resistance in Switzerland, now named Anresis). The Swiss Centre for Antibiotic Resistance **anresis.ch** is a regional and national surveillance and research program on antibiotic consumption in human medicine. In the field of veterinary medicine and livestock production, particular situations concerning antimicrobial resistance were also detected. Several measures were implemented to reduce consumption of antimicrobials and the legislation was modified accordingly. However, further measures are urgently needed in both human and veterinary medicine in order to reduce the devastating situation on AMRs.

By implementing the Strategy on Antibiotic Resistance Switzerland (StAR), the stakeholders are working together to improve the antibiotic resistance situation and to limit its spread and transfer. Eight main areas are involved in the strategy against antibiotic resistance, which affects humans, animals, agriculture and the environment following the One Health approach (StAR, 2016). The National Research Programme NRP 72 started in 2016 to give scientific support to this strategy (SNSF, 2017). Several research projects are designed to give new answers for the antibiotic stewardship in human and veterinary medicine. A milestone will be achieved in early 2019 when the database for recoding antimicrobial prescriptions by veterinarians (ISABV = Informationssystem Antibiotika in der Veterinärmedizin) will become operational. The database will cover all livestock and pet species and provide a basis for future risk assessments.

1.2 Risk based definition of antibiotic resistance (3 levels)

I) Resistance to antibiotics is defined as clinically relevant if the empiric therapy using the normally used antibiotics in 2000 is no longer effective in more than 10% of cases in 2020.

II) Resistance to antibiotics is critical if reserve antibiotics have to be regularly administered in hospital setting, e.g., colistin for Gram-negative bacteria.

III) Resistance to antibiotics is catastrophic if last resort antibiotics (e.g., vancomycin / colistin) are no longer effective.

2 Known events and development

2.1 Current situations in Switzerland

- Antimicrobial resistance (AMR) in public health is increasing in Switzerland. Compared to Southern European countries, the situation is better but compared to Northern European countries it is clearly worse.
- In a University Hospital of Zurich, ESBL (Extended-Spectrum Beta-Lactamase) *Escherichia coli* in blood cultures were not detected at all in 2000 but now 15% of all *E. coli* isolated from blood cultures are ESBL.
- A district hospital near Zürich did not detect any ESBL in 2000, while in 2018 two ESBL isolates per week are identified.
- Antibiotic resistances in agriculture and veterinary medicine: Half of the antibiotic consumption is caused by agriculture, in particular in livestock production. This led to an increase in antibiotic resistant zoonotic pathogens such as *Staphylococcus aureus* where methicillin resistance in slaughter pigs increased over seven years by 15 times due to one dominant clone or in poultry at slaughter where they currently carry over 50% Cipro-floxacin-resistant *Campylobacter jejuni* (FOPH/FFSVO, 2018). Similar problems are known in pet animals where resistances to modern last generation antibiotics are present.
- Antibiotic resistant pathogens can be transmitted to humans via the food chain or close contacts to pets. It is generally accepted that heat-treated food is not important in the transmission of resistance genes.

2.2 Current situations in countries with high incidence of AMR

Tuberculosis (TB):

Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. WHO estimates that in 2016 there were 600 000 new cases with resistance to rifampicin – the most effective first-line drug, of which 490 000 had MDR-TB. The MDR-TB burden largely falls on 3 countries – India, China and the Russian Federation – which together account for nearly half of the global cases. About 6.2% of MDR-TB cases were extensively drug-resistant (XDR-TB) in 2016 (WHO, February 2018). Globally 3,3% of patients developing TB in 2014 showed resistance. The proportion is 29% among people previously treated for TB. In 2015, there were about 480 000 new cases of MDR-TB, a form of TB that is resistant to the most powerful anti-TB drugs. An estimated 9.7% of people across 105 countries have a form of TB that is resistant to at least four core anti-TB drugs (OECD, 2017).

Antimicrobial resistance in common bacterial pathogens:

In G20 countries, levels of AMR are already high and will continue to rise unless effective interventions are put in place. OECD estimates that the prevalence of AMR for eight common bacteria in G20 countries has increased from about 18% in 2000 to 22% in 2014, and will continue to rise to reach 28% by 2030 under a scenario of increasing antibiotic consumption. The recent rise in resistance among difficult-to-treat Gram-negative bacteria (e.g., salmonella, gonorrhoea, etc.) is particularly worrisome and deserves specific attention (OECD, 2017).

High levels of antimicrobial use are also found in animals and plants and for some specific genes have been associated to the transmission of resistant pathogens from food animals. Transmission to humans is also expected to occur through environment contamination and direct contact with livestock and pets. Antimicrobials are used to a variable degree at all levels of food animal production to treat infectious diseases. Preventive use is also used but increasingly challenged and will no longer be allowed in the EU. In many countries, antimicrobials are also used as growth promotors to increase animal production rates (OECD, 2017) This practice is banned in Switzerland.

2.3 Potential incidents

As a consequence of travel multi-resistant bacteria increase with the consequence of therapeutic problems.

Agents causing hospital infection with autochthonous or travel-related introduction of resistance lead to more frequent therapeutic failure with fatal outcome.

Highly resistant bacteria are present in the food chain and in pet animals and have the capacity to cause infectious diseases in humans (e.g., systemic salmonellosis or MRSA) that are difficult or impossible to be treated.

3 Influencing factors

Fundamental change is required in the way that antibiotics are prescribed and consumed, to preserve the usefulness of existing products for longer times and to reduce the urgency of discovering new drugs. Governments should be held accountable on this goal to reduce the demand for antimicrobials and in particular antibiotics, as should the main sectors that drive antibiotic consumption: healthcare systems, the pharmaceutical industry as well as the farming and food production industries. We need to improve global awareness of AMR across the board, so that patients and farmers do not demand, and clinicians and veterinarians do not prescribe, antibiotics when they are not needed. Hence policy makers must ensure that policies to tackle AMR are taken forward now (O'Neill, 2016). The only hope one can have is not to prevent the emergence of resistance, which is a stochastic phenomenon, but rather to delay its spread (Courvalin, 2016). This opinion from a well-known basic antibiotic researcher is unfortunately probable, but if the influencing factors mentioned below develop in a favourable direction, the speed of the selection of new resistances can be lowered.

- Globalisation, travel activities and migration: Globally, antibiotic consumption rate in low- and middle-income countries has been converging to levels typically observed in high-income countries (Klein et al., 2018). This leads to an emerging resistant bacterial population in hospitals, communities and environment. Therefore, travellers and immigrants can import resistant bacteria because multi-resistant bacteria are not only present in hospitals but also in the environment. If adequate measures are rapidly taken, both in veterinary and human medicine, it is possible that the spread of such resistant bacteria may remain under control. Colonizing bacteria may develop into difficult-to-treat infections as observed for the ESBL producers acquired by people traveling from low- to high- prevalence countries (Bernasconi et al., 2016).
- Economic aspects: If the cumulative costs mentioned in the introduction develop, then authorities as well as the public are willing to accept restrictions. Emergence of resistance clearly correlates with the selective pressure applied, or in other words with the prescription of antibiotics (Courvalin, 2016). Therefore, as soon as the costs of therapy and of isolation in hospitals rise, the restrictions of antibiotic usage might be in favour of a slower development of further resistances.
- Development of novel antibiotics or antimicrobial agents: For antibiotics, the commercial return on R&D investment looks unattractive until widespread resistance has emerged against previous generations of drugs, by which time the new antibiotic may no longer have patent protection or may soon lose it. Better rewards for innovation or

prolonged patent protection, under various innovative forms, should stimulate development of novel antibiotics (O'Neill, 2016).

- Compliance in applying guidelines for treatment (humans and animals): The prevalence of resistance and antibiotic use needs to be monitored systematically in all areas. This is the only way to detect relationships between use, type of antibiotics and development of resistances, in order to evaluate the success of the various measures (StAR, 2015). Excessive and inappropriate use of antibiotics is the leading cause for the increase in resistance. Clear guidelines are required on the prescribing, dispensing and specific use of antibiotics by humans and animals, especially for newly developed antibiotics and antibiotics categorized as critical (StAR, 2016).

  The public also has an important role to play. Raising awareness at all levels will prepare individuals to their personal responsibilities in dealing with antibiotics. Specialists in this area should update their knowledge of resistance, preventive measures, diagnostic tests and the responsible application of antibiotics (StAR, 2015). The correct regulatory and political environment are important to ensure that antibiotics remain effective in future (StAR, 2016). Many production diseases in livestock can be prevented by management and preventive measures such as vaccinations hence reducing significantly the need for treatment. To this end, in-depth structural changes involving all stakeholders are required – from animal breeding to optimised feeding and improved animal husbandry (StAR, 2016).
- Hygiene: Improving hygiene and sanitation was essential in the 19th century to counter infectious diseases. Two centuries later, this is still true and is crucial for reducing the rise in drug resistance: the less individuals get infected, the less they need to use medicines such as antibiotics, and the less drug resistance arises (O'Neill, 2016). Proliferation of resistance must be prevented. In human and veterinary medicine, this requires reducing the risk of patients or animals introducing resistant microorganisms to a hospital or to a nursing home at admission – for example with precautionary examinations. In agriculture examinations of animals will be necessary to restrict the spread of resistant pathogens between livestock (Bernasconi et al., 2016).
- Food chain: Antibiotic resistant pathogens can be transmitted to humans via the food chain. Even in fresh herb production, multi-resistant bacteria can contaminate plants through the irrigation water chain (Stergiou-Gekenidis et al., 2018). Currently, there is significant ESBL contamination of delivered chicken meat. Current handling strategies can minimize the risks to transmit the AMRs to food handlers, hospital staff, and patients. However, bacteria from the food chain disseminate further via contamination in the catering system of healthcare institutions, causing infections with extended-spectrum ß-lactamase (ESBL)-producing *Enterobacteriaceae.* This delays initiation of appropriate antimicrobial therapy and causes increased patient morbidity and mortality rates (Stewardson et al., 2014). ESBL-types reveal clonal overlaps between the sources of livestock, poultry meat and healthy humans, suggesting livestock, in particular poultry husbandry, represents a potential reservoir for particular uropathogen *E. coli* clones (Müller et al., 2016). *E. coli* harbouring mobilizable colistin resistance (*mcr-1*) plasmids might increase in river water, imported vegetables and poultry meat (Zurfluh et al., 2016). Hence, hygienic measures and heat-treatment are important to assure food safety. Also, programmes targeted at the reduction of food-borne hazards such as salmonella or campylobacter are also relevant as these can also carry resistance determinants.
- Usage of antimicrobials in livestock: A particular threat represents also the use of colistin, a polymyxin, in pig production. This antibiotic currently represents an important

last resort antibiotic for the treatment of multi-resistant infections. The use of polymyxins in pigs, chickens and cattle constitute a driving force for the selection of MCR-1-producers (Nordmann et al., 2016). Although the prevalence of colistin resistance in *E. coli* from pigs and calves was found to be low in 2015 and mainly not associated with the transferable *mcr*-1 gene, it is necessary to take advantage of this favourable situation by preventing uncontrolled selection of colistin-resistant bacteria in food-producing animals in Switzerland and to further monitor resistance of clinically important antibiotics in the Swiss animal population (StAR, 2016). Further analysis of chicken meat from 2016 confirmed the presence of *mcr*-1 positive *E. coli* in imported meat (StAR, 2016). The comparison of the Swiss data with those from the EU shows that Switzerland is generally in a favourable situation. However, the risk of emergence of further plasmid-mediated colistin resistance in *E. coli* (StAR, 2016) is currently not managed other than usage reduction strategies.

- Co-resistance between disinfectants and antibiotics: Bacteria use efflux pumps and modifications of porins to get rid of damaging substances independent of the intended use by humans. Disinfectants can induce changes in the cell wall and cell membrane that create cross-resistance to antibiotics. Furthermore, specific resistance mechanisms towards commonly used disinfectants such as benzalconium chloride which is increasingly added as a biocide to detergents, laundry agents and cosmetics for marketing reasons, are located on multi-resistance plasmids and cause selection and enrichment of AMRs co-selection of antibiotic resistance genes. Concerns have been raised in recent years regarding enrichement and selection of antibiotic resistant bacteria exposed to biocides used as disinfectants, antiseptics and preservatives, and to heavy metals (particularly copper and zinc) used as growth promoters and therapeutic agents for some livestock species (Wales et al., 2015). A study sponsored by SECB showed that repeated exposure of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* to sub-inhibitory concentrations of Incidin® plus, a glucoprotamin disinfectant, reduced their susceptibility to antibiotics (Voumard et al, 2017).
- Antibiotic resistance in the environment (i.e., outside farms and hospitals): The widespread use of antibiotics results in the generation of antibiotic concentration gradients in humans, livestock and environment (Anderson et al., 2014). Antimicrobial substances are also used in crop and fruit production (McManus et al., 2002).Thus, bacteria are frequently exposed to nonlethal, i.e., sub-inhibitory concentrations of drugs, and recent evidence suggests its important role in the evolution towards antibiotic resistance. Sub-inhibitory antibiotic concentrations are found in many natural environments (such as sewage water and sludge, rivers, lakes and even drinking water) allow susceptible strains to continue to grow and acquire resistance (Anderson et al., 2014). These antibiotic reservoirs (treated humans, livestock, crops or aquaculture, and the wider environment) are intimately connected, which leads to the cycling of antibiotics and bacteria (including antibiotic-resistant bacteria) between the *in vivo* and *ex vivo* environments. Thus, antibiotics (and consequently antibiotic-resistant bacteria) can spread between environments and ecosystems, and sub-lethal concentrations can potentially select for resistance, generate genotypic and phenotypic variability and function in bacterial signalling (Anderson et al., 2014). In terms of the global strategy against AMR, the environmental sector is increasingly included (WHO, 2018).
- Rapid diagnosis of AMR: A rapid diagnosis of resistance is based on change in the diagnostic technology available. If this is feasible, the antibiotic prescription is based on rapid AST. Rapid diagnostics could transform the way we use antimicrobials in humans and animals: reducing unnecessary use, slowing AMR and hence preserve the

therapeutic use of current antibiotics. Research on resistance should be fundamental and trans-lational; fundamental because, at least under certain circumstances, understanding should precede action (e.g. rational design of new drugs) and translational to improve detection (rapid techniques, point of care) and better interpretation (expert systems) of resistance phenotypes for more adequate therapy (WHO, February 2018).

- Reporting of antibiotic treatment failures: Treatment failures as observed by medical doctors and veterinarians are the first signal of appearance of AMRs. Rapid reporting and rapid information of such failures to the medical and veterinary professionals in particular in relation to heard medication, will significantly reduce use of inappropriate medication and consequently avoid enrichment and proliferation of AMRs. Implementing or improving the reporting of antibiotic treatment failures are efficient and most cost effective measures in the fight against spread of AMSs.

4 Risk analysis

The risk analysis is based on the assumption that the Strategy on Antibiotic Resistance Switzerland (StAR) is realized as planned. The scenarios are realistic even if StAR is successful.

4.1 Scenarios

4.1.1 Scenario I, significant

The number of complications (estimated 2000 nosocomial infections with AMR bacteria in 2017) and (estimated 200 lethal infections) does not stagnate, but the increase is moderate

- the risk of therapies and interventions due to resistant nosocomial bacteria does not stagnate
- considerable costs to
    - increase prevention in all domains,
    - obtain a higher level of hygiene,
    - apply more analytical control on resistant bacteria
    - be very restrictive on the use of antibiotics in human and veterinary medicine
    - guarantee the efficiency of quarantine measures

4.1.2 Scenario II, major

The number of complications and victims increases slowly but steadily, 50% in the next 10 years.

- the risk of therapies and interventions due to resistant community and nosocomial bacteria increases significantly
- increasing costs in the mentioned areas of intervention
    - higher costs because of more complications and the resulting higher costs for treatment
    - higher costs of livestock production
- higher loss of human lives

4.1.3 Scenario III, extreme

The number of complications and victims increases as predicted by the O'Neill report (O'Neill, 2016), i.e., 500%

- antibiotics are no longer efficient
- a significant number of surgeries and therapies are no longer possible
- high loss of human lives and life expectancy

- epidemics and high loss of livestock

4.2 Frequency, Probability of incidents, plausibility

4.2.1 Significant

Scenario 1 is very likely even if StAR brings the expected success and all measures are taken or implemented to control all influencing factors.

4.2.2 Major

Scenario 2 is likely since epidemics with resistant bacteria will increase.

4.2.3 Extreme

Scenario 3 is very unlikely since the O'Neil report is mainly a report for the whole world.

4.3 Consequences

4.3.1 Significant

The estimated additional costs of a nosocomial infection with AMR bacteria are around 10'000 CHF because quarantine measures of patients in hospital require more medical persons and a hospital hygiene team. Therapeutic costs increase as well because reserve antibiotics are more expensive. The costs of 2000 infections with AMR are approximately 20 million CHF.

	0	1	2	3	4	5	6	7	8
Individuals: Fatalities	■	■	■	■	■				
Individuals: Casualties / sick people	■	■	■	■	■				
Economy: Asset losses and costs of coping	■	■							
Economy: Reduction of economic performance	■	■							
Society: Supply shortfalls and disruption	■	■							
Society: Reputational damage	■	■							
Society: Loss of confidence in state / institutions	■	■							

4.3.2 Major

Due to more epidemics in hospitals, the number of nosocomial infections with AMR bacteria rises to over 3000 and lethal infections to over 300.

	0	1	2	3	4	5	6	7	8
Individuals: Fatalities	■	■	■	■	■	■			
Individuals: Casualties / sick people	■	■	■	■	■	■			
Economy: Asset losses and costs of coping	■	■	■						
Economy: Reduction of economic performance	■	■	■						
Society: Supply shortfalls and disruption	■	■	■						
Society: Reputational damage	■	■	■						
Society: Loss of confidence in state / institutions	■	■	■						

4.3.3 Extreme

Due to more epidemics in hospitals and in the community, the number of nosocomial infections with AMR bacteria rises to 10000 and lethal infections to 1000. Epidemics and high loss of livestock will result in costs in the agriculture as well. The trust in authorities will decline.

	0	1	2	3	4	5	6	7	8
Individuals: Fatalities	■	■	■	■	■	■	■		
Individuals: Casualties / sick people	■	■	■	■	■	■	■		
Economy: Asset losses and costs of coping	■	■	■	■					
Economy: Reduction of economic performance	■	■	■	■					
Society: Supply shortfalls and disruption	■	■	■	■					
Society: Reputational damage	■	■	■	■					
Society: Loss of confidence in state /institutions	■	■	■	■					

5 Conclusion

The Swiss Expert Committee for Biosafety (SECB) supports the Strategy of Antibiotic Resistance (StAR) of the federal council and postulates in the context of a one-health concept several measures and restrictions in human and veterinary medicine as well as in livestock production and in environment protection. Furthermore, the legislation as well as the information to all stakeholders and to the public should help to lower the acute resistance problem (SECB, 2014).

Antibiotic stewardship is not only necessary in human medicine but also in the veterinary field. Veterinarians have a tool to report inefficient antibiotic therapy. Early warning of antibiotic resistant pathogens in animals requires rapid and accurate diagnostic procedures.

The SECB supports the research of elimination of antibiotics from water of the purification plant and studies of co-selection of resistance to antibiotics and disinfectants. It is mandatory that the different measures of StAR are not only discussed but realized.

Food production without the use of antibiotics is sensible but more costly. The declaration "Raised without antibiotics" should also be applied in Switzerland.

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