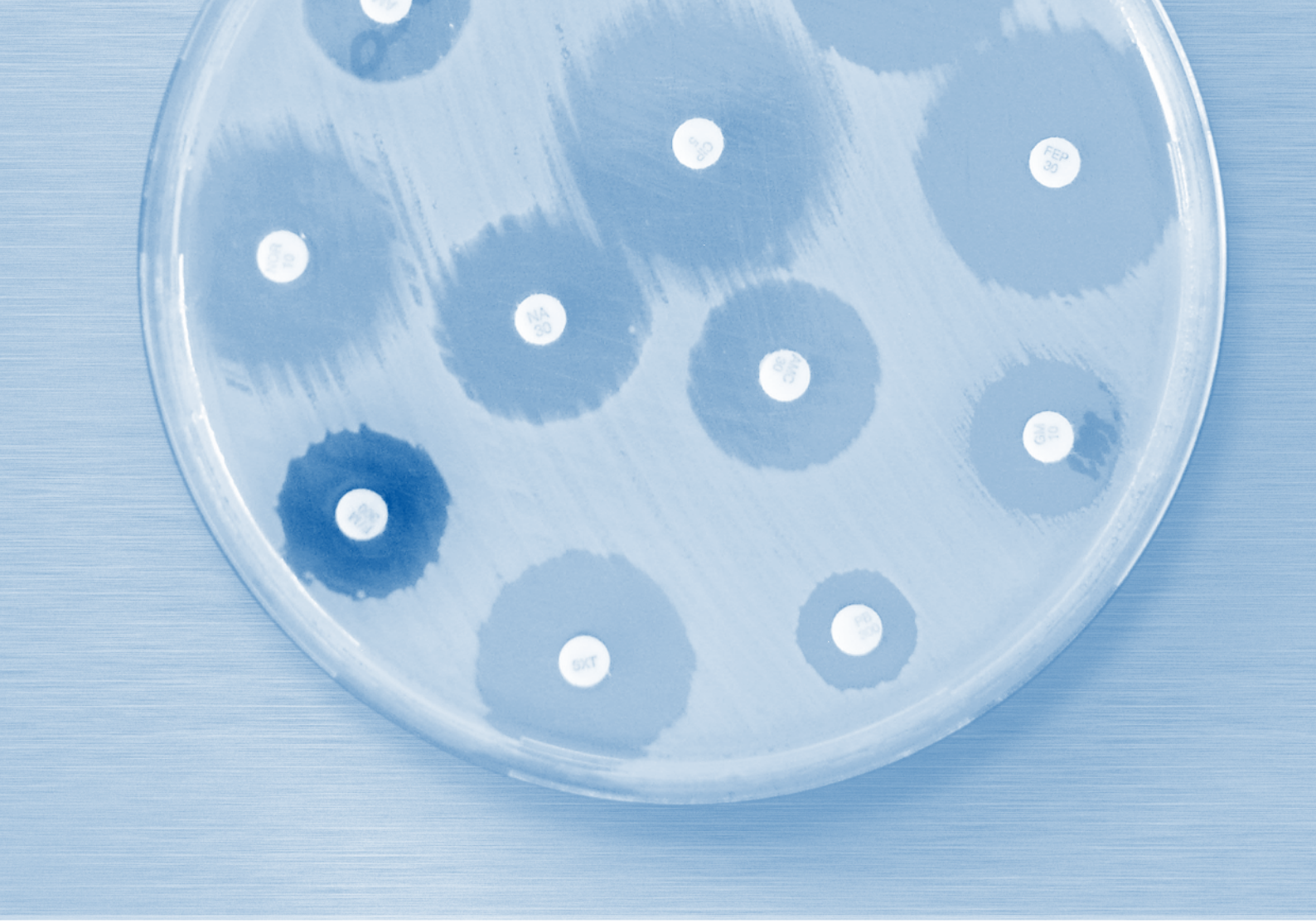

National Research Programme NRP 49
Antibiotic Resistance

Final Report

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National Research Programme NRP 49 Antibiotic Resistance

Final report and details of individual projects

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Antibiotic resistance worldwide: A global pandemic involving also Switzerland?

Antibiotic resistance is spreading in both the developed and developing countries, causing growing costs in terms of human lives, health care expenditures and economic losses.
A number of pathogenic bacteria are becoming more and more resistant to antibacterial drugs, and an increasing number of them, such as *Staphylococcus aureus,* gram-negative rods (*Acinetobacter, Serratia, Pseudomonas aeruginosa,* etc.) and *Mycobacterium tuberculosis,* are becoming extremely difficult to treat.
Although the concern is mainly for human medicine, antibiotic resistance must be addressed as a global issue for human and veterinary medicine, agriculture (animal farming), foodstuffs and the environment. Indeed, due to their use and misuse by humans, antibiotics can now be found nearly everywhere, and they exert a driving force in selecting for resistance genes and therefore resistant micro-organisms. Switzerland is also among the countries that are now in a kind of "pre-pandemic" situation, where the antibiotic resistance issue is not yet perceived as an important threat by the population, but where resistance will very likely progress if no containment measures are undertaken. In addition, and to worsen the situation, new antibiotics to fight resistant bacteria are difficult to discover and require large financial investments that are hard to find. This is why pharmaceutical companies have curtailed or even stopped research on new antibacterial drugs.
In 1998, the World Health Assembly adopted a resolution recognising the public health importance of antimicrobial resistance. The resolution urged WHO and its member states to undertake actions in surveillance, education and policy development and implementation. Countries were also encouraged to develop sustainable systems to detect resistant pathogens and to monitor volumes and patterns of use of antimicrobials and the impact of control measures.

Origin of National Research Programme "Antibiotic Resistance"

In the past in Switzerland, a number of individual studies were conducted to analyse resistance in human medicine and in the veterinary sector. Because they were limited in time, location and number of bacterial species considered, the surveys were not representative, and a global view of the antibacterial resistance could not be extrapolated. A study published in 1997 by the Laboratory of Food Microbiology at the ETH Zurich showed that lactic bacteria found in cheese may constitute a reservoir for resistance genes originating from pathogenic micro-organisms of human interest. These findings generated much concern in Switzerland, and a working group was mandated by the Federal Office of Public Health, the Federal Veterinary Office, the Federal Agriculture Office, and the Federal Office for External Economy Affairs (now State Secretariat of Economic Affairs or SECO) to perform a global analysis of the resistance situation. In the final report, the working group pointed up the lack of knowledge in this field in Switzerland and recommended the launch of an extensive research programme to fill the gaps.
In June 1999, in response to this recommendation and also to the WHO request, the Federal Council approved the launching of the National Research Programme "Antibiotic Resistance" (NRP 49), appropriating SFr. 12 million for a 5-year period.
The goals of NRP 49 were: 1) to produce a situational analysis of the antibiotic resistance burden in Switzerland and increased knowledge of the associated risks, 2) to establish the scientific basis for initiating appropriate preventive measures, 3) to give insight into the economic, legal and ethical aspects of antibiotic resistance, and 4) to promote basic research towards developing new antibiotics. Through NRP 49 the aim was to provide specific responses to the antibiotic resistance situation in the country, while also initiating cooperation at the international level, in particular with the European Union.

Projects supported by NRP 49

After careful review by international referees, a total of 27 projects were selected for funding under the programme, grouped in three main fields: 1) human and veterinary medicine, surveillance and environment (nine projects); 2) molecular biology (11 projects); and 3) society, law and economics (seven projects).
Most of these projects were submitted by researchers at universities or university hospitals, federal institutes of technology and related institutions (e.g., the Swiss Federal Institute of Aquatic Science and Technology, EAWAG) and a few by researchers at cantonal (Istituto Cantonale di Microbiologia, Bellinzona) or federal institutes (Agroscope Liebefeld-Posieux Research Station, ALP). Sixteen projects were from German-speaking, seven from French-speaking, and four from Italian-speaking Switzerland.

Outcomes of NRP 49

The main outcomes of NRP 49, listed by field (although a few of the projects overlap different fields), are:

Human medicine and surveillance

Undoubtedly, the most important and by now operational achievement of NRP 49 is the establishment of SEARCH (Sentinel Surveillance of Antibiotic Resistance in Switzerland). Based at the University of Bern (www.search.ifik.unibe.ch), it will provide representative data on antibiotic resistance in pathogenic and commensal human isolates from hospitals and the community throughout Switzerland. Antibiotic consumption data are planned to be integrated and analysed within the database. In spring 2007, SEARCH will be linked to EARSS

(European Antimicrobial Resistance Surveillance System). Hence, the SEARCH surveillance system will provide the ideal basis for early detection of problematic situations, allowing a prompt response with the instituting of specific preventive measures. In addition, it will allow monitoring of the outcomes of the control measures applied.
The first representative data will be available in April 2007. Preliminary results obtained so far for the years 2004-2005-2006 indicate that whereas overall antibiotic resistance is relatively low in Switzerland, in some geographic regions and in selected patients groups resistance levels are high. Most worrying, there is a marked trend towards increasing resistance.
Staphylococcus aureus is one of the major infectious pathogens. The emergence of methicillin-resistant (MRSA) and especially multidrug-resistant *S. aureus* strains raises serious clinical and health management problems in the hospital setting and now also in the community. A fast and reliable tool to genetically characterise the strains, and hence their epidemiology, has been developed and validated. It has already contributed to pointing up an unexpected emergence of CA-MRSA (community-acquired MRSA) in western Switzerland.
Another tool useful to track resistance genes in gram-positive bacteria has been developed and validated. Based on the microchip hybridisation technology (microarrays), it has been used to screen for resistance genes in pathogenic bacteria such as *B. anthracis* and in food products.
Finally, an opportunistic pathogenic fungus, *Aspergillus fumigatus,* has also been investigated. The data generated show that at the present time, antifungal resistance in clinical and environmental isolates of this microorganism is low in Switzerland.

Veterinary medicine and livestock production

An optimal and cost-effective monitoring strategy to track bacterial resistance in poultry, pig and cattle production was developed. The project also delivered baseline data on the resistance state in food animals in Switzerland. At present, compared to the situation abroad, the resistance state in Swiss livestock appears to be favourable. As to *Campylobacter,* the most-frequently reported zoonotic pathogen causing human illnesses in Switzerland, the data indicated that in general, the meat produced in Switzerland or on "animal-friendly" farms tends to harbour fewer resistant bacteria than the meat produced abroad or by traditional farms.
Regarding the common practice of using milk produced during antibiotic treatment for feeding calves and pigs, it was shown that this habit causes a marked selection for resistant bacterial strains (i.e., enterococci). However, further assessments are necessary in order to examine the fate of these resistant strains, ultimately to assess if there is any risk of these resistant bacteria entering the food chain.

Ready-to-eat food and food production

Also with the use of an innovative microchip hybridisation assay, ready-to-eat food (cheese and meat products) and starter and probiotic cultures were shown to be resistance genes reservoirs. The resistant genes could be successfully transferred to other bacterial hosts, indicating their mobility potential and suggesting a role in the spread of antibiotic resistance. These findings may raise concern for consumers' health and should be investigated further.

Environment

New analytical methods were developed that allow accurate and sensitive quantitative analysis (down to the ng/L range) of the presence and fate of the most important classes of both human and veterinary antibiotics in the environment.
The results obtained show that after their use in livestock, sulphonamides (SA) reach the soil after manure application in amounts comparable to herbicide application rate and may persist there for several weeks or months. Moreover, the soil was shown to be a considerable reservoir of resistance genes. On the other hand, concentrations of SA and other antibiotics measured in water bodies (i.e. lake water and groundwater) are generally very low.
The analysis of the presence of human-use antibiotics and antibiotic resistance in the aquatic environment revealed that while representatives of a number of antibiotics could be quantitatively measured in hospital wastewaters, in municipal wastewaters before and after mechanical-biological treatment, and in rivers, β-lactams could only be detected semi-quantitatively in hospital wastewaters. The concentrations found in wastewater correlated reasonably well with the known use data, and good knowledge on their behaviour during wastewater treatment could be established. Further, many antibacterial drugs were ubiquitously found in the lower ng/L range in Swiss rivers, and sulfamethoxazole also occurred in groundwaters. Finding low concentrations of antibiotics in groundwater used as drinking water raises the question of whether this contamination can be accepted or should be avoided following the precautionary principle.
Even if there are as yet no clear-cut data showing the impact of low levels of antibiotics on the development of resistance, an association was shown between the concentrations of antibiotics measured in hospital wastewaters and the antibiotic susceptibility of some waterborne bacteria (i.e. *Aeromonas and Acinetobacter*).

Molecular biology: Resistance mechanisms and new targets

The molecular biology projects were relatively numerous and addressed several pathogens. A number of new insights into the resistance mechanisms were produced, particularly with *S. aureus,* Bacilli, *E. coli, P. aeruginosa* and *A. fumigatus*. One project dealt in depth with the ribosomal mechanisms mediating drug resistance and opened new avenues for the development of innovative and less toxic drugs.

For *M. tuberculosis,* new potential targets were identified that, it is hoped, will lead to the generation of novel anti-mycobacterial antibiotics.
Regarding the fitness cost often connected with antibiotic resistance (which would favour reversibility of resistance), it was shown that in *S. aureus,* glycopeptide resistance associated with cell-wall physiological changes reduces the fitness of the microorganism. On the other hand, considering the drugs acting on the ribosome, it was demonstrated that the genetic background influences the fitness cost of resistance determinants and that these determinants do not unavoidably carry a fitness burden.

Antibiotics consumption

Based on commercial sales data, outpatient antibiotic consumption in Switzerland was investigated and compared with use data in other European countries. The analysis revealed that among European countries, Switzerland shows relatively low levels of per capita antibiotic consumption. However, within the country there are substantial differences across cantons and local areas in the use of antibiotics in the community, which can be explained mainly by socio-economic, demographic and epidemiological factors, access to medical practices and to antibiotic treatment (densities of physicians and pharmacies). It should be pointed out that the empirical framework developed in this project was applied in the study of outpatient antibiotic consumption in other European countries within the European Surveillance of Antimicrobial Consumption Project "ESAC" (funded by the European Union), to which Switzerland could now join as a participating country. In addition, two sentinel networks for the assessment of antibiotic use were designed for public acute care hospitals and the community, based on delivery data from either hospital or community pharmacies, respectively. The systems accurately reflected antibiotic use and allowed in-depth analyses and comparisons of the prescription patterns. The pilot projects can be extended to represent a larger proportion of hospitals and practitioners, thus gaining in accuracy. The interest of this additional study is that consumption data could now be provided to SEARCH without the need to buy the data at high cost from a commercial source.

Awareness of the antibiotic resistance problem

In general, awareness of and knowledge about antibiotics and antibiotic resistance are not very high among the Swiss population, with regional differences. In fact, information sources in Switzerland (e.g. newspapers) on the problem of antibiotic resistance are clearly unsatisfactory and inaccurate. Further, most drug package inserts for antibiotics do not even mention the problem of antibiotic resistance nor do they inform consumers as to how important it is to complete the entire course of the antibiotic treatment. Moreover, with the exception of very few and not widely distributed leaflets, no information on the problem of antibiotic resistance could be found for practitioners or for patients. There remains much to do to correctly inform the public.

Legal aspects related to antibiotic resistance

From a legal point of view, based on the legislation governing epidemics, food safety and health insurance, the federal government and the cantons already possess a wide and suitable range of legal instruments to implement the measures required to address the problem of antibiotic resistance. The division of responsibilities between the state and the cantons and the relationship between the authorities and service providers might be an issue. Political goodwill needs to be created to make use of these instruments.

Recommendations

The recommendations ensuing from NRP 49 are summarised in the table in section 5. The most important recommendation is to continue SEARCH and related activities through the establishment of a National Antibiotic Resistance Centre (NARC), to be located where SEARCH is presently operating, at the University of Bern. NARC should be sentinel-based and monitor antibiotic resistance and consumption in the different regions of Switzerland; it should integrate the veterinary data and be the national information and advice platform for all issues relating to antibiotic resistance; it should also interact with the EU and other countries; finally, it should constitute a platform to stimulate or back-up research activities related to antibiotic resistance issues.
NRP 49 has provided financial support to SEARCH up to the end of 2007. Because of the constant reductions of the federal budget, the financing of NARC after 2008 looks to be very difficult. Innovative solutions have to be found. A few solutions involving the organisation of health care and the cantons are presented in this report.

Conclusions

The National Research Programme "Antibiotic Resistance" contributed significantly to a better understanding of the antibiotic resistance issue in Switzerland. Most of the objectives that were defined at the beginning of the programme have been fulfilled. NRP 49 is to be considered an initial step in the management of antimicrobial resistance. We now dispose of established scientific knowledge and competence on the antibiotic resistance issue in all of the relevant areas. Switzerland is at last provided with a surveillance and alarm system detecting bacterial resistance in human clinical samples (SEARCH) and a monitoring strategy for bacteria isolated from animals for food consumption.

However, it is essential that the efforts undertaken with NRP 49 will not end with the conclusion of the programme. Although it continues to be underestimated in Switzerland, the antibiotic resistance problem is steadily progressing. Current actions have to be continued and new actions taken, at the level of both prevention and research.

La résistance aux antibiotiques dans le monde: une pandémie touchant aussi la Suisse?

La résistance aux antibiotiques se répand à la fois dans les pays développés et en voie de développement, provoquant des coûts croissants en termes de vies humaines, de dépenses de soins de santé et de pertes économiques. Plusieurs bactéries pathogènes développent une résistance accrue aux médicaments antibactériens et un nombre croissant d'entre-elles telles que *Staphylococcus aureus,* les bâtonnets gram négatif (*Acinetobacter, Serratia, Pseudomonas aeruginosa,* etc.) ou *Mycobacterium tuberculosis* deviennent très difficiles à traiter.
Bien que ce phénomène inquiète essentiellement la médecine humaine, la résistance aux antibiotiques doit être envisagée globalement, tenant compte de la médecine humaine et vétérinaire, de l'agriculture (élevage), des denrées alimentaires et de l'environnement. En effet, suite à l'usage et à l'abus commis par les humains, les antibiotiques sont maintenant présents presque partout et ont pour effet de sélectionner des gènes de résistance et donc de sélectionner des microorganismes résistants. La Suisse fait aussi partie des pays maintenant touchés par cette situation «pré-pandémique» où la résistance aux antibiotiques n'est pas encore considérée comme une menace importante par la population mais qui évoluera très probablement si aucune mesure d'endiguement n'est prise.
De plus, et pour encore noircir le tableau, la découverte de nouveaux antibiotiques destinés à combattre les bactéries résistantes est ardue et nécessite de gros investissements financiers difficiles à trouver. C'est la raison pour laquelle les industries pharmaceutiques ont ralenti ou même stoppé la recherche de nouveaux médicaments antibactériens.
En 1998, l'Assemblée mondiale de la Santé a adopté une résolution reconnaissant l'importance de la résistance aux antibiotiques pour la santé publique et encourageant l'OMS et ses Etats membres à entreprendre des actions de surveillance, à élaborer des programmes éducatifs et à développer des politiques nationales viables concernant l'usage rationnel des antimicrobiens. Les pays ont aussi été invités à développer des systèmes de surveillance cohérents et représentatifs pour dépister les agents pathogènes résistants, surveiller les volumes et les modes d'utilisation des antibiotiques ainsi que l'impact des mesures de contrôle introduites.

Origine du PNR 49 – la résistance aux antibiotiques

Au cours des années passées, plusieurs études individuelles ont été menées en Suisse pour analyser la résistance aux antibiotiques en médecine humaine et vétérinaire. Comme elles étaient limitées sur le plan temporel et géographique ainsi que sur le nombre d'espèces bactériennes, ces études n'étaient pas représentatives et il était impossible d'en déduire une vue globale de la résistance bactérienne. Une étude publiée en 1997 par le Laboratoire de Microbiologie alimentaire de l'EPF de Zurich a révélé que des bactéries lactiques présentes dans le fromage pouvaient constituer un réservoir pour les gènes de résistance provenant de microorganismes pathogènes d'intérêt humain. Ces découvertes ont généré de l'inquiétude en Suisse et un groupe de travail mandaté par l'Office Fédéral de la Santé Publique, l'Office Vétérinaire Fédéral, l'Office Fédéral de l'Agriculture et l'Office Fédéral des Affaires Economiques Extérieures (aujourd'hui Secrétariat d'Etat à l'Economie ou SECO) a été chargé de réaliser une analyse globale de l'état de la résistance. Dans son rapport final, le groupe de travail a reconnu le manque de connaissances dans ce secteur en Suisse et a recommandé le lancement d'un programme de recherche de grande envergure pour combler les lacunes.
En réponse à cette recommandation ainsi qu'à la demande de l'OMS, le Conseil fédéral a approuvé en juin 1999 le Programme National de Recherche «Résistance aux antibiotiques» (PNR 49), allouant une somme de CHF 12 millions pour une période de 5 ans. Le PNR 49 avait pour objectif: i) d'obtenir une analyse de l'état de la résistance aux antibiotiques en Suisse et d'améliorer les connaissances des risques associés; ii) de jeter les bases scientifiques pour entamer des mesures préventives appropriées; iii) d'approfondir les aspects économiques, légaux et éthiques de la résistance aux antibiotiques; iv) de promouvoir la recherche fondamentale pour le développement de nouveaux antibiotiques. Le PNR 49 devait fournir des réponses appropriées concernant la situation de la résistance aux antibiotiques dans le pays tout en collaborant avec les réseaux internationaux déjà en place ou en voie de l'être, particulièrement ceux de l'Union européenne.

Projets soutenus par le PNR 49

Après un examen minutieux par des experts internationaux, quelque 27 projets ont été soutenus par le programme.
Ces projets couvraient trois domaines principaux: i) 9 projets étaient consacrés à la médecine humaine et vétérinaire, à la surveillance et à l'environnement; ii) 11 projets à la biologie moléculaire; iii) 7 projets à la société, au droit et à l'économie.
La plupart des projets émanaient d'universités ou d'hôpitaux universitaires, des écoles polytechniques fédérales et d'institutions associées (ex. l'Institut fédéral pour l'aménagement, l'épuration et la protection des eaux, EAWAG). Quelques-uns provenaient d'instituts cantonaux (Istituto Cantonale di Microbiologia, Bellinzone) ou fédéraux (Centre de recherche Agroscope Liebefeld-Posieux, ALP). Seize projets ont été réalisés par la Suisse allemande, sept par la Suisse romande et quatre par la Suisse italienne.

Résultats du programme PNR 49

Les principaux résultats du PNR 49 sont présentés ci-dessous selon leur domaine d'intérêt, même si quelques projets peuvent couvrir plusieurs domaines.

Médecine humaine et surveillance

La réalisation la plus importante du PNR 49 est sans conteste l'établissement du système de monitorage de la résistance SEARCH (Sentinel surveillance of antibiotic resistance in Switzerland). Basé à l'Université de Berne (www.search.ifik.unibe.ch), il fournira des données représentatives sur la résistance aux antibiotiques des bactéries humaines pathogènes et commensales d'origine hospitalière et communautaire (médecine ambulatoire). Les données sur la consommation d'antibiotiques pourront y être intégrées et analysées. Au printemps 2007, SEARCH sera relié à l'EARSS (European Antimicrobial Resistance Surveillance System). Le système de surveillance SEARCH sera la base idéale pour une détection précoce des situations problématiques permettant une réaction rapide et l'établissement de mesures de prévention spécifiques. De plus, il permettra d'analyser les résultats des mesures d'intervention ou de prévention qui auront été appliquées.
Alors que les premières données représentatives ne seront disponibles qu'en avril 2007, les résultats préliminaires obtenus à ce jour pour les années 2004-2005-2006 indiquent que dans son ensemble le niveau de la résistance aux antibiotiques est relativement faible en Suisse, mais que ce même niveau de résistance est élevée dans certaines régions géographiques et/ou certains groupes de patients bien définis. Fait plus préoccupant, la tendance générale va nettement vers une résistance croissante.
Staphylococcus aureus est l'un des principaux agents pathogènes infectieux. L'émergence de souches de *S. aureus* résistantes à la méthicilline (MRSA) et surtout multirésistantes pose de graves problèmes cliniques et de gestion sanitaire non seulement dans les hôpitaux mais désormais aussi en médecine ambulatoire. Un outil rapide et fiable pour caractériser génétiquement les souches et donc leur épidémiologie a été développé et validé. Il a déjà contribué à déceler une émergence inattendue de CA-MRSA (MRSA acquis dans la communauté) en Suisse romande.
Un autre outil utile pour déceler les gènes de résistance des bactéries Gram positives a été développé et validé. Basé sur la technologie d'hybridation sur micropuce (puces à ADN ou microarrays), il a été utilisé pour détecter les gènes de résistance dans les bactéries pathogènes telles que *B. anthracis* et dans les produits alimentaires.
Enfin, un champignon pathogène opportuniste, *Aspergillus fumigatus,* a été étudié. Les données obtenues indiquent qu'actuellement la résistance de ce microorganisme aux antifongiques dans les isolats cliniques et environnementaux est faible en Suisse.

Médecine vétérinaire et production d'élevage

Une stratégie de surveillance optimale et de bon rapport coût-efficacité pour dépister la résistance bactérienne dans l'élevage avicole, porcin et bovin a été développée. Le projet a aussi fourni des données de base sur l'état de résistance chez les animaux destinés à la consommation en Suisse. Comparé à la situation à l'étranger, l'état de résistance actuel dans l'élevage suisse semble être favorable. En ce qui concerne *Campylobacter,* l'agent pathogène d'origine zoonotique transmissible à l'homme le plus fréquent en Suisse, les données ont révélé que, de façon générale, la viande produite en Suisse ou dans des fermes «respectueuses des animaux» tend à présenter moins de bactéries résistantes que la viande produite à l'étranger ou dans des fermes traditionnelles.
En ce qui concerne la pratique courante selon laquelle le lait produit pendant un traitement antibiotique est utilisé pour nourrir les veaux et les porcs, il s'avère que cette habitude provoque une sélection marquée de souches bactériennes résistantes (ex. les entérocoques). Toutefois, d'autres évaluations sont nécessaires pour examiner le devenir de ces souches résistantes et déterminer s'il y a un risque que ces bactéries résistantes entrent dans la chaîne alimentaire.

Aliments prêts à consommer et production alimentaire

En utilisant une méthode novatrice d'hybridation sur micropuce, il a été montré que des aliments prêts à consommer (fromage et produits carnés), des cultures starter et ou probiotiques peuvent être des réservoirs de gènes de résistance. Les gènes résistants ont pu être transmis à d'autres bactéries, ce qui indique leur potentiel de mobilité et laisse présager un rôle dans la propagation de la résistance aux antibiotiques. Ces constatations pourraient avoir une influence sur la santé du consommateur et nécessiteraient des études additionnelles.

Environnement

De nouvelles méthodes analytiques ont été développées pour permettre une analyse quantitative précise et sensible (jusqu'au ng/l) de la présence et du devenir dans l'environnement des plus importantes classes d'antibiotiques d'emploi humain et vétérinaire. Les résultats obtenus ont montré qu'après avoir été utilisés dans le bétail, les sulfamides (SA) se retrouvent dans le sol, après une application de fumier, dans des quantités comparables au dosage d'herbicide et peuvent y rester plusieurs semaines ou mois. De plus, le sol s'est révélé être un réservoir important de gènes de résistance.
Par ailleurs, les concentrations de SA et d'autres antibiotiques mesurées dans les plans d'eau (ex. lacs et nappes phréatiques) sont généralement très faibles.
L'analyse de la présence d'antibiotiques d'usage humain et de la résistance aux antibiotiques en milieu aquatique a montré que, tandis que des représentants de plusieurs classes d'antibiotiques peuvent être détectés dans les eaux usées des hôpitaux, dans les réseaux municipaux d'eaux usées avant et après un traitement biomécanique et dans les cours d'eau, les antibiotiques β-lactames ne peuvent être détectés semi-quantita-

tivement que dans les eaux usées des hôpitaux. Les concentrations trouvées dans les eaux usées correspondent raisonnablement bien aux données d'utilisation connues; on a pu aussi acquérir une bonne connaissance de leur comportement pendant le traitement des eaux usées. De plus, de nombreux antibiotiques ont été trouvés partout en basse concentration (limite inférieure du ng/l) dans les cours d'eau suisses; du sulfaméthoxazole a aussi été mesuré dans les nappes phréatiques. Trouver de faibles concentrations d'antibiotiques dans les nappes phréatiques utilisées comme eau potable soulève la question de savoir si cette contamination est acceptable ou devrait être évitée suivant le principe de précaution.
Même s'il n'existe pas encore de données claires et nettes démontrant l'impact de faibles niveaux d'antibiotiques sur le développement de la résistance, un lien a été mis en évidence entre la concentration d'antibiotiques mesurée dans les eaux usées hospitalières et la sensibilité aux antibiotiques de certaines bactéries véhiculées par l'eau (ex. *Aeromonas* et *Acinetobacter*).

Biologie moléculaire: mécanismes de résistance et nouvelles cibles

Les projets de biologie moléculaire étaient relativement nombreux et traitaient de différents agents pathogènes. De nouvelles connaissances concernant les mécanismes de résistance ont été acquises, notamment chez *S. aureus,* les bacilles, *E. coli, P. aeruginosa* et *A. fumigatus*. Un projet abordait de façon approfondie les mécanismes ribosomaux induisant la résistance aux antibiotiques, ouvrant ainsi la voie au développement de médicaments antibactériens novateurs et moins toxiques.
En ce qui concerne *M. tuberculosis,* de nouvelles cibles potentielles ont été identifiées, ce qui aboutira – espérons-le – à la mise au point de nouveaux antibiotiques efficaces pour traiter la tuberculose.
Pour ce qui est du «fitness-cost» souvent lié à la résistance aux antibiotiques (et qui favoriserait la réversibilité de la résistance), il a pu être montré que, dans le cas de *S. aureus,* la résistance aux glycopeptides liée aux changements physiologiques de la paroi cellulaire réduisait le fitness du microorganisme. D'un autre côté, en ce qui concerne les antibiotiques agissant sur le ribosome, il a été prouvé que le background génétique influence le fitness-cost des déterminants de la résistance et que ces déterminants ne portent pas inévitablement à une diminution du fitness.

Consommation d'antibiotiques

Sur base de données commerciales, la consommation d'antibiotiques en Suisse au niveau communautaire a été examinée et comparée à l'utilisation faite dans d'autres pays européens. L'analyse a révélé que la Suisse présente des niveaux de consommation d'antibiotiques per capita relativement faibles parmi les pays européens. Toutefois, sur le plan national, les cantons et les régions montrent des profils d'utilisation d'antibiotiques dans la population très différents, ce qui peut s'expliquer essentiellement par des facteurs socio-économiques, démographiques et épidémiologiques, l'accès aux cabinets médicaux et aux traitements antibiotiques (densité de médecins et de pharmacies).
Il faut noter que le cadre empirique développé dans ce projet a été appliqué à l'étude de la consommation d'antibiotiques chez les patients communautaires dans d'autres pays européens dans le cadre du projet ESAC (European Surveillance of Antimicrobial Consumption), projet financé par l'Union européenne et auquel la Suisse a pu se joindre.
En outre, deux réseaux sentinelles pour l'évaluation de l'utilisation d'antibiotiques ont été mis sur pied pour les hôpitaux publics de soins aigus et la médecine communautaire, sur la base des données fournies respectivement par les pharmacies des hôpitaux et celles communautaires. Ces systèmes ont reflété avec précision la consommation d'antibiotiques et ont permis d'analyser en détail et de comparer les schémas de prescription. Les projets pilotes peuvent être étendus à un plus grand nombre d'hôpitaux et de praticiens afin d'accroître la précision des résultats. Grâce à cette étude supplémentaire, les données de consommation pourront être fournies à SEARCH, sans devoir les acheter à prix fort auprès d'un fournisseur commercial.

Conscience du problème de la résistance aux antibiotiques

De façon générale, la conscience/connaissance des antibiotiques et de la résistance à ceux-ci n'est pas très répandue au sein de la population suisse, mais des différences régionales existent. En fait, en Suisse, les sources d'information (ex. journaux) sur le problème de la résistance aux antibiotiques sont insuffisantes et inappropriées. De plus, la plupart des notices des antibiotiques ne mentionnent même pas le problème de la résistance à ceux-ci et n'attire pas l'attention sur l'importance de suivre le traitement antibiotique jusqu'au bout. Par ailleurs, à l'exception de quelques rares brochures pas très répandues, aucune information n'est disponible ni pour les médecins ni pour les patients sur le problème de la résistance aux antibiotiques. Il y a encore beaucoup de travail à faire pour informer correctement la population suisse.

Aspects légaux liés à la résistance aux antibiotiques

D'un point de vue légal, grâce à la législation régissant les épidémies, la sécurité alimentaire et l'assurance santé, le gouvernement fédéral et les cantons disposent déjà d'une large gamme d'instruments légaux pour mettre en œuvre les mesures nécessaires pour traiter le problème de la résistance aux antibiotiques. La répartition des responsabilités entre l'Etat et les cantons et la relation entre les autorités et les prestataires de services pourraient constituer un problème. Il est nécessaire de développer une bonne volonté politique pour utiliser ces instruments.

Recommandations

Les recommandations issues du programme PNR 49 sont résumées dans le tableau de la section 5. La principale recommandation consiste à poursuivre SEARCH et les activités qui en découlent en créant un Centre national de résistance aux antibiotiques (CNRA) à l'endroit où SEARCH est actuellement opérationnel, c'est-à-dire à l'Université de Berne. Le CNRA devrait être basé sur un système sentinelle et monitorer la résistance aux antibiotiques ainsi que la consommation dans les différentes régions de Suisse ; il devrait intégrer les données vétérinaires et servir de plate-forme nationale d'information et de conseil pour tous les thèmes liés à la résistance aux antibiotiques ; il devrait aussi collaborer avec l'UE et d'autres pays; finalement, il devrait constituer une plate-forme pour soutenir ou stimuler les activités de recherche liées aux problèmes de la résistance aux antibiotiques.
Le PNR 49 fournit une aide financière au SEARCH jusque fin 2007. En raison de la réduction constante du budget fédéral, le financement du CNRA après 2008 semble très difficile.
Des solutions novatrices doivent être trouvées. Ce rapport en présente quelques-unes impliquant l'organisation des soins de santé et les cantons.

Conclusions

Le programme PNR 49 «Résistance aux antibiotiques» a nettement contribué à une meilleure compréhension de ce sujet en Suisse. La plupart des objectifs définis au début du programme ont été remplis. Le PNR 49 doit être considéré comme une étape initiale dans la gestion de la résistance bactérienne. Nous disposons à présent de connaissances scientifiques bien établies et de compétences en matière de résistance aux antibiotiques. La Suisse possède enfin un système de surveillance et d'alarme détectant la résistance bactérienne dans les échantillons cliniques humains (SEARCH) et une stratégie de surveillance pour les bactéries isolées des animaux destinés à la consommation.
Toutefois, il est essentiel que les efforts entrepris dans le cadre du PNR 49 ne s'achèvent pas avec la conclusion de ce programme. Le problème de la résistance aux antibiotiques, bien que toujours sous-estimé en Suisse, est en constante évolution, et pas dans le bon sens. Des actions doivent être poursuivies ou entreprises à la fois au niveau de la prévention et de la recherche.

Antibiotikaresistenzen weltweit: eine globale Pandemie, die auch die Schweiz betrifft?

Antibiotikaresistenzen sind in Industrie- wie auch in Entwicklungsländern ein sich ausbreitendes Problem, das immer häufiger Menschenleben fordert, die Kosten für das Gesundheitssystem erhöht und wirtschaftliche Verluste mit sich bringt. Eine Reihe pathogener Bakterien erweist sich als zunehmend resistent gegen antibakterielle Medikamente, und eine immer grössere Zahl dieser Bakterien wie z. B. *Staphylococcus aureus,* gram-negative Stäbchen (*Acinetobacter, Serratia, Pseudomonas aeruginosa,* etc.) oder *Mycobacterium tuberculosis* sind immer schwerer zu bekämpfen.
Wenngleich es sich hierbei vor allem um ein Problem der Humanmedizin handelt, muss das Thema Antibiotikarestistenz als globales Problem betrachtet werden, das für die Human- und Veterinärmedizin ebenso eine Rolle spielt wie für die Landwirtschaft (Tierhaltung), unsere Lebensmittel und die Umwelt. De facto können Antibiotika aufgrund ihres vielfachen Einsatzes und Missbrauchs heute nahezu überall nachgewiesen werden, so dass das Potenzial der Selektion von Resistenzgenen und die Selektion resistenter Mikroorganismen zunimmt. Auch die Schweiz gehört zu denjenigen Ländern, die sich in einer Art "prä-pandemischer" Situation befinden, derzufolge das Problem der Antibiotikaresistenz zwar noch keine wesentliche Bedrohung der Bevölkerung darstellt, sich aber sehr schnell zu einer solchen entwickeln könnte, wenn nicht entsprechende Massnahmen ergriffen werden. Zusätzlich erschwert wird die Situation dadurch, dass es schwierig ist und erhebliche finanzielle Aufwendungen erfordert, neue Antibiotika zur Bekämpfung resistenter Bakterien zu entwickeln. Dies hat dazu geführt, dass die Pharmaunternehmen sich bei der Erforschung neuer antibakterieller Medikamente sehr zurückhalten oder entsprechende Bemühungen sogar wieder eingestellt haben.
1998 verabschiedete die Weltgesundheitsversammlung eine Resolution, welche die Bedeutung antimikrobieller Resistenzen für die öffentliche Gesundheit hervorhebt und die WHO und ihre Mitgliedstaaten dringend auffordert, verschiedene Kontroll- und Bildungsmassnahmen einzuführen sowie politische Konzepte zu entwickeln und umzusetzen. Die Länder wurden darüber hinaus aufgefordert, nachhaltige Systeme für die Entdeckung resistenter Pathogene zu entwickeln, den quantitativen Verbrauch von antimikrobiellen Substanzen und die Verbrauchsmuster zu kontrollieren sowie die Wirksamkeit von Kontrollmassnahmen zu prüfen.

Ursprung des NFP Antibiotikaresistenz (NFP 49)

In der Schweiz wurde in den letzten Jahren eine Reihe von Einzelstudien durchgeführt, die das Problem von Resistenzen in der Humanmedizin und im Veterinärbereich analysierten. Aufgrund der zeitlichen, räumlichen und hinsichtlich der Anzahl der berücksichtigten Bakterienspezies gegebenen Beschränkungen waren diese Studien nicht repräsentativ und nicht dazu geeignet, ein globales Bild zum Thema Antibiotikaresistenzen zu extrapolieren. Eine 1997 veröffentliche Studie des Labors für Lebensmitteltechnologie der ETH Zürich zeigte, dass in Käse enthaltene Laktosebakterien potenziell Reservoire für Resistenzgene darstellen, die von pathogenen Mikroorganismen stammen, welche für Menschen gefährlich sind. Diese Erkenntnisse riefen in der Schweiz grosse Besorgnis hervor, und die Bundesämter für Gesundheit, Veterinärwesen, Landwirtschaft und Aussenwirtschaft (heute Staatssekretariat für Wirtschaft oder SECO) setzten eine Arbeitsgruppe ein, die eine umfassende Analyse der Resistenzsituation vornehmen sollte. In ihrem Abschlussbericht bescheinigte die Arbeitsgruppe der Schweiz mangelhafte Kenntnisse auf diesem Gebiet und empfahl die Einrichtung eines umfangreichen Forschungsprogramms, um die vorhandenen Lücken zu schliessen.
Als Antwort auf diese Empfehlung wie auch auf die Forderung der WHO verabschiedete der Bundesrat im Juni 1999 das NFP "Antibiotikaresistenz" (NFP 49) und stellte hierfür 12 Millionen Schweizer Franken über einen Zeitraum von 5 Jahren zur Verfügung. Das NFP hatte den Auftrag: i) eine Übersicht über die gegenwärtige Antibiotikaresistenzsituation in der Schweiz zu erstellen und die damit verbundenen Risiken zu ermitteln; ii) die wissenschaftlichen Grundlagen für angemessene Präventivmassnahmen zu schaffen; iii) die ökonomischen, rechtlichen und ethischen Konsequenzen von Antibiotikaresistenzen abzuschätzen; iv) die Grundlagenforschung zur Entwicklung neuer Antibiotika voranzutreiben. Das NFP 49 sollte konkrete Antworten auf die Resistenzsituation im Land liefern und zugleich die Kooperation auf internationaler Ebene, insbesondere mit der europäischen Union, anstossen.

Vom NFP 49 unterstützte Projekte

Nach sorgfältiger Prüfung durch internationale Gutachter wurden für das Programm insgesamt 27 Projekte bewilligt, die in drei Hauptgruppen unterteilt wurden: i) Human- und Veterinärmedizin, Überwachung und Umwelt (9 Projekte); ii) Molekulare Biologie (11 Projekte) und iii) Gesellschaft, Recht und Wirtschaft (7 Projekte).
Die meisten Projekte waren an Universitäten oder Universitätsspitälern, Bundesforschungsanstalten und angegliederten Institutionen angesiedelt (z. B. die Eidgenössische Anstalt für Wasserversorgung Abwasserreinigung und Gewässerschutz (EAWAG)). Aber auch Projekte kantonaler

(Istituto Cantonale di Microbiologia, Bellinzona) und eidgenössischer Forschungsanstalten (Agroscope Liebefeld-Posieux Research Station, ALP) waren vertreten. Sechzehn Projekte kamen aus der deutschsprachigen, sieben aus der französischsprachigen und vier aus der italienischsprachigen Schweiz.

Ergebnisse des NFP 49

Die wichtigsten Ergebnisse des NFP 49 sind nach den jeweiligen Fachgebieten unterteilt, wenngleich einige Projekten sich nicht eindeutig nur einem bestimmten Bereich zuordnen liessen.

Humanmedizin und Überwachung

Das zweifellos wichtigste, in der Zwischenzeit bereits in die Praxis umgesetzte Ergebnis des nationalen Forschungsprogramms NFP 49 ist der Aufbau von SEARCH (Sentinel surveillance of antibiotic resistance in Switzerland). Aufgabe des an der Universität Bern angesiedelten Projekts (www.search.ifik.unibe.ch) ist es, repräsentative Daten über Antibiotikaresistenzen bei pathogenen und kommensalen Humanisolaten aus Spitälern und ambulanten Versorgungseinrichtungen der gesamten Schweiz zu liefern. Die geplante Datenbank soll unter anderem Informationen und Analysen zum Antibiotikaverbrauch enthalten. Im Frühjahr 2007 wird SEARCH mit dem EARSS (European Antimicrobial Resistance Surveillance System) vernetzt. Das SEARCH-Überwachungssystem bietet eine ideale Grundlage, problematische Situationen frühzeitig zu erkennen und gegebenenfalls mit speziellen Präventionsmassnahmen zu reagieren. Darüber hinaus ermöglicht es die Überwachung der beschlossenen Kontrollmassnahmen. Obwohl die ersten repräsentativen Daten erst im April 2007 vorgelegt werden, deuten die im Vorfeld gesammelten Ergebnisse aus den Jahren 2004–2005–2006 darauf hin, dass das Gesamtvorkommen von Antibiotikaresistenzen in der Schweiz relativ gering, in einigen Regionen und ausgewählten Patientengruppen jedoch hoch ist. Am besorgniserregendsten ist die Tatsache, dass die Häufigkeit von Antibiotikaresistenzen tendenziell steigt.
Einer der wichtigsten Infektionserreger ist das Bakterium *Staphylococcus aureus*. Methicillin-resistente Staphylokokkenstämme (MRSA) und insbesondere multiresistente Stämme stellen Ärzte und Gesundheitsexperten in und inzwischen auch ausserhalb von Spitälern vor ernsthafte Probleme. Ein neu entwickeltes, bereits validiertes, schnelles und zuverlässiges System ermöglicht es, die genetisch und epidemiologisch relevanten Faktoren von Bakterienstämmen zu bestimmen. Es hat bereits dazu beigetragen, ein unerwartetes und alarmierendes Auftreten sogenannter CA-MRSA (ambulant erworbene MRSA) im Westen der Schweiz zu erkennen.
Darüber hinaus wurde ein weiteres nützliches Instrument entwickelt und validiert, das die Rückverfolgung resistenter Gene in gram-positiven Bakterien ermöglicht. Das auf Microchip-Hybridisierung und Microarrays basierende System wird dafür verwendet, krankheitserregende Bakterien wie *B. anthracis* und Lebensmittelprodukte auf Resistenzgene zu untersuchen. Schliesslich wurde der opportunistische humanpathogene Pilz *Aspergillus fumigatus* untersucht. Die hierbei gewonnenen Daten ergaben, dass derzeit die Häufigkeit von Resistenzen gegen Antimykotika bei Krankenhaus- und Umweltisolaten dieser Mikroorganismen in der Schweiz gering ist.

Veterinärmedizin und Viehwirtschaft

Es wurde ein hoch leistungsfähiges und kostengünstiges Überwachungssystem entwickelt, mit dem Bakterienresistenzen in der Geflügel-, Schweine- und Rinderzucht aufgespürt werden können. Das Projekt lieferte ausserdem Grundliniendaten über die Resistenzsituation in schweizerischen Viehzuchtbetrieben. Im Vergleich zum Ausland ist die Situation in der schweizerischen Viehzucht in Bezug auf die Antibiotikaresistenz derzeit relativ günstig. Die Untersuchung auf *Campylobacter,* dem in der Schweiz am häufigsten auftretenden, auf den Menschen übertragbaren Zoonoseerreger, ergab, dass Fleisch, das in der Schweiz oder auf Höfen mit artgerechter Haltung produziert wurde, grundsätzlich tendenziell weniger resistente Bakterien enthält als ausserhalb der Schweiz oder auf Höfen mit konventioneller Haltung produziertes Fleisch.
Bezüglich der allgemeinen Praxis, Milch, die während einer Antibiotikabehandlung erzeugt wurde, für die Fütterung von Kälbern und Schweinen zu verwenden, zeigte sich, dass dieses Vorgehen zu einer markanten Selektion resistenter Bakterienstämme (d. h. Enterokokken) führt. Es bedarf jedoch weiterer Analysen, um das Verhalten dieser resistenten Stämme zu untersuchen und letztendlich beurteilen zu können, ob ein Risiko besteht, dass diese Bakterien in die Nahrungskette gelangen.

Verzehrfertige Nahrungsmittel und Nahrungsmittelproduktion

Die Untersuchungen mittels Microchip-Hybridisierung ergaben auch, dass verzehrfertige Nahrungsmittel (Käse- und Fleischprodukte), Starter- und probiotische Kulturen Reservoire für Resistenzgene darstellen. Die Resistenzgene konnten erfolgreich auf andere Wirtsbakterien übertragen werden, was auf ein vorhandenes Mobilitätspotenzial und somit eine mögliche Rolle bei der Verbreitung von Antibiotikaresistenzen schliessen lässt. Da diese Ergebnisse wichtige Fragen für die Gesundheit der Konsumenten aufwerfen, sollten sie weiter untersucht werden.

Umwelt

Es wurden neue Analysemethoden entwickelt, die eine exakte und präzise quantitative Analyse (bis zu ng/l-Werten) des Vorkommens und Verhaltens der wichtigsten Klassen von Human- und Veterinärantibiotika in der Umwelt ermöglichen. Die so ermittelten Ergebnisse zeigten, dass in der Tiermast eingesetzte Sulphonamide (SA) durch das Ausbringen der Gülle in vergleichbar hoher Konzentration wie Herbizide ins Erdreich gelangen und dort mehrere Wochen oder Monate persistie-

ren. Darüber hinaus wurde nachgewiesen, dass das Erdreich ein beträchtliches Reservoir für Resistenzgene darstellt. Die Konzentration von SA und anderen Antibiotika in Gewässern (d. h. in Seen und im Grundwasser) hingegen erwies sich als in der Regel sehr niedrig.
Die Analyse des Vorkommens von Humanantibiotika und antibiotikaresistenten Bakterien in aquatischem Milieu ergab, dass im Abwasser von Spitälern, in Siedlungsabwässern (vor und nach der Behandlung in mechanisch-biologischen Kläranlagen) und auch in Flüssen eine ganze Reihe von Antibiotika quantitativ messbar sind, wohingegen β-Laktame in Spitalabwässern nur semiquantitativ messbar waren. Die im Abwasser nachgewiesenen Konzentrationen korrelierten relativ gut mit den bekannten Daten, und es wurden nützliche Erkenntnisse über das Verhalten dieser Substanzen während der Behandlung von Abwässern gewonnen. Darüber hinaus fanden sich in Schweizer Flüssen im niedrigeren ng/l-Bereich ubiquitär zahlreiche antibiotische Substanzen, von denen Sulfamethoxazol auch im Grundwasser nachgewiesen wurde. Das Vorkommen niedriger Konzentrationen von Antibiotika in Grundwasser, das als Trinkwasser verwendet wird, wirft die Frage auf, ob diese Kontaminierung akzeptabel ist oder dem Prinzip der Vorsorge entsprechend verhindert werden sollte. Auch, wenn noch keine eindeutigen Daten über die Auswirkungen niedriger Antibiotika-Konzentrationen auf die Entwicklung von Resistenzen vorliegen, wurde doch nachgewiesen, dass ein Zusammenhang zwischen der in Spitalabwässern gemessenen Konzentration von Antibiotika und der antibiotischen Anfälligkeit einiger durch Wasser übertragbarer Bakterien (z. B. *Aeromonas* und *Acinetobacter*) besteht.

Molekularbiologie: Resistenzmechanismen und neue Targets

Die Projekte im Bereich der Molekularbiologie waren vergleichsweise zahlreich vertreten und befassten sich mit verschiedenen Krankheitserregern. Als Resultat liegt eine Reihe neuer Erkenntnisse über Resistenzmechanismen, insbesondere bei *S. aureus,* Bacilli, *E. coli, P. aeruginosa* und *A. fumigatus* vor. Ein Projekt befasste sich intensiv mit den ribosomalen Mechanismen verantwortlich für Antibiotikaresistenzen und zeigte neue Wege für die Entwicklung innovativer und weniger toxischer Medikamente auf.
Für das Bakterium *M. tuberculosis* wurden neue potenzielle Targets identifiziert, die, so die Hoffnung, zur Entwicklung neuartiger antimikrobieller Antibiotika führen könnten.
Bezüglich der mit Antibiotikaresistenzen häufig verbundenen Fitnesskosten (was die Reversibilität der Resistenz begünstigen würde) wurde nachgewiesen, dass bei *S. aureus* die mit physiologischen Veränderungen der Zellwände verbundene Resistenz gegen Glycopeptide die Fitness der Mikroorganismen herabsetzt. Die Betrachtung der Substanzen, die auf das Ribosom einwirken, ergab hingegen, dass der genetische Hintergrund die Fitnesskosten bei Resistenzdeterminanten beeinflusst und dass diese Determinanten nicht unbedingt mit einer Belastung der Fitness einhergehen müssen.

Antibiotikaverbrauch

Auf der Grundlage von Handelsdaten wurde der Antibiotikaverbrauch der ambulanten Patienten in der Schweiz untersucht und mit den Verbrauchszahlen anderer europäischer Länder verglichen. Die Analyse deckte auf, dass der Pro-Kopf-Verbrauch von Antibiotika in der Schweiz im Vergleich zu anderen europäischen Ländern relativ gering ist. Allerdings zeigte sich, dass es beim Antibiotikaverbrauch im Land erhebliche Unterschiede zwischen verschiedenen Kantonen und Regionen gibt, was sich im Wesentlichen auf sozioökonomische, demographische und epidemiologische Faktoren sowie die ärztliche und pharmazeutische Versorgungssituation (Ärzte- und Apothekendichte) zurückführen lässt.
Es wird darauf hingewiesen, dass der in diesem Projekt entwickelte empirische Rahmen zur Untersuchung des ambulanten Antibiotikaverbrauchs in anderen europäischen Ländern in Zusammenhang mit dem von der europäischen Union finanzierten ESAC-Projekt (European Surveillance of Antimicrobial Consumption Project) herangezogen wurde, dem sich die Schweiz als repräsentativer Partner anschliessen könnte.
Darüber hinaus wurden zwei Überwachungsnetzwerke zur Beurteilung des Antibiotikaverbrauchs in öffentlichen Akutspitälern und im ambulanten Bereich eingerichtet; Grundlage der Beurteilung sind die von Spitälern bzw. Apotheken zur Verfügung gestellten Daten. Die Systeme ergaben ein präzises Bild über den Einsatz von Antibiotika und ermöglichten eine umfassende Analyse und den Vergleich der Verschreibungsmuster. Die Pilotprojekte können, um für eine grössere Anzahl von Spitälern und Ärzten repräsentativ zu sein und somit die Genauigkeit zu erhöhen, ausgeweitet werden. Das Interessante an dieser Zusatzstudie ist, dass die Verbrauchsdaten nun für SEARCH zur Verfügung gestellt werden könnten, ohne sie einem kommerziellen Anbieter teuer abkaufen zu müssen.

Bekanntheit des Antibiotikaresistenz-Problems

Das allgemeine Bewusstsein für und Wissen über Antibiotika und das Thema Antibiotikaresistenz ist in der schweizerischen Bevölkerung – mit regionalen Unterschieden – nicht allzu gross. Die zum Problem Antibiotikaresistenzen erhältlichen Informationen in den in der Schweiz angebotenen Quellen (z. B. Zeitungen) sind eindeutig unzureichend und ungenau. Hinzu kommt, dass die meisten Beipackzettel für Antibiotika das Thema Antibiotikaresistenz noch nicht einmal erwähnen und auch nicht darüber informieren, wie wichtig es ist, die Antibiotikabehandlung konsequent bis zum Ende durchzuführen. Hinzu kommt erschwerend, dass mit Ausnahme einiger sehr weniger und nicht weit verbreiteter Broschüren, weder für Ärzte noch für Patienten Informationen zum Problem Antibiotikaresistenz erhältlich sind. Um die Schweizer Bevölkerung korrekt zu informieren, ist also noch viel zu tun.

Rechtliche Aspekte in Zusammenhang mit Antibiotikaresistenz

Legt man die Gesetzgebung zur Regelung von Epidemien, Lebensmittelsicherheit und Gesundheitssicherung zugrunde, verfügen Bund und Kantone aus rechtlicher Sicht bereits über eine breite und angemessene Palette an rechtlichen Instrumenten zur Umsetzung der für den Umgang mit dem Antibiotikaresistenz-Problem erforderlichen Massnahmen. Die Aufteilung der Zuständigkeiten zwischen dem Bund und den Kantonen sowie die Beziehungen zwischen den verschiedenen Behörden und Dienstleistungsanbietern könnten sich als problematisch erweisen. Um die vorhandenen Instrumente zu nutzen, ist es wichtig, politisch guten Willen zu zeigen.

Empfehlungen

Die aus den Erkenntnissen des NFP 49 resultierenden Empfehlungen sind in der Tabelle unter Kapitel 5 zusammengefasst. Die wichtigste Empfehlung ist die Fortführung des SEARCH-Projekts und der damit verbundenen Aktivitäten in Form der Einrichtung eines Nationalen Antibiotikaresistenzzentrums (NARC) am gleichen Ort des derzeitigen SEARCH-Projekts an der Universität von Bern. Das NARC sollte sich auf konkrete Beobachtungen stützen und die Antibiotikaresistenz-Situation und den Verbrauch von Antibiotika in den verschiedenen Regionen der Schweiz unter Berücksichtigung der relevanten Veterinärdaten überwachen; das NARC sollte als nationale Informations- und Beratungsplattform für alle mit dem Thema Antibiotikaresistenz assoziierten Fragen fungieren; darüber hinaus sollte es mit den EU- und anderen Ländern zusammenarbeiten, und es sollte eine Plattform schaffen, die weiterführende Forschungsaktivitäten zum Thema Antibiotikaresistenzen anstösst und unterstützt.
Das NFP stellt die Finanzierung des SEARCH-Projekts bis Ende 2007 sicher. Angesichts der stetigen Reduzierung der Bundeszuschüsse stellt sich die Finanzierung des NARC ab 2008 als sehr schwierig dar. Hier bedarf es dringend innovativer Lösungen. Einige dieser Lösungen, welche die Organisation des Gesundheitswesens und die Kantone betreffen, werden im vorliegenden Bericht erläutert.

Fazit

Das NFP 49 "Antibiotikaresistenz" hat erheblich zum besseren Verständnis des Antibiotikaresistenzproblems in der Schweiz beigetragen. Die meisten zu Beginn des Programms formulierten Ziele wurden erreicht. Das "Antibiotikaresistenz"-Programm NFP 49 ist als ein erster Schritt im Umgang mit dem Problem mikrobieller Resistenzen zu bewerten. Wir verfügen heute bezüglich des Problems Antibiotikaresistenz auf allen relevanten Gebieten über fundierte wissenschaftliche Kenntnisse und Kompetenzen. Die Schweiz verfügt endlich über ein Überwachungs- und Warnsystem zur Entdeckung resistenter Bakterien in klinisch untersuchten Humanproben (SEARCH) und ein Konzept zur Überwachung von Bakterienisolaten von für den Verzehr bestimmten Tieren. Es ist jedoch von grösster Wichtigkeit, die im Rahmen des NFP 49 unternommenen Anstrengungen nach Beendigung des Programms nicht abzubrechen. Das Antibiotikaresistenzproblem nimmt, wenngleich es in der Schweiz nach wie vor unterschätzt wird, immer grössere Ausmasse an. Hier bedarf es sowohl auf Präventions- als auch auf Forschungsebene weiterhin aktiver Massnahmen.

La resistenza agli antibiotici nel mondo: una pandemia globale che interessa anche la Svizzera?

La resistenza agli antibiotici si sta diffondendo sia nei paesi sviluppati che in quelli in via di sviluppo, comportando un incremento dei costi in termini di vite umane, spese sanitarie e perdite economiche. Esiste una serie di batteri patogeni che sta sviluppando una resistenza sempre maggiore ai farmaci antibiotici. Un numero crescente di essi, come lo *Staphylococcus aureus,* i bacilli gram negativi (*Acinetobacter, Serratia, Pseudomonas aeruginosa,* ecc.), o il *Mycobacterium tuberculosis,* stanno diventando estremamente difficili da curare.
Sebbene le preoccupazioni riguardino soprattutto la medicina umana, la resistenza agli antibiotici deve essere affrontata in modo globale. La problematica riguarda in effetti, oltre la medicina umana, anche la medicina veterinaria, l'agricoltura e l'allevamento di animali, le derrate alimentari e l'ambiente. In realtà, a causa del loro uso e abuso da parte dell'uomo, gli antibiotici si possono ora trovare pressoché ovunque e influire fortemente sulla selezione di geni di resistenza e quindi di microrganismi resistenti. Anche la Svizzera fa parte dei paesi che attualmente si trovano in una sorta di situazione "pre-pandemica", in cui la questione relativa alla resistenza agli antibiotici non viene ancora percepita come una importante minaccia per la popolazione ma che, con molta probabilità, degenererà se non vengono adottati provvedimenti volti a contenerla. Per di più, e ciò peggiora ulteriormente la situazione, scoprire nuovi antibiotici che combattano i batteri resistenti è difficile e richiederebbe ingenti investimenti finanziari non facili da reperire. Ecco perché le industrie farmaceutiche stanno limitando, o addirittura sospendendo, la ricerca relativa a nuovi farmaci antibatterici.
Nel 1998, l'Assemblea Mondiale della Sanità ha adottato una risoluzione che riconosce l'importanza della resistenza antimicrobica per la salute pubblica e sollecita l'OMS e i relativi stati membri a intraprendere una serie di iniziative in termini di sorveglianza, di formazione e di sviluppo e attuazione di specifiche strategie politiche. I Paesi sono stati anche incoraggiati a sviluppare sistemi sostenibili per individuare i patogeni resistenti, monitorare i volumi e le modalità di utilizzo degli antibiotici e l'impatto delle misure di controllo.

Origine del PNR 49: la resistenza agli antibiotici

Nel corso degli ultimi anni, in Svizzera è stata condotta una serie di studi individuali finalizzati all'analisi della resistenza nella medicina umana e veterinaria. Poiché limitati in termini temporali, geografici e riguardo al numero di specie batteriche esaminate, i risultati di queste indagini non sono rappresentativi. Per questo motivo non è stato possibile delineare un quadro globale per quanto concerne la resistenza agli antibiotici in Svizzera. Uno studio pubblicato nel 1997 dal Laboratorio di Microbiologia Alimentare dell'ETH di Zurigo ha dimostrato che i batteri lattici trovati nel formaggio potrebbero costituire un ricettacolo per i geni di resistenza presenti nei microrganismi patogeni di interesse umano. Questi risultati hanno generato molta apprensione in Svizzera e un gruppo di lavoro ha ricevuto il mandato dall'Ufficio Federale di Sanità Pubblica, dall'Ufficio Federale di Veterinaria, dall'Ufficio Federale dell'Agricoltura e Ufficio Federale per l'Economia Esterna (oggi Segretariato di Stato dell'economia o SECO) di svolgere un'analisi globale sulla situazione relativa alla resistenza. Nel suo resoconto finale, il gruppo di lavoro ha riconosciuto che in Svizzera mancano le necessarie conoscenze in questo campo e ha consigliato il lancio di un programma di ricerche di ampio respiro volto a colmare tali lacune.
Per rispondere a questa raccomandazione e anche alla richiesta dell'OMS, il Consiglio federale ha approvato, nel giugno 1999, il Programma Nazionale di Ricerca 49 "La resistenza agli antibiotici" e ha stanziato 12 milioni di franchi per un periodo di cinque anni. Gli obiettivi del PNR 49 possono essere riassunti nei punti seguenti: i) analizzare la situazione relativa alla resistenza agli antibiotici in Svizzera e conoscere meglio i rischi ad essa correlati; ii) definire la base scientifica per dare inizio ad appropriate misure preventive; iii) fornire informazioni in merito agli aspetti economici, legali ed etici della resistenza agli antibiotici; iv) promuovere la ricerca fondamentale al fine di sviluppare nuovi antibiotici. Il PNR 49 aveva lo scopo di fornire risposte specifiche inerenti alla situazione della resistenza agli antibiotici nel paese avviando, al contempo, una collaborazione a livello internazionale, in particolare con l'Unione Europea.

Progetti sostenuti dal PNR 49

In seguito a un attento esame da parte di esperti internazionali, il programma ha sostenuto 27 progetti di ricerca, suddivisi in tre settori principali: i) 9 progetti inerenti la medicina umana e veterinaria, la sorveglianza e l'ambiente; 11 progetti inerenti la biologia molecolare; iii) 7 progetti inerenti la società, la legislazione e l'economia.
La maggior parte dei progetti sono stati presentati da università o cliniche universitarie, Istituti federali di tecnologia e altre istituzioni analoghe (ad es., l'Istituto federale svizzero di scienze acquatiche e tecnologia, EAWAG). Alcuni progetti, tuttavia, sono stati proposti anche da istituti cantonali (Istituto Cantonale di Microbiologia, Bellinzona) o federali (Agroscope Liebefeld-Posieux Research Station, ALP). Per quello che concerne la ripartizione geografica, sedici progetti sono stati svolti nella Svizzera tedesca, sette in quella francese e quattro in quella italiana.

Esiti del Programma di Ricerca Nazionale 49

I principali esiti del PNR 49 sono classificati in base al loro campo d'interesse, sebbene alcuni progetti interessassero più campi d'interesse.

Medicina umana e sorveglianza

Senza dubbio il risultato più importante, attualmente operativo, del PRN 49 è l'istituzione del SEARCH (Sentinel Surveillance of Antibiotic Resistance in Switzerland). Il sistema di sorveglianza SEARCH, con sede presso l'Università di Berna (www.search.ifik.unibe.ch), fornirà dati rappresentativi sulla resistenza agli antibiotici in Svizzera in batteri patogeni e commensali isolati da campioni clinici umani d'origine ospedaliera e non ospedaliera, ossia comunitaria. Si prevede anche di integrare e analizzare i dati relativi al consumo di antibiotici. Nella primavera del 2007, il SEARCH si collegherà all'EARSS (European Antimicrobial Resistance Surveillance System). SEARCH costituisce, quindi, la base ideale per un'individuazione precoce di situazioni problematiche, consentendo di reagire tempestivamente con l'adozione di specifiche misure preventive. SEARCH permetterà, inoltre, di monitorare gli esiti delle misure di controllo messe in atto. Sebbene i primi dati rappresentativi saranno disponibili solamente ad aprile 2007, i risultati preliminari ottenuti finora in relazione agli anni 2004-2005-2006 indicano che, in generale, il livello di resistenza agli antibiotici in Svizzera è relativamente basso, tuttavia in alcune zone geografiche e in determinati gruppi di pazienti si osservano livelli di resistenza elevati. Ciò che preoccupa di più è la netta tendenza verso un aumento della resistenza.

Lo *Staphylococcus aureus* è uno dei principali patogeni infettivi. La comparsa di ceppi di *S. aureus* meticillino-resistente (MRSA) e specialmente di quello multi-resistente comporta seri problemi clinici e di gestione sanitaria negli ospedali, e ora anche a livello comunitario (non ospedaliero). Nell'ambito del NRP 49 è stata sviluppata una metodologia rapida e affidabile per caratterizzare geneticamente i ceppi MRSA e quindi di seguirne l'epidemiologia. Questa tecnica ha permesso di mettere in evidenza un'inaspettata e allarmante comparsa di CA-MRSA (MRSA d'origine comunitaria) nella Svizzera occidentale.

Nell'ambito del NRP49 è stato inoltre sviluppato un altro strumento utile per monitorare la presenza di geni di resistenza nei batteri gram positivi: basato sulla tecnologia di ibridizzazione su microchip (microarray), è stato utilizzato con successo per analizzare i geni di resistenza in batteri patogeni come il *B. anthracis* ed in prodotti alimentari.

Infine, è stato esaminato anche un fungo patogeno opportunistico, l'*Aspergillus fumigatus*. I dati generati hanno dimostrato che, in Svizzera, il livello di resistenza antifungina negli isolati clinici e ambientali di questo microrganismo è attualmente basso.

Medicina veterinaria e allevamento di bestiame

E' stata sviluppata una strategia di monitoraggio efficace ed economica per monitorare la resistenza batterica nella produzione di pollame, suini e bovini. Il progetto ha anche fornito dati di base in merito allo stato della resistenza negli animali destinati al consumo umano in Svizzera. Al momento, rispetto alla situazione all'estero, lo stato di resistenza del bestiame svizzero appare favorevole. Per quanto concerne il *Campylobacter,* l'agente patogeno d'origine zoonotica trasmissibile all'uomo (e che causa malattie) più frequente in Svizzera, i dati indicano che, in generale, la carne prodotta in Svizzera o in fattorie "animal-friendly" tende a presentare batteri meno resistenti rispetto alla carne prodotta all'estero o in fattorie tradizionali.

Riguardo alla pratica, molto comune, di utilizzare il latte prodotto durante il trattamento antibiotico delle mucche per alimentare vitelli e maiali, è stato dimostrato che questa consuetudine causa una marcata selezione di ceppi batterici resistenti (ad esempio enterococchi). Tuttavia, sono necessarie ulteriori valutazioni per poter studiare dove possano andare a finire questi ceppi resistenti, nonché per comprendere se esista un rischio che questi batteri resistenti possano finire nelle derrate alimentari.

Alimenti pronti per la consumazione e produzione di generi alimentari

Sempre con l'ausilio di un innovativo test basato sull'ibridizzazione su microchip, è stato dimostrato che alimenti pronti per la consumazione (formaggi e prodotti a base di carne) così come colture starter e probiotiche, costituiscono un ricettacolo per i geni di resistenza. Questi geni di resistenza hanno potuto essere trasferiti ad altri batteri, indicandone la potenziale mobilità e lasciando presagire che possano svolgere un ruolo nella propagazione della resistenza agli antibiotici. Queste scoperte potrebbero suscitare preoccupazione per la salute dei consumatori e dovrebbero quindi essere analizzate in maniera più approfondita.

Ambiente

Sono stati sviluppati nuovi metodi analitici che consentono un'analisi quantitativa precisa e molto sensibile (nell'ordine dei ng/L) della presenza nell'ambiente delle classi più importanti di antibiotici ad uso umano e veterinario. I risultati hanno dimostrato che, per quanto concerne i sulfonamidici (SA), dopo essere stati utilizzati per il trattamento del bestiame finiscono, in seguito alla concimazione, nel terreno in quantità comparabili al tasso di spargimento di erbicidi, e possono permanervi per diverse settimane o mesi. E' stato inoltre dimostrato, che il terreno costituisce un importante ricettacolo per i geni di resistenza. D'altro canto, le concentrazioni di SA e di altri antibiotici rilevati nelle acque (acque di lago e acque freatiche) sono generalmente molto basse.

L'analisi della presenza di antibiotici ad uso umano e della resistenza agli antibiotici nell'ambiente acquatico ha mostrato che, mentre alcuni antibiotici possono essere rilevati nelle acque di scarico ospedaliere, municipali (sia prima che dopo

il trattamento meccanico-biologico), e nei fiumi, gli antibiotici appartenenti alla classe dei β-lattamici possono essere rilevati unicamente nelle acque di scarico degli ospedali. Le concentrazioni riscontrate nelle acque di scarico correlano con una certa ragionevolezza ai dati relativi al loro consumo. Inoltre è stato possibile acquisire una buona conoscenza sui procedimenti di trattamento delle acque di scarico per quanto concerne la loro efficacia nell'eliminazione di alcune classi di antibiotici. In alcuni fiumi svizzeri è stata rilevata la presenza, a bassa concentrazione (dell'ordine dei ng/L), di antibiotici, mentre nelle acque freatiche è stata osservata la presenza di sulfametossazolo. La presenza, sebbene a basse concentrazioni, di antibiotici nelle acque freatiche utilizzate come acqua potabile fa sorgere la domanda se, secondo il principio precauzionale, questa contaminazione possa essere accettata o debba essere evitata.
Anche se non sono ancora disponibili dati definitivi che dimostrino l'impatto della presenza di basse concentrazioni di antibiotici sullo sviluppo della resistenza, è stata dimostrata una correlazione fra la concentrazione degli antibiotici rilevati nelle acque di scarico ospedaliere e la suscettibilità agli antibiotici in alcuni batteri d'origne acquatica (ossia *Aeromonas* e *Acinetobacter*).

Biologia molecolare: meccanismi di resistenza e nuovi target

I progetti di microbiologia molecolare, relativamente numerosi, si sono occupati di svariati agenti patogeni. Sono state acquisite nuove ed imprtanti conoscenze sui meccanismi di resistenza, in particolare in batteri quali *S. aureus,* Bacilli, *E. coli, P. aeruginosa* e nel fungo *A. fumigatus*. Uno dei progetti ha studiato a fondo i meccanismi responsabili della resistenza agli antibiotici che agiscono sui ribosomi, aprendo nuove strade allo sviluppo di farmaci innovativi e meno tossici.
Per quanto concerne il *M. tuberculosis,* sono stati individuati nuovi potenziali target che, si auspica, porteranno alla generazione di nuovi agenti terapeutici antimicobatterici.
Riguardo al cosiddetto costo in termini di fitness spesso collegato alla resistenza agli antibiotici (che potrebbe favorire la reversibilità della resistenza), è stato dimostrato che, nello *S. aureus,* la resistenza ai glicopeptidi associata a cambiamenti fisiologici della parete cellulare, riduce il fitness del microrganismo. D'altro canto, considerando i farmaci che agiscono sul ribosoma, è stato dimostrato che il background genetico influisce sul costo in termini di fitness dei fattori determinanti la resistenza, e che questi non comportano inevitabilmente una diminuzione del fitness.

Consumo di antibiotici

Il consumo di antibiotici in Svizzera a livello comunitario (non ospedaliero) è stato esaminato sulla base di dati commerciali e confrontato con il consumo di antibiotici in altri paesi europei. L'analisi ha rivelato che in Svizzera, il consumo di antibiotici pro capite è relativamente basso rispetto agli altri paesi europei. Entro i confini svizzeri, tuttavia, si osservano differenze sostanziali a livello cantonale e locale nell'utilizzo degli antibiotici da parte della popolazione. Queste variazioni si possono ricondurre principalmente a fattori socio-economici, demografici ed epidemiologici, nonché al grado di accesso alle strutture sanitarie e al trattamento antibiotico (densità di medici e farmacie).
E' opportuno evidenziare il fatto che la metodologia empirica sviluppata nell'ambito di questo progetto è stata applicata nello studio del consumo di antibiotici a livello comunitario in altri paesi europei nell'ambito dell progetto European Surveillance of Antimicrobial Consumption ESAC, finanziato dall'Unione Europea, a cui la Svizzera ha dato il suo contributo in veste di paese partecipante.
Sono state progettate, inoltre, due reti sentinella per il monitoraggio dell'uso di antibiotici negli ospedali pubblici acuti e a livello comunitario (non ospedaliero), sulla base dei dati forniti, rispettivamente, dalle farmacie degli ospedali o dalle farmacie presenti sul territorio. Questi due sistemi hanno permesso di valutare con precisione il consumo di antibiotici e hanno permesso di effettuare analisi e comparazioni approfondite delle modalità di prescrizione. Questi progetti pilota possono essere ampliati per rappresentare una percentuale maggiore di ospedali e medici, aumentando così la precisione dei dati rilevati. Questo studio si dimostra interessante in quanto i dati di consumo potrebbero ora essere forniti al SEARCH, senza la necessità di acquistarli a caro prezzo da una fonte commerciale.

Consapevolezza del problema della resistenza agli antibiotici

In generale, la consapevolezza e la conoscenza degli antibiotici e del problema della resistenza agli antibiotici non è molto elevata fra la popolazione svizzera, sebbene vi siano delle differenze a livello regionale. In effetti, le fonti di informazione in Svizzera (ad esempio, i quotidiani) sul problema della resistenza agli antibiotici sono insoddisfacenti e molto approssimative. Inoltre, la maggior parte dei foglietti illustrativi contenuti nelle confezioni di antibiotici non cita neanche il problema della resistenza agli antibiotici, né informa in merito all'importanza di portare a termine la terapia antibiotica. In aggiunta, ad eccezione di pochissimi e mal distribuiti opuscoli, non è stato possibile trovare alcuna informazione, né per medici né per pazienti, circa il problema della resistenza agli antibiotici. Occorre, pertanto, fare molto per informare correttamente la popolazione svizzera.

Aspetti legali relativi alla resistenza agli antibiotici

Da un punto di vista legale, sulla base della legislazione che disciplina le epidemie, la sicurezza alimentare e l'assicurazione sanitaria, il governo federale e i cantoni svizzeri possiedono già un'ampia e adeguata gamma di strumenti legali per l'attuazione di misure necessarie ad affrontare il problema della resistenza agli antibiotici. La divisione delle responsabilità fra lo stato e i cantoni, e il rapporto fra le autorità e i fornitori di servizi potrebbero tuttavia costituire un problema.

Per fare un buon uso degli strumenti a disposizione, è necessario porre delle buone basi a livello politico.

Raccomandazioni

Le raccomandazioni derivanti dal programma PNR 49 sono riassunte nella Tabella al capitolo 5. La raccomandazione più importante è quella di proseguire il SEARCH e le attività ad esso correlate mediante l'istituzione di un Centro Nazionale sulla Resistenza agli Antibiotici (NARC, "National Antibiotic Resistance Centre") che avrà sede presso la struttura in cui il SEARCH sta attualmente operando, ossia l'Università di Berna. Il NARC dovrebbe essere basato su un sistema sentinella e monitorare la resistenza agli antibiotici e il consumo di antibiotici nelle diverse regioni della Svizzera; dovrebbe integrare i dati veterinari e rappresentare, a livello nazionale, un polo di consulenza e informazione per tutte le questioni correlate alla resistenza agli antibiotici; dovrebbe, inoltre, interagire con l'UE e gli altri paesi; infine, dovrebbe costituire una piattaforma per stimolare o sostenere le attività di ricerca relative alle problematiche riguardanti la resistenza agli antibiotici.
Il PNR 49 sosterrà finanziariamente il SEARCH fino alla fine del 2007. A causa della costante riduzione del budget federale, i finanziamenti al NARC dopo il 2008 appaiono tuttavia molto incerti. Occorre trovare soluzioni innovative. Alcune di esse, che coinvolgono le organizzazioni sanitarie e i cantoni, sono illustrate nel presente rapporto.

Conclusioni

Il PNR "La resistenza agli antibiotici" ha dato un significativo contributo a una migliore comprensione della questione relativa alla resistenza agli antibiotici in Svizzera. La maggior parte degli obiettivi definiti all'inizio del programma è stata conseguita. Il Programma Nazionale di Ricerca 49 "La resistenza agli antibiotici" va considerato come un primo passo nella gestione della resistenza antimicrobica. Attualmente disponiamo di conoscenze e competenze scientifiche consolidate sulla questione della resistenza agli antibiotici in tutte le aree toccate dal problema. La Svizzera è finalmente dotata di un sistema di sorveglianza e di allarme in grado di individuare la resistenza batterica nei campioni clinici umani (SEARCH) e di una strategia di monitoraggio per batteri isolati dagli animali destinati al consumo umano.
Tuttavia, è essenziale che gli sforzi intrapresi con il PNR 49 non terminino con la conclusione del programma. Il problema della resistenza agli antibiotici, sebbene ancora sottovalutato in Svizzera, sta già guadagnando terreno. Per questo occorre proseguire con le iniziative adottare e avviarne di nuove, sia a livello di prevenzione che di ricerca.

1. Introduction and goals of the programme

The discovery of antibiotics and their use in fighting infections was one of the most spectacular medical advances of the twentieth century. From the beginning, however, it became apparent that bacterial pathogens have the ability to defend themselves against antimicrobial agents. Bacteria acquire resistance to antibiotics by means of changes in the bacterial genome, either by mutation and selection or by exchanging genes with other micro-organisms through various genetic transfer mechanisms.
A number of bacteria are naturally resistant to antibiotics, since they develop resistance in response to antibiotics naturally occurring in their habitats. However, the main contributor to the emergence and spread of resistance genes in bacteria is the use of antibiotics by man. Use, and in particular overuse, greatly accelerates the process of selection of resistant strains and the shift from antibiotic sensitive to antibiotic resistant populations. The resistance genes can spread rapidly; when transferred to pathogenic bacteria, they make effective therapeutic use of antibiotics difficult or impossible.

Antibiotic resistance worldwide and in Switzerland: An alarming issue

Antibiotic resistance is spreading in both the developed and developing countries. Among many others, the examples reported below illustrate the present situation:

Staphylococcus aureus: Methicillin-resistant *S. aureus* (MRSA) is one of the most well-known bacteria that represent a serious medical, hygienic and economic problem in hospitals and homes for the elderly and handicapped. Because this bacterium has developed resistance to many antibiotics, the range of therapeutic drugs for treating infections caused by it has diminished. In Swiss hospitals, the globally increasing share of MRSA among all *Staphylococcus* isolates is around 4%–5% (in a few hospitals, up to 20%). In Spain, Italy and France, this figure can even go as high as 30% or more.[1] Patients who have been infected with MRSA can be treated with only a limited number of effective antibiotics (e.g. glycopeptides, linezolid). However, resistance to these second-line drugs has already appeared. In the United States as in Europe, the authorities are particularly concerned, because these bacteria have found their way into the general population (CA-MRSA).[2] In a study conducted at Vanderbilt University in Nashville, Tennessee, scientists took nasal smears of 500 healthy children and found CA-MRSA in 9.2% of these samples. In a similar investigation conducted three years earlier, only 0.8% of the children participating had tested positive for CA-MRSA.[3] CA-MRSA strains are also being found in Switzerland and already appear to be an emerging problem in the Canton of Geneva.[4] Interestingly, the CA-MRSA that are emerging in the population belong to completely new strains and produce a variety of exotoxins.[5]
Very recently, worrying reports indicated that pigs might be a new source of particular MRSA variants, which have been found in Holland and very likely also in France, that are transmitted and spread to man.[6]

1 EARSS, http://www.rivm.nl/earss/database/

2 Community-acquired MRSA

3 Creech CB 2nd, Kernodle DS, Alsentzer A, Wilson C, Edwards KM. Increasing rates of nasal carriage of methicillin-resistant *Staphylococcus aureus* in healthy children. *Pediatr Infect Dis J.* 2005 Jul;24(7):617-21.

4 Aramburu C, Harbarth S, Liassine N, Girard M, Gervaix A, Scherenzel J, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in Switzerland: first surveillance report. *Euro Surveill.* 2006 Jan;11(1):42-3.

5 Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis.* 2003 Aug;9(8):978-84.

6 Huijsdens XW, van Dijke BJ, Spalburg E, van Santen-Verheuvel MG, Heck ME, Pluister GN, et al. Community-acquired MRSA and pig-farming. *Ann Clin Microbiol Antimicrob.* 2006 Nov 10;5:26.

Streptococcus pneumoniae: Pneumococci are frequent pathogens within the community, especially among children. However, bacteria that are moderately resistant and highly resistant to antibacterial drugs are appearing worldwide. For instance, in the United States 33% of the strains were non susceptible to penicillin in 2002, and in European countries such as France or Spain more than 50% in 2001.[7] In Switzerland, in a study of children with respiratory infection, 13.4% of the 1179 pneumococcal strains were non susceptible to penicillin.[8] Unfortunately, combined resistance to other current antibiotics, such as macrolides, is also frequently found in penicillin-resistant isolates.

Mycobacterium tuberculosis: According to the World Health Organization (WHO), about one-third of the world population is infected by this bacterium. Multi-drug resistant strains have emerged and are increasing especially in a number of European Eastern countries, forcing the use of second-line drugs, which are less active, more toxic, and 100-fold more expensive than the traditional ones. In 2006, a joint report by the WHO and the Centers for Disease Control and Prevention (CDC) in the United States expressed deep concern about the emergence of XDR-TB (extensive drug-resistant tuberculosis) strains resistant not only to first-line but also to second-line drugs.[9] XDR-TB has been identified in all regions of the world but is most frequent in the countries of the former Soviet Union and in Asia. Data from South Africa highlighted the extremely deadly association of XDR-TB and HIV infection. According to WHO, these findings open up the possibility that epidemics of virtually untreatable tuberculosis may develop.[10]

Salmonella typhimurium: Food-borne salmonella infections have become a major problem in industrialized countries. Each year, bacteria of the genus *Salmonella* infect an estimated 1.4 million persons, resulting in several hundred deaths in the United States alone.[11] One of the most recent and common variants isolated from humans is multi-drug-resistant *S. typhimurium* DT104, which is resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline. DT 104 emerged in 1991 in cattle and pigs and has subsequently been transmitted to humans through the food chain. This strain turned quickly into a major cause of human illness in the United Kingdom in the late 1980s and afterwards in other European countries, including Switzerland, and in the United States, rapidly becoming a world-wide health problem.[12, 13, 14]

7 Vicente M, Hodgson J, Massidda O, Tonjum T, Henriques-Normark B, Ron EZ. The fallacies of hope: will we discover new antibiotics to combat pathogenic bacteria in time? *FEMS Microbiol Rev.* 2006 Nov;30(6):841-52.

8 Muhlemann K, Matter HC, Tauber MG, Bodmer T; Sentinel Working Group. Nationwide surveillance of nasopharyngeal *Streptococcus pneumoniae* isolates from children with respiratory infection, Switzerland, 1998-1999. *J Infect Dis.* 2003 Feb 15;187(4):589-96. Epub 2003 Jan 29.

9 Centers for Disease Control and Prevention (CDC). Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs – worldwide, 2000-2004. *MMWR Morb Mortal Wkly Rep.* 2006 Mar 24;55(11):301-5.

10 World Health Organization (WHO). Addressing the threat of tuberculosis caused by extensively drug-resistant *Mycobacterium tuberculosis. Wkly Epidemiol Rec.* 2006 Oct 13;81(41):386-90.

11 Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, et al. Food-related illness and death in the United States. *Emerg Infect Dis.* 1999 Sep-Oct;5(5):607-25.

12 Glynn MK, Bopp C, Dewitt W, Dabney P, Mokhtar M, Angulo FJ. Emergence of multidrug-resistant *Salmonella enterica* serotype *typhimurium* DT104 infections in the United States. *N Engl J Med.* 1998 May 7;338(19):1333-8.

13 Threlfall EJ. Epidemic *Salmonella typhimurium* DT 104--a truly international multiresistant clone. *J Antimicrob Chemother.* 2000 Jul;46(1):7-10.

14 http://www.who.int/mediacentre/factsheets/fs139/en

As stated above, these are only examples of the trend that is observed worldwide with many bacterial pathogens. At the end of the twentieth century, health authorities realised the extent of the problem and its potential impact on the treatment of infections. Antibiotic resistance costs money and lives, not only at the hospital level but also in the community. For instance, a report by the Institute of Medicine in 1998[15] estimated that the overall cost of antibiotic resistance in the United States is at least 5 billion dollars annually. Even though it is extremely difficult to calculate the burden of this phenomenon, it can be expected that the costs in a country such as Switzerland are proportionally similar.
From a global perspective, it has been also realised that the antibiotic resistance issue is not only limited to humans. It also involves veterinary medicine, agriculture, the food industry and the environment. Indeed, resistant organisms and resistance genes are found nearly everywhere. As a consequence, the management of the resistance problem requires a global and multidisciplinary approach.

In 1998, the World Health Assembly adopted a resolution that recognises the public health importance of antimicrobial resistance and urges WHO and its member states to undertake a number of actions in surveillance, education and policy development and implementation. Countries were also encouraged to develop sustainable systems to detect resistant pathogens and to monitor volumes and patterns of use of antimicrobials and the impact of control measures.[16] Further, in 2005, WHO called again for urgent action on antimicrobial resistance.[17]
In addition to the initiatives undertaken by the single states (see section 7 below "Vision after NRP 49"), the European Commission, through the Quality of Life programme of the Fifth Framework Programme, supported a comprehensive strategy for research on antimicrobial resistance and published an inventory encompassing approximately 80 projects.[18] Within the antimicrobial resistance research supported by the Fifth Framework Programme, there are a number of surveillance networks and databases that will certainly be of interest for Switzerland: EARSS (European Antimicrobial Resistance Surveillance System), ESAC (European Surveillance of Antimicrobial Consumption), ARPAC (Antibiotic Resistance Prevention and Control) project for European hospitals.

Origin of the programme

In Switzerland, too, antibiotic resistance has been a matter of concern. At the end of the 1990s, a considerable number of studies, many of them instigated by pharmaceutical companies, were conducted to analyse resistance in human medicine. Because they were limited as to time, location and number of bacterial species considered, these surveys were not representative, and a global view of the antibacterial resistance could not be extrapolated. Initiatives to monitor the resistance of a few particular bacterial species were also launched by the Federal Office of Public Health (FOPH) and by the Federal Veterinary Office (FVO).

15 Institute of Medicine of the National Academies. Antimicrobial Resistance: Issues and Options. Washington, DC: The National Academies; 1998.

16 World Health Organization. World Health Assembly (fifty-first). WHA51.17, agenda item 21.3 (1998).

17 http://www.wpro.who.int/media_centre/press_releases/pr_20050609.htm

18 Lönnroth A, editor. Antimicrobial Resistance Research 1999-2002. Revised and extended ed. EUR 20495. European Commission Directorate-General for Research. Luxembourg: Office for Official Publications of the European Communities; 2003.

However, the acquisition of resistance is of concern not only for pathogenic bacteria from humans. For foodstuffs, reports from the Swiss Federal Institute of Technology Zurich (ETH Zurich) indicated that lactic bacteria found in cheese had likely accumulated resistance genes originating from other pathogenic micro-organisms, such as *Listeria, Staphylococcus, Enterococcus.*[19] These findings generated much concern in Switzerland, and a "co-ordination group for antibiotic-resistant micro-organisms" of representatives of the FOPH, FVO, the Federal Office for Agriculture, research institutes and universities and the Federal Office for External Economy Affairs (now State Secretariat of Economic Affairs, or SECO) mandated working groups to conduct a global analysis of the resistance situation. In the final report, the co-ordination group recognized the lack of knowledge on this field in Switzerland and recommended the launch of an extensive research programme to fill the gap.[20]
Partially in response to that report, in June 1999 the Federal Council approved National Research Programme 49: "Antibiotic resistance". NRP 49 was intended 1) to deliver a situational analysis of the antibiotic resistance burden in Switzerland and increased knowledge of the associated risks, 2) to establish the scientific basis for initiating appropriate preventive measures, 3) to give insight into the economic, legal and ethical aspects of antibiotic resistance, and 4) to promote fundamental research towards developing new antibiotics.
The National Research Programme "Antibiotic Resistance" represents also Switzerland's counterpart to what is being done abroad at the request of the World Health Organization. It aimed to provide specific responses to the situation in the country, while co-operating at an international level (in particular with the European Union). Bacteria, after all, do not respect national borders!

Goals of NRP 49 "Antibiotic Resistance"

The National Research Programme "Antibiotic Resistance" (NRP 49) was launched in 2001 with the intention to:
- develop scientific strategies and new methods for a prospective resistance surveillance system;
- analyse resistance in Switzerland, in all affected areas (human and animal populations, livestock production, food production and the environment);
- determine the spread of resistant bacteria and resistance genes, and assess the risk posed by the emergence of resistance for medical treatment options;
- promote molecular studies of bacterial resistance with a view to promoting the development of new antibiotics and new methods of *in vitro* detection;
- evaluate the social, legal and economic consequences of antibiotic resistance and make recommendations for new regulations on the use of antibiotics.

Over a 5-year period, 27 research projects, grouped in three research areas (human and veterinary medicine, surveillance and environment; molecular biology; society, law and economics) were selected for inclusion in the programme in order to achieve the multidisciplinary objectives.

[19] Perreten V, Schwarz F, Cresta L, Boeglin M, Dasen G, Teuber, M. Antibiotic resistance spread in food. Nature. 1997;389:801-802. ; and: Teuber M., Perreten V, and Wirshing F. Antibiotikum resistente Bakterien. Eine Neue Dimension. *Lebensmitteltechnologie.* 1996;29:182-198.

[20] Bakterielle Antibiotikaresistenz in den Bereichen Humanmedizin, Veterinärmedizin und Lebensmittel – Eine Situationsanalyse der "Koordinationsgruppe antibiotikaresistente Mikrooganismen". BAG, 15. Juni 1999.

Steering Committee of NRP 49

President
Prof. Dr. Jean-Claude Piffaretti, Istituto Cantonale di Microbiologia, Bellinzona

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Prof. Dr. Patrice Courvalin, Institut Pasteur de Paris, Unité des agents antibactériens, Paris
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PD. Dr. Pierre-Alain Raeber, Federal Office of Public Health, Bern
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Prof. Dr. Michael Teuber, Institute of food science, Swiss Federal Institute of Technology, Zurich
Dr. Sandra Nocera, Institute of Social and Preventive Medicine, University of Zurich

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Dr. Francesco Lurati, Faculty of Communication Sciences, University of Lugano

Delegate of the Research Council, Division IV, SNSF
Prof. Dr. Felix J. Frey, Division of Nephrology and Hypertension, Inselspital, University of Bern

Programme coordinator
Dr. Barbara Flückiger Schwarzenbach, Secretariat of Division IV, Swiss National Science Foundation, Bern

Structure of the report

The report is divided into sections corresponding to the three research areas mentioned above. Each section considers the specific objectives of the programme, the outcomes achieved by the NRP 49 research, the situation at the end of the programme and recommendations addressed to the specific authorities, organisations or associations concerned. For convenience, a summary of all of the recommendations is provided in section 5. Following the concluding remarks, the final section proposes a vision after NRP 49 with the establishment in Switzerland of a National Antibiotic Resistance Centre. Indeed, the aim of NRP 49 was not only to stimulate scientific research but also to look towards future dealing with this issue in Switzerland. The problem of antibiotic resistance will not resolve itself on its own!

The accompanying CD-ROM contains this final scientific report, the details of the results of each project supported by NRP 49 and other documents. Clicking on the blue hyperlinks (listing the name of the project leader) in the final report on the CD-ROM takes the reader directly to the different projects and descriptions of the findings.

The projects

Research field Human and veterinary medicine, surveillance and environment

Occurrence of human-use antibiotics and antibiotic resistance in the aquatic environment (HUMABRA)

4049-063273, 01.07.2001-30.09.2006
Prof. Dr. Walter Giger, EAWAG, Swiss Federal Institute of Aquatic Science and Technology, Ueberlandstrasse 133, 8600 Dübendorf

An interventional study to evaluate the impact of a rapid on-admission screening strategy in preventing nosocomial MRSA infection

4049-106294, 01.07.2004-31.01.2007
PD Dr. Stephan Harbarth, Service Prévention et Contrôle de l'Infection, Direction médicale, Hôpitaux Universitaires de Genève (HUG), 24, rue Micheli-du-Crest, 1211 Genève 14

Antibiotic resistance genes in food: Molecular identification and transfer between micro-organisms (ABRFOOD)

4049-063242, 01.07.2001-31.12.2004
Prof. Dr. Leo Meile, Institut für Lebensmittel- und Ernährungswissenschaften (ILW), Labor für Lebensmittelbiotechnologie, ETHZ, Schmelzbergstrasse 7, 8092 Zürich

Sentinel surveillance of antibiotic resistance in Switzerland (SEARCH)

4049-063269, 01.01.2001-31.12.2007
Prof. Dr. Kathrin Mühlemann, Institut für Infektionskrankheiten, Universität Bern, Friedbühlstrasse 51, 3010 Bern

Role of residual antibiotics in aquatic environments on selection and diffusion of bacterial resistances (RASDI)

4049-063257, 01.10.2001-30.09.2005
Prof. Dr. Raffaele Peduzzi, Istituto Cantonale di Microbiologia, via Mirasole 22A, 6500 Bellinzona

Assessment of antibiotic use and antibiotic resistance in long-term care facilities

4049-063276, 01.10.2001-31.01.2007
Prof. Dr. Christian Ruef, Spitalhygiene HAL 14C, Klinik für Infektionskrankheiten und Spitalhygiene, Universitätsspital Zürich, Rämistrasse 100, 8091 Zürich

Evolution of macrolide resistance of enterococci isolated from faeces of calves fed with antibiotic contaminated milk

4049-063236, 01.03.2002-29.02.2004
Prof. Dr. Melchior Schällibaum, Agroscope Liebefeld-Posieux Eidg. Forschungsanstalt für Nutztiere & Milchwirtschaft (ALP), Schwarzenburgstrasse 161, 3003 Bern

Induction and spread of antibiotic resistance in livestock

4049-063282, 01.10.2001-30.06.2006
Dr. Christian Stamm, EAWAG, Das Wasserforschungs-Institut des ETH-Bereichs, Ueberlandstrasse 133, 8600 Dübendorf

Development of an optimal strategy for monitoring antimicrobial resistance in bacteria from food animals in Switzerland

4049-063244, 01.07.2001-31.08.2006
Dr. Katharina Stärk Spallek, Bundesamt für Veterinärwesen (BVET), Schwarzenzenburgstrasse 161, 3003 Bern

Research field Molecular biology

Genetic basis of glycopeptide resistance in Staphylococcus aureus

4049-063201, 01.01.2002-31.08.2005
Prof. Dr. Brigitte Berger-Bächi, Universität Zürich, Institut für Medizinische Mikrobiologie, Gloriastrasse 32, 8006 Zürich

Identification of ribosomal mechanisms mediating drug resistance

4049-064554, 01.01.2002-30.06.2006
Prof. Dr. Erik Christian Böttger, Universität Zürich, Institut für Medizinische Mikrobiologie, Gloriastrasse 32, 8006 Zürich

Rapid characterisation of methicillin-resistant Staphylococcus aureus clinical isolates for an improved drug prescription

4049-106296, 01.11.2004-31.10.2006
Prof. Dr. Patrice François, Laboratoire de Recherche Génomique, Service des Maladies Infectieuses, Hôpitaux Universitaires de Genève, 24, rue Micheli-du-Crest, 1211 Genève 14

Antimicrobial resistance in Bacilli, transfer and detection

4049-067448, 01.03.2002-28.02.2005
Prof. Dr. Joachim Frey, Institut für Veterinärbakteriologie, Universität Bern, Länggassstrasse 122, 3012 Bern

Effect of teicoplanin resistance on host response to Staphylococcus aureus

4049-106295, 01.07.2004-31.08.2006
Prof. Dr. Regine Landmann-Suter, Departement Forschung, Abteilung Infektiologie, Universitätsspital Basel, Hebelstrasse 20, 4031 Basel

Targeting tuberculosis inside its host cells

4049-063237, 01.04.2002-31.03.2006
Prof. Dr. Jean Pieters, Biozentrum, University of Basel, Abt. Biochemie, Klingelbergstrasse 70, 4056 Basel

Molecular evolution of pathogenicity and resistance in Escherichia coli

4049-063270, 01.09.2001-31.12.2005
Prof. Dr. Jean-Claude Piffaretti, Istituto Cantonale di Microbiologia, via Mirasole 22A, 6500 Bellinzona

Resistance of the fungal pathogen Aspergillus fumigatus to antifungal agents

4049-063256, 01.07.2001-30.06.2006
Prof. Dr. Dominique Sanglard, Institut de Microbiologie de l'Université de Lausanne, Rue du Bugnon 44, 1011 Lausanne

Overcoming intrinsic multidrug resistance to discover and expand the repertoire of antibiotics active against mycobacterial pathogens

4049-069384, 01.10.2002-31.03.2006
Prof. Dr. Charles J. Thompson, Prof. Dr. Stephan Grzesiek, Biozentrum, University of Basel, Division of Molecular Microbiology, Klingelbergstrasse 70, 4056 Basel

Novel approaches to detect and circumvent antibiotic resistance in Pseudomonas aeruginosa

4049-063239, 01.10.2001-30.09.2006
Dr. Christian van Delden, Département de Médecine, Division des Maladies Infectieuses, Hôpital Cantonal Universitaire, 24, rue Micheli-du-Crêt, 1211 Genève 1

Mechanisms of glycopeptide resistance in staphylococci

4049-063250, 01.10.2001-30.09.2004
Dr. Pierre Vaudaux, Division des Maladies Infectieuses, Hôpital Cantonal Universitaire de Genève, 24, Rue Micheli-du-Crest, 1211 Genève 14

Research field Society, law and economics

Economic analysis of outpatients' antibiotic consumption in Switzerland

4049-101253, 01.11.2003-31.01.2007
Prof. Dr. oec. publ. Massimo Filippini, Istituto di Finanza, Facoltà di economia, Università della Svizzera italiana, via Giuseppe Buffi 13, 6900 Lugano

Biological terrorism and crisis management in Switzerland – Lessons learned from the anthrax alert and steps ahead

4049-069385, 01.01.2003 – 31.12.2004
Dr. Jan Metzger, Forschungsstelle für Sicherheitspolitik ETH Zürich, Swiss Federal Institute of Technology, 8092 Zurich

Towards judicious use of antibiotics by doctors and patients

4049-065786, 01.05.2001-31.10.2006
Prof. Dr. Peter Schulz, Institute of Communication and Health, Facoltà di scienze della comunicazione, Università della Svizzera Italiana, Via Giuseppe Buffi 13, 6900 Lugano

Prediction and predictability of resistance to antibiotics: Studies based on coupled map lattices

4049-063267, 01.07.2001-30.06.2004
PD. Dr. John Shiner, Bergacher 3, 3325 Hettiswil

Legal implications of antibiotic resistance: Analysis of Swiss legislation and comparative law (D, F, UK)

4049-103165, 01.03.2004-30.09.2006
Prof. Dr. jur. Dominique Sprumont, Institut de droit de la santé, Université de Neuchâtel, Avenue du 1er-Mars 26, 2000 Neuchâtel

Individual decision on antibiotic treatment. A case for utility assessment

4049-063278, 01.07.2001-30.04.2006
Prof. Dr. Dominik Uehlinger, Klinik und Poliklinik für Nephrologie und Hypertonie, Universität Bern, Inselspital, Freiburgstrasse 3, 3010 Bern

Use of antibiotics in Switzerland: Investigation of a monitoring system

4049-112739, 01.10.2005-30.09.2006
MD Giorgio Zanetti, Service of Infectious Diseases and Division of Hospital Preventive Medicine, University Hospital, 46, Bugnon Street 1011 Lausanne

Human and veterinary medicine, surveillance and environment

2. Human and veterinary medicine, surveillance and environment

Summary
One of the main goals of NRP 49, the National Research Programme "Antibiotic resistance", was to analyse the burden of antibiotic resistance in Switzerland in all areas where antibacterial agents are used, i.e. human and veterinary medicine, agriculture, food production and the environment, and to increase knowledge on the associated risks.
The projects selected to cover these fields highlighted relevant aspects of the problem of antibiotic resistance in Switzerland and provided valuable practical applications and recommendations. The data that will be collected by the monitoring programmes on antibiotic resistance in Switzerland for both bacteria isolated from human clinical samples (SEARCH) and for bacteria isolated from animals for food consumption, as well as the data on antibiotic consumption in Switzerland (at the hospital and community level) are of central importance. In particular, they will allow the dynamics of antibiotic resistance and consumption to be followed, providing the ideal basis for an early establishment of preventive measures and control protocols.
Particularly useful in this context was the development of new molecular tools for better identification of resistant micro-organisms that represent a special challenge to human health (i.e. MRSA) and for rapid and complete identification of antibiotic resistance genes in highly pathogenic bacteria, like *B. anthracis,* or in other gram-positive bacteria, such as those found in starter and probiotic cultures used in food production. These well-designed methods resulted from close cooperation between molecular biologists, food microbiologists, epidemiologists and health care professionals directly confronted with infectious diseases.
In veterinary medicine, although the resistance situation in bacteria isolated from Swiss livestock seems to be favourable, some particular situations concerning antimicrobial resistance are of concern and definitely need further monitoring.
However, concrete effects of the extensive use of antibiotics in animal production could be detected through analysis of ready-to-eat food products (meat and cheese) and starter and probiotic cultures on the Swiss market. These products were shown to contain resistance genes that might be a concern for consumers' health.
At the environmental level, we now dispose of new analytical methods that allow accurate and sensitive analysis of the presence and fate of the most important classes of both human and veterinary antibiotics in the environment (soils, wastewaters, sewage sludge and ambient waters). These methods made it possible to recognize potential hazardous situations concerning the presence of antibiotics in the environment and their potential effects on the persistence, emergence and spread of antibiotic resistant bacteria.

2.1. Human medicine and surveillance

2.1.1. Objectives of NRP 49

In Switzerland, as elsewhere, concerned parties (i.e. public health authorities and specialists in such areas as human medicine, internal medicine and surgery, infectious disease specialists, veterinary medicine, the food industry and agriculture) are alarmed by the serious threat posed by the emergence and spread of bacterial resistance to antibiotics. However, the global situation of resistance in our country is not well known. Therefore, the research foci of NRP 49 in the area of human medicine were the following:

- Develop a surveillance and alarm system for pathogenic and commensal antibiotic resistant human isolates, allowing a global view of the resistance situation and its dynamics for Switzerland as a whole. This surveillance system should allow identification of the emergence of resistance and control of its spread.
- Obtain data on the consumption of antibiotic substances in Switzerland in quantitative terms.
- Obtain data on the current resistance situation in Switzerland with reference to pathogenic, non-pathogenic and commensal bacteria and determine the risk factors for infection and colonisation by resistant bacteria in human and veterinary medicine.
- Develop new and rapid methods of *in vitro* detection of resistance, supporting development of strategies for detecting the emergence and spread of resistance.

Eight projects addressing these issues were selected for funding. In particular, one project, the most significant, aimed to establish a sentinel surveillance system of antibiotic resistance in human isolates in Switzerland. Two other projects planned to collect data on the state of antibiotic consumption in both hospitals and the community (one of these projects is considered in the section on "Society, law and economics"). Since most elderly persons spend the last years of their lives in nursing homes and long-term care facilities (LTCFs), one project focused on the use of antimicrobial agents in LTCFs and their role in promoting antibiotic resistance. Three projects aimed to develop new methods to improve surveillance and contact tracing of patients infected by MRSA (methicillin-resistant *Staphylococcus aureus*), the most challenging and feared antibiotic-resistant organism in the hospital setting. Another project aimed to study resistance among gram-positive bacteria, to which important human and animal pathogens belong, as well as bacteria used in food preparation and animal farming.

2.1.2 Outcomes of NRP 49

2.1.2.1 Surveillance of antibiotic resistance

Despite the fact that antibiotic resistance is on the rise, current surveillance of antibiotic resistance is clearly insufficient in Switzerland. A considerable number of studies were conducted in the past to assess resistance in human medicine; however, many of them were conducted by pharmaceutical companies. Because they generally focused on a specific city, hospital or region and on only a few pathogenic bacteria, they are not representative of the situation in Switzerland. In addition, being limited in time, the studies do not allow the monitoring of the emergence and spread of resistant strains. Thus, even considering only the area of human medicine, the overall situation of resistance in Switzerland, though perceived as still acceptable but potentially problematic, is not documented with hard data, in particular not with data concerning the dynamics of resistance. As to antibiotic consumption, except for market-oriented data on manufacturers' sales that are available from a private provider, there are at present no means to obtain independent data on antibiotic consumption. Since there can be a time lag between the use of antibiotics and the appearance of resistance, surveillance systems for both antibiotic resistance and antibiotic consumption are needed. Only joint data originating from both monitoring activities would allow us to better understand the driving forces of resistance, to obtain data to be used in models predicting the evolution of resistance and to provide support for the choice of interventions aimed to prevent or counteract antibiotic resistance and to check the efficacy of such measures. The outcomes of the projects selected to cover these needs can be summarised as follows:

K. Mühlemann

Project Sentinel surveillance of antibiotic resistance in Switzerland (SEARCH)

Undoubtedly, the most important outcome of NRP 49, and one that is already operational, is the **Sentinel surveillance of antibiotic resistance in Switzerland (SEARCH)**. Due to its complexity, the monitoring system has taken a long time to develop and implement. Because it was planned that all the data would be sent from the laboratories to the SEARCH centre in Bern, the informatic systems of a number of different laboratories first of all had to be made compatible! The main features of SEARCH are the following:

– Data on antibiotic resistance in pathogenic and commensal human isolates will be sent regularly to SEARCH by 22 linked medical microbiology laboratories representing the major public and private medical microbiology laboratories presently operating in Switzerland: SEARCH will cover 60% of all hospital patients and 30% of all practicing medical doctors in Switzerland. Because of the broad coverage of bacteria, epidemiological indicators and hospitalised as well as community patients, the collected data will be highly representative of the resistance situation of human isolates in the country. In particular, the regular input of data will provide a constant

up-to-date and global view of antibiotic resistance in Switzerland and a view of the dynamics of resistance. The system will be fully operational by April 2007. The preliminary results obtained so far for the years 2004, 2005 and 2006 indicate a relatively low rate of resistance in Switzerland but an increasing resistance trend and significant differences in resistance levels in distinct geographical regions.

M. Filippini

- Antibiotic sales (data for the years 2002 to 2005 purchased from IMS health GmbH, Hergiswil, Switzerland) and consumption data (see M. Filippini and G. Zanetti projects) can be analysed within the SEARCH database.

G. Zanetti

- The database will also be linked with the European database EARSS (European Antimicrobial Resistance Surveillance System) once the database is representative (spring 2007).
- A SEARCH Web site will be accessible at www.search.ifik.unibe.ch (spring 2007), providing public access to aggregated resistance data.

The SEARCH surveillance system will provide the ideal basis for early detection of problematic situations, allowing prompt reactions with the establishment of specific preventive measures. In addition, it will allow monitoring of the success of the control measures. It is important to note that particular care was taken to assure the data protection of all patients whose data are sent to the SEARCH system.

G. Zanetti **Project** **Sentinel monitoring of antibiotic use in Switzerland**

Two sentinel networks for the assessment of antibiotic use were designed for:

- **Public acute care hospitals** (period 2004-2005). Data were gathered by hospital pharmacists and covered 50 (49 for 2004 data) of the 158 Swiss public acute care hospitals, thus representing 49% of all beds in this category.
- **The community** (as opposed to hospitals) (period 2002-2004). Data collection was based here on the details of the prescriptions reimbursed by health insurance companies of the patients of a sentinel group of primary care physicians. The prescriptions were available through the billing data of the Swiss Association of Pharmacists elaborated by the "Office de Facturation" (OFAC, Geneva). For particular and confidentiality reasons, this part of the project was limited geographically to the Cantons of Fribourg, Valais, Neuchâtel, Geneva, Jura and Vaud.

Findings from the sentinel networks showed similar trends compared with the data purchased from a private provider of health market data based on manufacturers' sales (IMS Health GmbH, Hergiswil). The sentinel networks based on either hospital or community pharmacies thus provide reliable antibiotic use data and allow in-depth analyses and comparisons of the prescription patterns. Furthermore, the collected data can be analysed within the SEARCH system. The pilot projects can be extended to represent a larger proportion of hospitals and practitioners, thus gaining in accuracy.

2.1.2.2 Long-term care facilities (LTCFs)

In Switzerland the elderly segment of the population continues to grow. Most elderly persons spend the last years of their lives in nursing homes and long-term care facilities (LTCFs). However, little is known about the use of antimicrobial agents in LTCFs and their role in promoting antibiotic resistance. The outcomes of the project examining these questions can be summarised as follows:

C. Ruef **Project** **Assessment of antibiotic use and antibiotic resistance in long-term care facilities**

In the long-term care facility (LTCF) investigated (in the Zurich area), antibiotic use was not found to be the driving force in the increase of antibiotic resistance. This increase was the result of the spread of several clones of *E. coli* with resistance to one or several antibiotics among the residents. Furthermore, contrary to what is often believed, MRSA or VRE (vancomycin-resistant enterococci) were not commonly found to colonize or infect patients in the LTCF examined. As the study considered only one LTCF, the findings can unfortunately not be generalised.

2.1.2.3 Methicillin-resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus (SA) is one of the major infectious pathogens. The emergence of methicillin-resistant (MRSA) and especially multidrug-resistant *S. aureus* strains poses serious clinical and health management problems. Infection control programmes have been repeatedly called into question, partly because of the increasing reservoir of nosocomial MRSA, the impossibility to eradicate endemic MRSA and the significant costs and discomfort in patient care associated with surveillance, control and intervention measures. Control of community MRSA represents an additional challenge for the future, requiring new methods for improved surveillance, contact tracing, education and treatment of infected cases as well as their colonised relatives. The outcomes of the projects that addressed the burden of MRSA can be summarised as follows:

P. François — **Project** **Rapid characterisation of methicillin-resistant *Staphylococcus aureus* clinical isolates for an improved drug prescription**

This molecular biology project was designed to meet an important need of epidemiologists and health care professionals facing the burden of MRSA hospital infections. The project developed and validated a fast and reliable genotyping method for a real-time epidemiologic characterisation of these isolates. The concomitant establishment of the related database containing numerous strains from all geographical or epidemiological origins allows typing of unknown or newly identified strains (whatever their origin). This tool will be an aid in following the dynamics of MRSA infections for the purpose of developing rapid control measures and guiding clinicians in identifying patients at high risk of infection with these highly resistant strains. The new genotyping assay for real-time epidemiology and genotyping of MRSA is rapid and cost-effective. Using this method, it was shown that, in contrast to other European Countries showing a limited number of CA-MRSA (community acquired MRSA) clonetypes, the area of Geneva appears to be exposed to numerous importation events.

S. Harbarth — **Project** **An interventional study to evaluate the impact of a rapid on-admission screening strategy in preventing nosocomial MRSA infection**

The use of a rapid, cost-effective, on-admission screening method for MRSA based on most advanced molecular techniques allowed rapid screening of admitted patients. The excellent compliance allowed the screening of 93% of admitted patients. Without on-admission screening, a majority of MRSA patients (77%) would have been missed, because they were not previously known as MRSA carriers. However, the rapid MRSA screening upon admission failed to decrease healthcare-associated MRSA infections, for only a small decrease in MRSA colonisation was observed. The number of severe surgical site infections was not reduced and remained stable across the study phases. Thus, in endemic settings, rapid on-admission screening for MRSA may not be helpful to reduce the burden of nosocomial MRSA infections in surgery.

P. Vaudaux — **Project** **Mechanisms of glycopeptide resistance in staphylococci**

This molecular biology project identified a simple, reliable and low-cost screening assay for MRSA exhibiting intermediate susceptibility to vancomycin and teicoplanin (glycopeptide intermediate *S. aureus* (GISA)). The method proposed has important practical advantages for:

- clinical microbiology laboratories, because it can be implemented easily and would help to minimise the risk of missing potential GISA or even highly resistant GISA isolates;
- any hospital setting, since it can be used for prospective screening for decreased susceptibility to glycopeptides of *S. aureus* isolates.

2.1.2.4 Resistance among gram-positive bacteria

Among the gram-positive bacteria, we can find important human and animal pathogens as well as bacteria used in food preparation and animal farming (i.e. probiotics). The intensive use of antibiotics in both human medicine and animal husbandry has led to the emergence of antibiotic resistance in some of these micro-organisms. However, little is known about the extension of this phenomenon in gram-positive organisms, and new and efficient methods for detecting antibiotic resistance are urgently required for implementation of surveillance and prevention protocols. The outcomes of the NRP 49 project dealing with these concerns can be summarised as follows:

J. Frey

Project Antimicrobial resistance in Bacilli, transfer and detection

This project is another example of methods developed by molecular biologists with practical applications for analytical and surveillance purposes. The project developed and validated a microarray-based system for the detection of antibiotic resistance genes in gram-positive bacteria including highly pathogenic bacteria (i.e. *Bacillus anthracis*). The method is suitable for rapidly evaluating and surveying the antibiotic resistance gene situation in gram-positive bacteria. In a collaboration study, it was used to screen food products for the presence of antibiotic resistance genes (see L. Meile project). Ready-to-eat food products and starter and probiotic cultures on the Swiss market were shown to be a reservoir for antibiotic resistance genes.

L. Meile

2.1.3 Situation at the end of NRP 49

Although we do not have yet the data on the real situation of antibiotic resistance in Switzerland, we are now in a position to produce them very shortly (April 2007). Indeed, we are already benefiting in Switzerland from the unique and very efficient **sentinel surveillance of antibiotic resistance (SEARCH)** programme. Data on antibiotic resistance in pathogenic and commensal human isolates will be sent regularly to the SEARCH programme by 22 linked medical microbiology laboratories. The collected data will therefore be highly representative of the resistance situation of human isolates in Switzerland. In particular, the regular input of data will provide a constant, updated view of antibiotic resistance in Switzerland as a whole or broken down according to different geographical regions and will allow the dynamics of resistance to be followed in real time. This surveillance system provides the ideal basis for early detection of problematic situations, allowing prompt reactions with the implementation of specific preventive measures. In addition, it will allow the monitoring of the success of the control measures. A public Web site will be accessible at www.search.ifik.unibe.ch by spring 2007.

Besides continuous monitoring of antibiotic resistance (SEARCH), it is essential to continue the established **sentinel networks for monitoring of antibiotic consumption** based on delivery data from both hospital and community pharmacies. Monitoring of antibiotic use is indispensable if the aim is interventions for a more judicious use of antibiotics, which would preserve the efficacy of current antibiotics and possibly prevent resistance problems.

As to the situation related to **long-term care facilities,** the limited data collected unfortunately do not allow any general conclusions to be drawn.

In close cooperation with molecular biologists, new tools were developed for a better identification of resistant micro-organisms representing particular challenges for human health. In particular, for **methicillin-resistant *Staphylococcus aureus*** (MRSA), we now have a rapid and efficient screening method for the detection of strains with decreased susceptibility to glycopeptides (GISA). Thanks to NRP 49, we dispose also of a rapid method for a real-time epidemiological typing of unknown or newly identified MRSA strains, optimised to ensure rapid turnaround time (4 hours, >100 strains/day)

and at moderate costs (<4–5 CHF/strain), as well as another method for the rapid assessment of the MRSA status of patients at hospital admission. However, the utility and the accuracy of these achievements must be constantly assessed, updated and linked to epidemiological and surveillance tools for controlling the spread of these multiresistant organisms. In fact, in the prevention and treatment of MRSA infections, only strategies that consider the evolution and dynamic of MRSA infections and MRSA strains will be successful for patient management (a really challenging task – in particular for the emergence in the community of new strains of MRSA causing skin and soft tissue infections in otherwise healthy people). Further, we also now have at our disposal new tools that allow the detection of specific antibiotic resistance genes in specific organisms (see

J. Frey

J. Frey and V. Perreten project). In particular for the group of the **gram-positive bacteria,** which include important human and animal pathogens as well as bacteria used in starter and probiotic cultures in food production, the assay allows rapid tracking of newly emerging resistance genes and the detection of silent resistance genes that might be turned on *in vivo* or spread to other bacteria. This tool has already found application in the screening of food products for the presence of antibiotic resistance genes that

L. Meile

could reach consumers directly through the food chain (see L. Meile project), and it is used for surveillance of antibiotic resistance genes in the animal hospital of Bern. The microarray-based method has been shown to be useful in the detection of antibiotic resistance genes that were transferred into avirulent strains of *Bacillus anthracis,* and it demonstrated that field strains did not harbour antibiotic resistance genes.

To conclude this section on the research field of human medicine and surveillance, it is useful also to summarise the findings relevant for human medicine but referred to in other sections of this scientific report. For *Pseudomonas aeruginosa,* a quantitative real-time PCR for the analysis of antimicrobial resistance gene expression was developed, which has already proved to be useful in detecting the timing of resistance appearance and the underlying resistance mechanisms, thus helping to optimisse antibiotic therapy

C. van Delden

(see C. van Delden project). In *Legionella pneumophila,* a waterborne organism that can cause severe infections with a mortality rate of about 10%, a high level erythromycin resistance mutation was identified and a real-time assay for its rapid detection was

R. Peduzzi

developed (see R. Peduzzi project). Finally, for the mould *Aspergillus fumigatus,* there are at the present time are no particular problems in terms of antifungal drug resistance in Switzerland, and voriconazole was confirmed as the most active agent in both clinical

D. Sanglard

and environmental isolates (see D. Sanglard project).

2.1.4 Recommendations

Politicians/Federal authorities

Most European countries, including Switzerland's neighbouring countries Austria, Germany, Italy and France, have responded to the growing threat of antimicrobial resistance by setting up national surveillance systems and by co-operating internationally in the context of the European Antimicrobial Resistance Surveillance System (EARSS) and the European Surveillance on Antimicrobial Consumption (ESAC). The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA), the Danish Integrated Antimicrobial Resistance and Research Programme (DANMAP) and the National Antimicrobial Resistance Monitoring System (NARMS) in the United States are just three of a number of institutions that have been established in different countries to deal with the problem.

Clearly, in Switzerland (which, thanks to NRP 49, is now a participating country in the ESAC, European Surveillance of Antimicrobial Consumption) continuation of the monitoring of both antibiotic resistance and antibiotic consumption in the long term has to be secured after the completion of NRP 49: this is a main concern of the NRP 49 Steering Committee. In fact, given the complexity of the matter, the many areas involved and the still open questions, ending monitoring would entail great and unforeseeable risks. It is the opinion of the NRP 49 Steering Committee that the best way to secure

monitoring and to bring together a team of experts to deal with the data collected is to create a **national antibiotic resistance centre** in Switzerland (see section 7, Vision after NPR 49: A National Antibiotic Resistance Centre). Through continuous monitoring and data collection (including additional data at the regional and local level) on antibiotic resistance and antibiotic consumption, the centre would serve as the indispensable link for clinicians, veterinarians, consumers, authorities, politicians and policy makers in different sectors such as public health, agriculture and the pharmaceutical industry.
To conclude, surveillance of antimicrobial resistance on a national as well as international level is a political necessity in the context of the state's public health mandate in most European countries. Creating a national antibiotic resistance centre in Switzerland is now an unavoidable step.

Long-term care facilities (LTCFs)
The NRP 49 outcomes of a study of a single long-term care facility (LTCF) produced the recognition that LCTFs in Switzerland are most likely not surveyed regarding the prevalence of nosocomial infections, the use of antibiotics and antibiotic resistance. Furthermore, the results clearly indicate that to control antibiotic resistance in facilities of this kind, greater emphasis should be placed on the prevention of spread through implementation of new or improved infection control measures (i.e. improve compliance with hand hygiene, improve diagnostic efforts in the workup of patients with suspected urinary tract infections). In particular, highly recommended is the establishment of a simplified nosocomial infections prevalence or incidence surveillance system to be used in LTCFs. This would allow comparisons between institutions and also the monitoring of resistance rates and the prevalences of pathogens with particular resistance patterns such as MRSA (see C. Ruef project).

C. Ruef

2.2 Veterinary medicine: From livestock production to food products

2.2.1 Objectives of NRP 49

Although the use of antimicrobials for growth promotion in food-producing animals has been officially banned in Switzerland since July 1999, antibiotics are still widely used for prophylactic and treatment purposes in animals. The use of antimicrobials in farming may therefore lead to food-producing animals harbouring antibiotic resistant bacteria. Obviously, the consumption of products made from these animals may be relevant for humans with regard to infection by resistant micro-organisms, pathogenic or not. Alternatively, the presence of resistant bacteria and resistance encoding genes in animals may play a significant role in their spread in the environment as well as in food derived directly or indirectly from animal products. The worldwide increase of foodborne infections with antibiotic resistant pathogens is of growing concern and has been identified by WHO as an emerging public health problem. Unfortunately, in Switzerland no precise information on the occurrence of resistant bacteria in food animals or on antibiotic consumption (e.g. species and amount) in livestock production is currently available. This situation is regrettable, since it does not allow estimation of possible risks for consumers and may well trigger insecurity on a hot topic like food safety. In order to avoid this situation and to contribute to the knowledge on the occurrence of resistant bacteria in food animals and food products and on antibiotic consumption in livestock production – and their possible impacts for human health – the goals of NRP 49 were to:

- Analyse the current resistance situation in Switzerland with reference to pathogenic, non-pathogenic and commensal bacteria of animal origin.
- Determine the consumption of antibiotic substances in livestock production in Switzerland in quantitative terms.
- Investigate possible methodological issues relative to a surveillance system allowing identification of the emergence and control of the spread of resistance, including resistance genes, in livestock production and in the food chain.

- Develop new methods for *in vitro* detection of resistance (including resistance genes).
- Establish possible relationships between resistances in the various areas (human beings, animals, environment, including foodstuffs).
- Determine the risk factors for infection and colonisation by resistant bacteria in human and veterinary medicine.

To fulfil these goals, the National Research Programme launched two lines of research. The first line was aimed at obtaining detailed information on the occurrence of resistant bacteria in food animals and on antibiotic consumption in livestock production and at developing an optimal strategy to monitor antimicrobial resistance in food animals. Since on traditional Swiss dairy farms calves and milking cows are usually kept together in the same barn, NRP 49 selected a research project that would ascertain whether the feeding of calves and pigs with milk from cows treated with antimicrobials may select for the emergence of resistant bacteria or resistance genes in the fed animals. In the second research line, a project was selected that would test foodstuffs available on the market for the presence of resistant bacteria and their encoding genes. The ultimate goal of this project was to help to establish measures to increase food safety by the elimination or reduction of resistance organisms or genes from foodstuffs.

2.2.2 Outcomes of NRP 49

2.2.2.1 Antibiotic resistance in livestock production

K. Stärk Spallek

Project Development of an optimal strategy for monitoring antimicrobial resistance in bacteria from food animals in Switzerland

This project delivered a cost-effective monitoring programme for bacterial resistance in poultry, pig and cattle production. With a simulation model, the sampling strategy (the number of samples to be taken and the respective step in the production line) was optimised taking into account the costs for sample collection, transportation and the representativeness of the laboratory analysis. The model allows determination of the optimal and cost-effective sampling strategy for given bacterial species and antibiotics to be monitored. The project also delivered baseline data on the resistance situation in food animals in Switzerland: at present, compared to the situation abroad, the resistance situation in Swiss livestock appears to be favourable. In particular, the project focused on *Campylobacter,* the most frequently reported zoonotic pathogen causing human illnesses in Switzerland, and determined the following:

- Poultry farming: At retail the resistance situation in strains isolated from raw poultry meat produced in Switzerland is acceptable. In fact, the prevalence of *Campylobacter spp.* in live animals decreased from 2002 to 2003 and was stable in 2004 (41.6% in 2002, 24.1% in 2003 and 25.6% in 2004). The prevalence of *Campylobacter spp.* isolates with resistance to more than one antibiotic decreased significantly from 2002 to 2004 (8.4% in 2002, 7.6% in 2003 and 3.7% in 2004). However, the observation of 19% ciprofloxacin resistant isolates in poultry meat is of concern; this needs further monitoring. In foreign meat production, a significantly higher prevalence of *Campylobacter* resistant isolates against ciprofloxacin, ampicillin and tetracycline was found compared to Swiss meat production. Further, *Campylobacter spp.* isolates from meat labelled as animal-friendly were less likely to be resistant than isolates from conventional production.
- Pig farming: As compared to traditional farms, a decrease in antibiotic resistance in *Campylobacter* isolates from the faeces of Swiss "animal-friendly" pig fattening farms (20% resistance to fluoroquinolones, versus 31% in traditional farms) as well as a reduction in the number of isolates with three or more resistances (less than 20% in animal friendly, versus about 30% in traditional farms) was observed.
- Cattle farming: Fresh beef sampled in 2005 at retail showed a very low prevalence of *Campylobacter* and indicator bacteria (*E. coli* and *Enterococcus*).

– Genotyping assays showed that *Campylobacter jejuni* can show both a high degree of genetic diversity in one animal species but also closely related isolates originating from different animal species and humans, suggesting the importance of animal reservoirs for human infections (albeit the contribution of different animal sources is difficult to quantify).

C. Stamm **Project Induction and spread of antibiotic resistances in livestock**

This first part of this project dealt with the question of "how to get more precise and reliable data on the use of veterinary antibiotics in Swiss farming". Possible approaches to obtain the data under Swiss (legal) conditions were summarised in a feasibility study.[21] Since then, several of the resulting suggestions have been implemented, and more precise data are available on the use of veterinary antibiotics in Swiss agriculture through:

– Swissmedic, which for 2004 provided more detailed use data (sales data) for the different compound classes.
– farming records, because the legal situation has changed («Tierarzneimittelverordnung, TAMV», valid since January 2004) and farmers have to report not only medications used but also the administered dosages of antibiotics. Unfortunately, researchers generally have no access to these data.

M. Schällibaum **Project Evolution of macrolide resistance of enterococci isolated from faeces of calves fed with antibiotic contaminated milk**

The common practice of using milk produced during antibiotic treatment for feeding calves and pigs was shown to cause a marked selection of resistant bacterial strains (i.e. enterococci). Further assessments are necessary in order to examine the fate of these resistant strains, ultimately to assess if there is any risk of these resistant bacteria entering the food chain.

2.2.2.2 Antibiotic resistance in food

Inappropriate use of antibiotics (overuse) may lead to foodstuffs of animal and plant origin harbouring antibiotic resistant bacteria. There is also a major concern that resistance conferring genes may be transferred from foodstuffs to human intestinal microflora. In order to produce foodstuffs containing low levels of antibiotic resistant bacteria, broad analysis of antibiotic resistance flow is required.

L. Meile **Project Antibiotic resistance genes in food: Molecular identification and transfer between micro-organisms (ABRFOOD)**

Ready-to-eat food, starter and probiotic cultures were shown to be reservoirs of resistance genes. For example, approximately 40% and 60% of the cheeses examined were found to contain erythromycin and tetracycline-resistant enterococci, respectively. However, no vancomycin-resistant enterococci were detected in any sample. The resistant genes could be successfully transferred *in vitro* to other gram-positive hosts, indicating their spread capacity. These findings could be of direct concern for consumers' health. Next, in collaboration with J. Frey and V. Perreten, bacteria from ready-to eat food as well as starter and probiotic cultures were screened for the presence of about 100 resistance genes using a microchip hybridisation assay. This allowed the finding of tetracycline resistance genes in some staphylococci used as meat starters and in probiotic bacteria *Bifidobacterium lactis* and *Lactobacillus reuteri* SD 2112. These findings were not expected, and they are clear indications that probiotic and starter cultures are also antibiotic resistance gene reservoirs.

J. Frey

[21] Spring P, Busato A, Tanner M. Flow of antibiotics in Swiss livestock production: a feasibility study. Schweizerische Hochschule für Landwirtschaft, Zollikofen. 2003 Nov 12.

A new qPCR (quantitative PCR) technique was developed that allowed the quantitative detection of enterococci and tetracycline *tet*(M) and erythromycin *erm*(B) resistance genes in ready-to-eat foods. These three assays are key tools for specifically detecting the copy number of enterococci (genomes), *tet*(M) and *erm*(B) in any environment.

2.2.3 Situation at the end of NRP 49

There is no longer a lack of primary **information on antibiotic consumption in Swiss livestock production.** Swissmedic is now able to provide more detailed data on the veterinary use of the different antibiotic classes. Because of a change in legislation, farmers are now obliged to report in their log-books not only medications used but also the dosages of antibiotics administered.
As compared to other countries, the **resistance situation in bacteria isolated from Swiss livestock** seems to be favourable. However, for *Campylobacter* (the most frequently reported zoonotic pathogen causing human illnesses in Switzerland) some particular situations concerning antimicrobial resistance (i.e. quinolone resistance) are of concern. These definitely need further monitoring along the entire production chain (farm, slaughterhouse and retail), and the surveillance programme should be extended to include imported meats. For these purposes, we now dispose of a cost-effective and well-established **resistance monitoring programme for farm animals in Switzerland,** functioning as an early warning system for the emergence of antimicrobial resistance patterns of human health relevance. In practice, sample collection is co-ordinated by the Federal Veterinary Office (FVO), and susceptibility testing is performed at the National Centre for Zoonoses, Bacterial Animal Diseases and Antimicrobial Resistance (ZOBA) of the University of Bern. Consequently, in case of an increase in the frequency of resistance, proper measures can be taken in time to maintain the effectiveness of antimicrobials and to minimise risks for consumers. Results of the monitoring will be published by the Federal Veterinary Office in the annual *Swiss Zoonoses Report*.
Concerning the **food chain,** ready-to-eat food and starter and probiotic cultures were shown to contain resistance genes, which might be a concern for consumers' health.
Further, the use of milk produced during cows' antibiotic treatment for feeding calves and pigs was shown to trigger a selection of resistant bacterial strains. Yet, with the present data it is not possible to estimate if there is any risk for these resistant strains to enter the food chain. Further assessment of the fate of resistant strains on dairy farms is necessary.

2.2.4 Recommendations

Politicians/Federal authorities/Livestock production/Husbandry
The most effective way to limit potential resistance problems due to the veterinary use of antibiotics would consist in prudent and judicious use of antibiotics to maintain animal health. As confirmed by a number of studies, the use of veterinary antibiotics varies strongly between different farms and the prescribed antibiotic depends on the veterinarian.[22] Furthermore, in farms having and maintaining good herd health status and optimal farm management, the prevalence of antimicrobial resistance is more favourable (see K. Stärk Spallek project). This indicates that there is in fact a substantial potential to minimise the use of veterinary antibiotics by measures to foster animal health. Through providing extensive information to farmers and veterinarians as well as through increased monitoring and control activities, efforts should be undertaken to convince the concerned actors that the use of antibiotics can still be decreased without affecting animal health and production rates.

K. Stärk Spallek

[22] Schaeren W. Antibiotikaverbrauch 2003 und 2004 in der Milchproduktion. *Agrarforschung*. 2006;13(06): 234–239.

M. Schällibaum

On dairy farms, use of milk produced during antibiotic treatment for feeding calves and pigs was shown to select for resistant bacterial strains (see M. Schällibaum project). Thus, it would be wise to advise milk producers not to use antibiotic contaminated milk as animal feed and to find possible alternative destinations for this product.

L. Meile

Politicians/Federal authorities/Food industry
Since ready-to-eat food and starter and probiotic cultures were shown to be resistance genes reservoirs that could directly concern consumers' health (see L. Meile project), a closer look at the live bacteria directly eaten by consumers is mandatory. The federal authorities should define the antibiotic resistance level (e.g. the antibiotic resistance gene copy number) as a food quality parameter. In this way, quantitative assessment of antibiotic resistance genes would be implemented in industrial applications. It is important to note that the European Commission has proposed that live bacteria entering the food chain via animal feed or live and dead bacteria directly consumed by humans should be free of any acquired resistance to antibiotics of importance in clinical and veterinary medicine (see European Commission, Health & Consumer Protection Directorate-General, "On a generic approach to the safety assessment of micro-organisms used in feed/food and feed/food production"[23]).

2.3 Environment

2.3.1 Objectives of NRP 49

About 50% of the antibiotics consumed in Switzerland are used in animal production.[24] These are mainly excreted in urine and faeces in unaltered form. Residues of antibiotics are regularly detected in manure, soil and water (surface water and groundwater are the major sources of water for human and animal consumption). It is important to note that since 1998, in order to minimise the risk to the environment and humans, EU regulations require that environmental risk assessments be conducted for all new antibiotics to be introduced on the market. However, the fate, behaviour and effect of these antibiotics on the environment (ecosystem, agriculture, aquatic bacteria, etc.) and on humans and animals still have to be clarified. It is generally assumed that even small amounts of antibiotics can induce bacterial resistance. The spread of resistant bacteria or the induction of resistance, for instance in the commensal flora of humans and animals, may therefore have serious health consequences (in terms of treatment failures and higher treatment costs). Increased knowledge of the persistence of and the mechanisms responsible for dissemination of antibiotic resistance in the environment is urgently needed. This information is indispensable for an evaluation of the environmental risks generated by antibiotics and in order to produce recommendations concerning elimination/decontamination processes.
To fill these gaps, three research projects were selected for NRP 49. The first aimed to study the fate of antibiotics administered to animals (for prophylaxis or treatment) once the drugs reach the soil. The other two projects aimed to examine the presence of antibiotics (of human and veterinary origin) in the aquatic environment and the possible effects on potential pathogenic waterborne bacteria.

2.3.2 Outcomes of NRP 49

Spread and environmental fate of veterinary antibiotics
Residues of antibiotics are regularly detected in manure, soil and water. Since availability, consumption data, fate, behaviour and effects of veterinary antibiotics in Switzerland are not yet clear, clarifications are needed.

[23] Available at http://europa.eu.int/comm/food/fs/sc/scf/out178_en.pdf

[24] Müller SR, Singer HP, Stoob K, Burkhardt M, Hartmann N, Götz C, et al. Occurrence and fate of antibiotics in manure, soil and water. *Mitt. Lebensm. Hyg.* 2003;94: 574–578.

C. Stamm

Project Induction and spread of antibiotic resistance in livestock

After their use in livestock, sulphonamides (SA) reach the soil through manure. Needed new analytical procedures were developed to quantify sulphonamides fluxes from manure to soils and water bodies. The innovative methodologies allow measurements of many (hundreds) of samples and reliable quantification to the low ng/L range. They take into account what is called "aging" of substances in soils, namely, the contact time that affects extraction efficiencies. It was also shown that extraction efficiencies were dependent on the extraction temperature (an effect completely overlooked so far, so that we now know that data on the persistence of SA are underestimated in previous studies). The main outcomes of the analyses can be summarised as follows:

- SA residues may reach agricultural soils in amounts comparable to herbicide application rates (tens to several hundred g of antibiotics per ha and yr). Residues were quite persistent, even exceeding 100 ng/g soil (a value corresponding to the trigger value in the guidelines for registration of new veterinary pharmaceuticals above which further investigations are required) over more than 3 months.
- Crucial factors controlling the mobility of SA for transport in the soil are contact time, pH and the organic carbon content of a soil.
- Field-scale experiments and monitoring studies at the scale of small catchments, including tributaries of Lake Sempach (a region characterised by intensive animal husbandry) as well as in ground and lake water demonstrated that SA are lost to surface waters during a few discharge events causing high SA concentrations for relatively short periods. Furthermore, SA residues can be detected in lake and groundwater in very low concentrations (about 0.5–1 ng/L). The relevance of these trace concentrations remains an open question.
- The manure used in the study contained a high diversity of resistance genes (i.e. resistance against tetracyclines and sulphonamides). The spreading of manure clearly increased the abundance of resistance genes in the soil. However, the diversity of tetracycline and sulphonamide resistance genes was high already prior to the manure application, although manure from intensive farming had not been applied in the previous years. This indicates that soils are a considerable pool of resistance genes. Whether it is the result of 50 years of tetracycline use or whether it is due to the natural background, these findings emphasize the role that environmental reservoirs might play in resistance gene capture.
- The persistence of SA in soils raised the question about their bioavailability, and a new methodology was sought to directly measure this quantity by quantifying products of the biochemical pathways disturbed by the SA. In bacteria, SA interfere with the biosynthesis of folic acid, forming dihydropterin-sulphonamides (DH-SA). The results showed that dihydrofolic acid (DHF, a structural analog of DH-SA) is not stable outside the organisms. The excreted pterin-SA, however, could be used as proxy for the bio-availability of SA. Interestingly, the DH-SA set free by a bacterial cell may be cleaved into p-ABG (p-aminobenzoyl-glutamic acid) or, more importantly, into the structural analogous, which is the original SA, suggesting a kind of recycling of SA once removed from the organism.

W. Giger

Project Occurrence of human-use antibiotics and antibiotic resistance in the aquatic environment (HUMABRA)

New analytical methods allowing qualitative determination of the β-lactam antibiotics and quantitative determination of trace concentrations of the antibiotics fluoroquinolones, macrolides and sulphonamides in wastewater, sewage sludge and ambient water were developed. Efficient enrichment techniques (solid-phase extraction and accelerated solvent extraction) and liquid chromatography were directly coupled to electro spray ionisation mass spectrometry. Using these methods, it was found that:

- While representatives from the classes of fluoroquinolones, macrolides and sulphonamides could be quantitatively measured in hospital wastewaters, in municipal wastewaters (before and after mechanical-biological wastewater treatment) as well as in rivers, the extensively used β-lactams could only be detected semi-quantitatively in hospital wastewaters.

– The concentrations found in wastewater correlated reasonably well with the known consumption data, and in-depth knowledge of their behaviour during wastewater treatment could be established.
– Ciprofloxacin, norfloxacin, clarithromycin, azithromycin, trimethoprim, sulfamethoxazole and sulfapyridine were ubiquitously found in the lower ng/L range in Swiss rivers, and sulfamethoxazole also occurred in groundwaters, which contain high amounts of bank filtrates. However, the concentrations of sulfamethoxazole observed in the groundwater, which is pumped for drinking water usage, is very low, and a negative influence on human health can be excluded based on current knowledge. However, these findings raise the question of whether this contamination can be accepted or should be avoided in accordance with the precautionary principle.
– In wastewater treatment plants (WWTPs) macrolides are only partly eliminated and can therefore reach the aquatic environment. Only ozonation proved to be efficient for the removal of sulphonamide and macrolide antimicrobials from wastewater effluents. An ozone dose of 2 mg/L resulted in a reduction of the respective loads by over 90%, interdependently of the amount of suspended solids present.

R. Peduzzi

Project Role of residual antibiotics in aquatic environments on selection and diffusion of bacterial resistances (RASDI)

The resistance analysis of *Aeromonas, Acinetobacter* and *Legionella* strains isolated from hospital wastewaters (Ticino and Zurich), two wastewater treatment plants, two rivers and a mountain stream, Lakes Ceresio and Cadagno and tap waters in Ticino revealed that:

– For *Aeromonas* and *Acinetobacter,* resistant or intermediate strains were more often isolated from hospital wastewaters and wastewater treatment plants than from rivers or lakes. For hospital wastewaters strains, susceptibility was correlated with the concentration of antibiotics (the higher the antibiotic concentration, the smaller the diameter of the inhibition zone, thus indicating a decrease in susceptibility of the strain). In particular, the susceptibility of *Aeromonas* strains was highly correlated with the concentration of ciprofloxacin. *In vitro* experiments demonstrated that in some *Aeromonas* strains, the presence of a mixture of antibiotics (ceftriaxone, ciprofloxacin and erythromycin) at concentrations similar to those measured in hospital wastewaters, influenced their susceptibility profiles. The induced profiles (slight reduction of susceptibility) were stable after 10 passages on Mueller Hinton agar without antibiotics. Class 1 integrons were found in 48% of the *Aeromonas* and *Acinetobacter* analysed strains. In *Aeromonas,* the number of the strains harbouring integrons was high in the wastewaters from both treatment plants and in the sludge of Ticino hospitals. This suggests that in sludge, *Aeromonas* can acquire resistance genes from other bacteria or can develop resistance to antibiotics.
– For *Legionella* a significant statistical correlation was found between MIC (Minimal Inhibitory Concentration) values for erythromycin and *Legionella* SBT (Sequence Based Typing) type 1,4,3 regardless of the origin of the strains. At the molecular level, three different types of resistance to macrolides were identified and characterised. In particular, a high level erythromycin resistance (C2611 with a MIC>256µg/ml) was found, and a real-time assay for its detection was developed.

2.3.3 Situation at the end of NRP 49

We now dispose of new analytical methods that allow accurate and sensitive quantitative analysis (down to the ng/L range) of the presence and fate of the most important classes of both human and veterinary antibiotics in the environment (soils, wastewaters, sewage sludge and ambient waters). As a result, we now have new insight into their behaviour in the soil, wastewater treatment plants and in natural waters, including rivers and groundwater.

The results obtained showed that after their use in livestock, sulphonamides (SA) reach the **soil** after manure application in amounts comparable to herbicide application rates, and they can persist in soils for several weeks or months. Moreover, soil was shown to be

a considerable reservoir of resistance genes. Manure was shown to influence largely the fate and transport of SA in the soil, so that in surface waters the highest concentrations of SA are generally measured only during the first rain event after manure application and concentrations of SA and other antibiotics measured in water bodies (i.e. lake water and groundwater) are generally very low (ng/L).

The analysis of the presence of human-use antibiotics and antibiotic resistance in the **aquatic environment** revealed that while representatives from the classes of fluoroquinolones, macrolides and sulphonamides could be measured quantitatively in hospital wastewaters, in municipal wastewaters (before and after mechanical-biological wastewater treatment) and in rivers, β-lactams could be detected only semi-quantitatively in hospital wastewaters. The concentrations found in wastewater correlated reasonably well with the known use data, and good knowledge of their behaviour during wastewater treatment could be established. Further, ciprofloxacin, norfloxacin, clarithromycin, azithromycin, trimethoprim, sulfamethoxazole and sulfapyridine were ubiquitously found in the lower ng/L range in Swiss rivers, and sulfamethoxazole also occurred in groundwaters. However, the finding of low concentrations of antibiotics in groundwater used as drinking water raises the question of whether this contamination can be accepted or should be avoided following the precautionary principle.

Even if there are yet no clear-cut data showing the impact of antibiotics on the development of resistance, an association was clearly shown between the low level of antibiotics measured in waters and the antibiotic susceptibility of some **waterborne bacteria** (i.e. *Aeromonas* and *Acinetobacter*). In particular, a high level erythromycin resistance mutation was identified in the waterborne microorganism *Legionella pneumophila* (responsible for severe human infections with a mortality rate of about 10%), and a real-time assay for the rapid screening of this mutation was developed.

2.3.4 Recommendations

Agriculture

Since sorption of antibiotics to soil influences their losses over a short period, achieving correct timing of manure application is critical. Furthermore, manure application should be avoided on areas prone to surface runoff or preferential flow to subsurface draining systems. Particle-bound losses of antibiotics can be diminished by adopting well-known strategies for erosion control (see C. Stamm project).

C. Stamm

Politicians/Federal and/or cantonal authorities

- Since the effects on bacterial resistance induced by low concentrations of antibiotics are not yet definitely known, further studies are needed to gain more insight into these issues, in particular to help to determine the limit of acceptability of the antibiotic residual concentrations found in groundwater used as drinking water (see W. Giger project).

W. Giger

- With the finding of wastewater treatment inadequacies regarding elimination of antibiotic compounds, emphasis should be put on methods aiming at better removal of antibiotics, e.g. by establishing the best operating conditions or by considering advanced treatments like ozonation or activated carbon adsorption. The importance of prudent and restrained use of antibiotics as well as thoughtful waste disposal of unused antibacterial products should be strongly emphasized. Ozonation processes or membrane bioreactor technology could also contribute to the elimination of resistant micro-organisms (see W. Giger project).

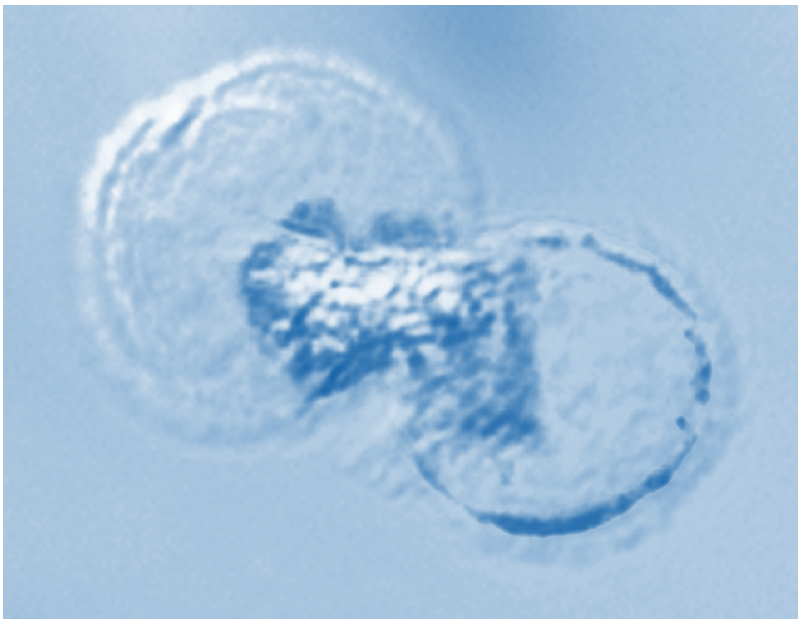
W. Giger

- Hospitals are important point sources contributing to the spread of antibiotics into the aquatic environment. Treating of hospital wastewater before discharging into municipal sewers should be encouraged (see W. Giger project).

W. Giger

- The mobility of SA for transport in the soil is strongly influenced by contact time and by pH, and the presence of organic carbon in soils influences the sorption of SA. Therefore, risk assessment for veterinary antibiotics has to consider not only substance properties but the physical and chemical influence of the application matrix – manure or excrements – and of the soils as well (see C. Stamm project).

C. Stamm



Molecular Biology

3. Molecular biology

Summary
One of the purposes of NRP 49 was to promote molecular studies of bacterial resistance as well as to sustain efforts in favour of practical applications. The different projects addressed several pathogens, some of them responsible for severe human infections and known to be particularly challenging because few, if any, treatment options are left. The outcomes of the molecular investigations of bacterial resistance provided considerable advancements, in particular:
– Close cooperation between molecular biologists and epidemiologists/health care professionals daily confronted with infectious diseases led to the development of new methods for rapid detection of bacterial resistance. These are already proving their usefulness for detection, surveillance and epidemiological investigations of nosocomial infections.
– Better understanding of the mechanisms of action of some anti-infective agents and the discovery of new potential drug targets provided opportunities for the development of new antibiotics as well as for the clinical management of resistance.
Thus, the outcomes of various molecular biology projects will provide significant help to clinicians in the management of patients and daily prescription of anti-infective drugs.

3.1 Objectives of NRP 49

Molecular studies on the emergence of antibiotic resistance are essential to gain knowledge for the development of both new antibiotics and new methods for *in vitro* detection of the resistances. Thus, the call for proposals for NRP 49 addressed the following research foci:
– Identification of the presence of clones of resistant bacteria and the analysis of how they spread.
– Analysis of possible relationships between resistance to antibiotics and the virulence of bacteria.
– Better understanding of the resistance biochemical mechanisms.
– The development of potential new therapeutic drugs.
– Better understanding of the genetic mechanisms of resistance acquisition and transfer, particularly between pathogenic and non-pathogenic bacteria.

Eleven research projects were selected for inclusion in the programme. One project aimed to investigate the ribosomal mechanisms involved in the development of resistance at a molecular level. One project aimed to develop new and rapid tools for the detection of antibiotic resistance genes in gram-positive bacteria to be implemented in the areas of clinical and veterinary medicine, the food industry, animal husbandry and bioterrorism. One of the most feared bacteria representing a serious medical, hygienic and economic problem in Swiss hospitals is methicillin-resistant *Staphylococcus aureus* (MRSA). Treatment of MRSA infections is more and more complicated. This not only increases direct costs but also prolongs hospitalisation and thus increases the risk of the patient acquiring additional nosocomial infections. Two research projects aimed to improve knowledge of the resistance mechanisms in *Staphylococcus aureus,* and two other projects planned to improve investigative tools, i.e. new molecular methods for the rapid tracking of MRSA.

Some infections believed to be under control, such as tuberculosis, are becoming a problem again worldwide because of the emergence of multi-resistant strains of mycobacteria. Two projects were designed to identify possible new antimycobacterial drugs. Finally, three projects were undertaken to study antibiotic resistance mechanisms and the spread of resistance determinants, as well as to investigate virulence aspects in other important pathogens like *E. coli, Pseudomonas aeruginosa* and in the fungus *Aspergillus fumigatus.*

3.2 Outcomes of NRP 49

3.2.1 Ribosomal mechanisms of antibiotic resistance

Many important anti-infective agents target the ribosome. Despite decades of use of ribosomal drugs, we still do not understand the principles governing the selectivity and toxicity of these agents – mainly because of the lack of suitable models. In addition, there is a need for increased knowledge on the fitness cost of defined resistance determinants, as this is the single most important parameter that determines the spread of resistance.

E. C. Böttger

Project Identification of ribosomal mechanisms mediating drug resistance

To learn more about ribosomal mutations conferring resistance to anti-infective agents and to learn how these agents work, a derivative of *M. smegmatis* was rendered single rRNA operon allelic by means of gene inactivation techniques. In this system, genetic manipulation of the single rRNA operon results in cells carrying homogeneous populations of mutant ribosomes. This model allows the isolation of recessive drug resistance mutations within *rrn* (rRNA operon). The studies on drug-target interactions of anti-infective agents targeting the ribosome identified the mechanisms involved in the development of resistance at a molecular level and defined the biological importance of the different structural interactions observed by crystallographic studies. The elucidation of these mechanisms identifies the molecular basis for the large differences in drug susceptibility observed in phylogenetically distinct ribosomal systems, e.g. bacterial, protozoal, cytoplasmatic, mitochondrial ribosomes. These findings provide the rational basis for understanding the mechanisms that determine the selectivity and toxicity of ribosomal antibiotics. This should help in developing future drugs with activity against prevailing resistance determinants and in the synthesis of antibiotics endowed with less toxicity and defined specificity.

In addition, it could be demonstrated that the genetic background influences the fitness cost of resistance determinants, providing contrary evidence against the current perception that drug resistance determinants inevitably carry a fitness burden.

3.2.2 Resistance among gram-positive bacteria

Bacteria can be divided into two main groups according to the structure of their cell wall. These groups can usually be visualised by a simple staining procedure called Gram staining, which differentiates between gram-positive and gram-negative bacteria. Gram-positive and gram-negative bacteria differ also in their genetic set-up, virulence mechanisms, antibiotic susceptibility profiles, etc. In the group of gram-positive bacteria, we can find important human and animal pathogens as well as bacteria used in food preparation and animal farming. The intensive use of antibiotics in both public health and animal husbandry has led to the emergence of antibiotic resistance in some of these micro-organisms. Although progress is being made, we still lack extensive knowledge on the mechanisms of antimicrobial resistance and transfer. There is also a great need for rapid and direct detection of antibiotic resistance genes in a number of domains: clinical and veterinary medicine, the food industry, animal husbandry and bioterrorism.

J. Frey

Project Antimicrobial resistance in Bacilli, transfer and detection

A novel microarray hybridisation system for the detection of antibiotic resistance genes among gram-positive bacteria was developed and validated. The system was optimised for use with highly pathogenic bacteria (Ba*cillus anthracis*). The technology was tested using wild strains of *B. anthracis* that cause animal deaths in Africa. They were shown to be susceptible to the major class of antibiotics and to be free of known transmissible antibiotic resistance genes. However, using avirulent strains, it was shown that *B. anthracis* is able to acquire antibiotic resistance genes from other bacteria by conjugation.

The microarray method allows the rapid detection of antibiotic resistance genes in gram-positive bacteria, thus filling an important gap and providing a very useful tool for application in different domains. In particular, in clinical microbiology laboratories, it can be applied to slow-growing bacteria for which standard antibiotic resistance determinations are difficult and also to rapid antimicrobial testing of highly pathogenic organisms. In addition, it can be used as a tool to rapidly track antibiotic resistance genes in specific bacteria such as *B. anthracis* or staphylococci. In the clinic, it can detect silent antibiotic resistance genes that might be turned on *in vivo* or spread to other bacteria. In the food industry, it can help to determine whether antibiotic-susceptible starter cultures harbour silent antibiotic resistance genes, which could reach consumers directly through the food chain (see L. Meile project).

L. Meile

The project also focused on investigation of the mechanisms governing resistance transfer in *Bacillus*. Although the majority of *Bacillus* species are rarely associated with disease in humans and animals, the principal exceptions are *B. anthracis* (the agent of anthrax) and *B. cereus* group (implicated in food poisoning). The study showed that *Bacillus* of the *cereus* group from different environmental sources harboured tetracycline resistance genes. Among them, a new tetracycline resistance mechanism was found to be localised on a conjugative plasmid. Moreover, the presence of sub-inhibitory concentration of tetracycline and ciprofloxacin could induce resistance to these antibiotics in *Bacillus thuringiensis*.

3.2.3 Resistance in *Staphylococcus aureus*

Staphylococcal infections, in particular those acquired in hospital settings, are often severe or fatal. Efforts to treat them are complicated by the fact that many hospital-acquired strains are resistant to many or nearly all currently available antibiotics; an example is methicillin-resistant *Staphylococcus aureus* (MRSA). The recent emergence of *S. aureus* strains with decreased susceptibility or even full resistance to glycopeptides (GISA, glycopeptide intermediate *S. aureus*), which are among the last antibiotics to be used when no other drug is active, raises an additional threat. There is a great need to increase knowledge on these resistant *S. aureus* strains: are they more or less virulent than the susceptible ones, are they still competitive, or does their fitness cost increase with the susceptibility decrease? Since the emergence and spread of MRSA in hospital settings often depend on the admission of patient who is an unknown carrier (e.g. from a long-term care facility), there is a need to develop rapid and reliable molecular tools to detect these resistant strains in the admission room (see S. Harbarth project). Furthermore, for the investigation of outbreaks, and also for the epidemiological surveillance of strain dissemination, it is crucial to rapidly and reliably identify the relatedness between clinical isolates as well as to rapidly detect epidemiological changes of MRSA populations. The new assays have to be rapid and inexpensive, thus allowing the analysis of many samples at once (high throughput) with high sensitivity.

S. Harbarth

3.2.3.1 Improved knowledge of the resistance mechanisms

R. Landmann-Suter **Project** **Effect of teicoplanin resistance on host response to *Staphylococcus aureus***

In close collaboration with B. Berger it was shown that glycopeptide resistance *in vivo* is accompanied by a downregulation of virulence genes, which is associated with increased cell wall synthesis and a thickened cell wall. The changes associated with teicoplanin resistance reduce the fitness of *S. aureus*. Remarkably, when the resistant bacteria get into the host in the absence of drug, they can regain fitness and survive at the price of resistance.

B. Berger-Bächi **Project** **Genetic basis of glycopeptide resistance in *Staphylococcus aureus***

On the genetic level, the membrane protein TcaA was shown to have a direct impact on glycopeptide resistance. The loss or inactivation of TcaA increases glycopeptide resistance, and it is genotypically linked to some clinical GISA isolates.

3.2.3.2 Improved investigative tools (new molecular methods)

P. François

Project Rapid characterisation of methicillin-resistant *Staphylococcus aureus* clinical isolates for an improved drug prescription

Based on a database containing numerous strains from many geographical or epidemiological origins, a fast and reliable genotyping method for a real-time epidemiological characterisation of MRSA was developed. The method allows typing of unknown or newly identified strains (whatever their origin) as well as the characterisation of MSSA (methicillin-susceptible *S. aureus*), thus helping to develop, in time, control measures and helping to guide clinicians in identifying patients at high risk carrying these highly resistant strains. A shared database is being set up on the World Wide Web. The whole assay procedure was successfully transferred to the "Laboratoire Central de Bactériologie" of the Geneva University Hospitals. Using this method, it was shown that, in contrast to other European countries showing a limited number of CA-MRSA (community-acquired MRSA) clonetypes, the area of Geneva appears to be exposed to numerous importation events. The assay is now used to prospectively collect epidemiological information and to document possible spread of clinical clones in the Geneva University Hospitals, in constant contact with the Infection Control Team.

P. Vaudaux

Project Mechanisms of glycopeptide resistance in staphylococci

A simple, reliable and low-cost screening assay to detect MRSA strains exhibiting intermediate susceptibility to glycopeptides (GISA) was validated. This method can be easily implemented in clinical microbiology laboratories to minimise the risk of missing potential GISA or even highly resistant isolates, and it can be used for prospective screening of decreased susceptibility to glycopeptides in any hospital setting.
In addition, the researchers developed a reliable and fully validated oligoarray (microarray technology) for the identification of *S. aureus* genes whose induction/repression plays a key role for expression of glycopeptide resistance *in vivo*. This system is useful for gene expression profiling, comparative genome hybridisation, gene deletion mapping and molecular epidemiology. Free software has been made available at www.genomic.ch. Another tool that was developed is a real-time quantitative PCR (TaqMan®) for the evaluation of gene expression of teicoplanin resistant *S. aureus* strains.

Relevant practical aspects of these two projects on the improvement of investigative tools for human medicine are also reported in sections 2.1.2 and 2.1 3 above.

3.2.4 Mycobacteria

Mycobacterium tuberculosis, the causative agent of tuberculosis, is responsible for more deaths worldwide than any other pathogenic bacterium (tuberculosis kills nearly three million people annually). The emergence of multi-drug, and even extremely-multi-drug, resistant strains as well as a deadly synergy with the human immunodeficiency virus (HIV) is threatening both the developing and the industrialised countries. Due to the frequent emergence of antibiotic resistance, chemotherapeutic treatments are complex and long. In addition, *M. tuberculosis* can persist in the infected host in a latent state and be reactivated decades later. The fight against tuberculosis advances not only through a better understanding of the mechanisms governing intrinsic resistance but also through the identification of the mechanisms involved in mycobacterial survival within the host cells. In order to better fight tuberculosis, it is essential to have new and effective drugs and vaccines. There is a need to improve knowledge on the mechanisms of the current antimycobacterial drugs and, concomitantly, the mechanisms generating resistance. There is also a great need to discover new molecular functions or structures that would serve as targets for new chemotherapeutic drugs or vaccines.

J. Pieters

Project Targeting tuberculosis inside its host cells

The work conducted on this topic has shown that the eukaryotic-like serine/threonine protein kinase G (PknG) expressed by pathogenic mycobacteria is secreted within macrophage phagosomes. PknG functions by inhibiting phagosome-lysosome fusion, thus mediating intracellular survival of these bacteria. Mycobacteria lacking PknG are viable outside host cells but are immediately transferred to lysosomes and rapidly destroyed within infected macrophages. Since PknG is secreted within the macrophage cytoplasm, pharmaceutical inactivation of PknG is not hampered by the impermeable barrier created by the mycobacterial cell wall, thus providing a new treatment regimen targeting intracellular residing mycobacteria and allowing the macrophage to carry out its innate bactericidal activity (by shuttling these bacteria to lysosomes), thereby potentially circumventing antibiotic resistance. It is to be noted that specific inhibitors of serine/threonine kinases have been successfully developed for therapeutic usage against a variety of diseases.

C. J. Thompson

J. Pieters

Project Mycobacterial pathogens: Overcoming multidrug resistance

The research work by C. J. Thompson and S. Grzesiek and by J. Pieters showed that the *whiB7* gene of *M. tuberculosis* is a central regulator that coordinates the expression of a family of resistance genes able to inactivate antibiotics that have penetrated into the cytoplasm. These genes act synergistically with envelope exclusion (the multi-layer cell envelope functions as an effective barrier to the penetration of antibiotics) to render *M. tuberculosis* resistant to many antibiotics. Therefore, components of the identified *whiB7* system could serve as novel drug targets (i.e. inhibitors) rendering *M. tuberculosis* or multidrug-resistant derivatives more antibiotic-sensitive.

3.2.5 *Escherichia coli*

This organism is the predominant aerobic commensal micro-organism present in the bacterial gut flora of humans and animals, including pets (i.e. dogs and cats). However, according to the genetic set-up of the strains, it can also cause diarrhoea, urinary tract infections, pneumonia and other diseases. Since humans, farm animals (i.e. bovine and pigs) and pets often live in close contact to one another, there might well be exchange of genes encoding pathogenicity properties or resistance determinants. However, transfers of that kind have not been investigated in depth. Because of the technical progress in molecular biology that now allows large collections of strains to be analysed, it is now possible and desirable to assess the role of host-specificity in the population genetics of human and animal *E. coli,* as well as the evolution and spread of antibiotic resistance and virulence genes.

J.-C. Piffaretti

Project Molecular evolution of pathogenicity and resistance in *Escherichia coli*

In *E. coli* a correlation between integron carriage and farm animals was shown. This link suggests that animals raised for economic purposes might be subjected to a major antibiotic pressure. Even if the genetic diversity among different *E. coli* isolates is very high, genes that may contribute to *E. coli* pathogenicity were also found in commensal strains isolated from the intestinal flora of healthy animals. Therefore, given the evidence of horizontal gene transfer in *E. coli,* healthy animals may represent an important reservoir of genes that might be transferred to other micro-organisms.

3.2.6 *Pseudomonas aeruginosa*

Because of its predilection and ability to survive in water environments, *Pseudomonas aeruginosa* has become a concern in the hospital environment. The bacterium has been found in a variety of aqueous solutions (such as disinfectants, ointments, soaps, irrigation fluids, eye drops and dialysis fluids), in aerators or traps of sinks, in respiratory equipment, etc. *P. aeruginosa* is an important opportunistic pathogen in humans, causing diseases ranging from superficial skin infections to fulminant sepsis.

Since *P. aeruginosa* is well known for its intrinsic and acquired resistance to antibiotics, it is particularly feared in hospitals. New methods for investigating its resistance mechanisms and for novel treatment approaches that weaken its virulence determinants are urgently required.

C. van Delden **Project Novel approaches to detect and circumvent antibiotic resistance in *Pseudomonas aeruginosa***

This research team developed a quantitative real-time PCR reaction for the analysis of the antimicrobial resistance gene expression in *P. aeruginosa,* which was then applied for the detection of resistance in clinical isolates. This method allows detection of the timing of resistance appearance and of the underlying resistance mechanisms, thus helping to optimise antibiotic therapy. It was shown that antimicrobial therapies can rapidly (within 6 to 10 days) select resistant isolates, which may persist for several weeks in the lungs of patients once the selecting agent is withdrawn. The persistence of resistance, once the selecting agent is stopped, depends on the resistance mechanism involved.

Further, it was shown that macrolides, at subinhibitory concentrations, have "quorum-sensing" inhibition properties by interacting with the ribosome. "Quorum sensing" was shown to be associated with the progression of colonization by *P. aeruginosa* of intubated patients towards pneumonia. These observations open the way for clinical use of anti-virulence strategies as a novel approach to circumvent antibiotic resistance.

3.2.7 *Aspergillus fumigatus*

Although *Aspergillus fumigatus* is not a bacterium but a fungus, the NRP 49 Steering Committee decided to include a project on this organism because of the possible emergence of antifungal resistance. This organism is widespread in the environment. It may be pathogenic to plants and animals, but above all, it is the most prevalent airborne fungal pathogen causing severe and often fatal invasive aspergillosis in immunocompromised patients. Moreover, *A. fumigatus* is able to develop in the respiratory tract without causing apparent disease. For the treatment of aspergillosis in humans, a few antifungal agents are available, and among them, azoles are used in both hospital and agricultural settings. Thus, being widely spread in the environment, *A. fumigatus* isolates are often exposed to agricultural antifungals. As *A. fumigatus* infections in humans and the use of antifungal agents are increasing, emergence of resistant *A. fumigatus* isolates can be expected. In fact, the number of clinical isolates with *in vitro* itraconazole resistance is increasing in many developed countries. However, in Switzerland little is known about the resistance situation. In addition, the mechanisms responsible for the development of antifungal resistance in *A. fumigatus* of hospital and environmental isolates are not well known. In particular, insights into a possible relationship between the use of fungicides in agriculture and the emergence of infections with resistant *A. fumigatus* strains in humans would be useful.

D. Sanglard **Project Resistance of the pathogen *Aspergillus fumigatus* to antifungal agents**

For the first time in Switzerland, the level of antifungal drug resistance in *A. fumigatus* isolates originating from clinical centres and from different environmental sites was established. At present, only a few isolates exhibited resistance to azoles, even though these drugs are being used in both hospitals and environmental settings (agriculture). In Switzerland, resistance to azoles is therefore not a problem at present. Further, the results obtained demonstrate that among the antifungal tested and used in medicine (i.e. amphotericin B, itraconazole and voriconazole), voriconazole is the most active agent on both clinical and environmental isolates, confirming that voriconazole has a broader activity spectrum than its predecessors (i.e. itraconazole).

To study the resistance mechanisms to antifungal drugs, a novel analytical tool, based on *S. cerevisiae,* was established. This approach made it possible to discover several azole resistance genes (including multidrug transporter genes), thus helping to elucidate the mechanisms by which resistance can develop. Unfortunately, the involvement of

the identified resistance genes in azole resistance in *A. fumigatus* could not be clearly demonstrated.

3.3 Situation at the end of NRP 49

The findings of the studies on **ribosomal mechanisms** mediating drug resistance are of general relevance with respect to both understanding mechanisms of drug resistance and developing new, less toxic antibiotics. In addition, the research group conducting the studies showed that the bacterial genetic background influences the fitness cost of resistance determinants. This argues against the current perception that drug resistance determinants inevitably carry a fitness burden.

With the microarray system, we now dispose of a new tool that allows the rapid detection of antibiotic resistance genes in **gram-positive bacteria.** This fills an important gap and provides significant and useful applications. In particular, since the system was optimised for use with highly pathogenic bacteria, it is suitable to be used to screen potential bioterrorism agents like *Bacillus anthracis* for the presence of antibiotic resistance genes. The system has already proved to be successful in screening ready-to-eat foods and starter and probiotic cultures from the Swiss market for the presence of resistant genes.

As to the mechanisms of **glycopeptide resistance in *Staphylococcus aureus,*** the observation that the fitness cost of glycopeptides resistance might be directly involved in the instability of the resistance is important for the therapeutic use of glycopeptides. In fact, the finding offers an explanation for the clinical observation that glycopeptide resistance is unstable in the absence of the drugs; this finding encourages the use of these antibiotics to fight MRSA infections. Furthermore, the finding that the loss or inactivation of a membrane protein (TcaA) increases glycopeptide resistance is important, since its characterisation may shed light on the molecular interaction of glycopeptides to its target.

For **mycobacteria,** novel putative targets related to regulation or pathogenicity processes were identified. These targets represent an important step forward in the development of new specific drugs.

In ***Escherichia coli,*** genes that may contribute to pathogenicity are found also in commensal strains of the intestinal flora of healthy animals. Given the evidence of horizontal gene transfer in *E. coli,* healthy animals may represent an important reservoir of genes that might be transferred to other micro-organisms. The widespread presence in *E. coli* strains of genetic elements able to recognise and capture mobile elements carrying antibiotic resistance genes (i.e. integrons) suggests a relationship between animals raised for economic purposes and major antibiotic pressure.

In ***Pseudomonas aeruginosa,*** it was demonstrated that antimicrobial therapies can select resistant isolates and that the persistence of resistance, once the selecting agent is stopped, depends on the mechanisms involved. Furthermore, it was shown that a phenomenon called "quorum sensing" is associated with the progression of colonisation by *P. aeruginosa* of intubated patients towards pneumonia and that macrolides, at subinhibitory concentrations, have quorum-sensing inhibition properties by interacting with the ribosome. This observation opens the way for the clinical use of anti-virulence strategies for circumventing antibiotic resistance.

Although several antifungal drug resistance genes were identified in ***Aspergillus fumigatus,*** the incidence of antifungal resistance in clinical and environmental isolates is low. Therefore, at the present time, *A. fumigatus* does not represent a particular threat in terms of antifungal drug resistance in Switzerland.

As for **practical applications,** the molecular biologists, in close collaboration with epidemiologists and clinicians, developed new, fast, cost-effective and reliable tools. In particular a new genotyping assay was developed and has already been implemented in Geneva that allows automated real-time epidemiology and genotyping of **methicillin-resistant *Staphylococcus aureus*** (MRSA) as well as the characterization of methicillin-sensitive *Staphylococcus aureus* (MSSA). This tool has already proved to

be very useful for investigating MRSA outbreaks in the neonatology ward, for documenting community-acquired MRSA recovered from patients at admission and for characterising MRSA strains of community origin. Furthermore, clinical microbiology laboratories now have at their disposal a simple, reliable and low-cost screening assay for the detection of MRSA strains exhibiting intermediate susceptibility (GISA) or even high resistance to the glycopeptides vancomycin and teicoplanin. For ***Pseudomonas aeruginosa,*** another relevant nosocomial pathogen, a quantitative real-time PCR for the analysis of antimicrobial resistance gene expression was developed. It has already proved to be useful in detecting the timing of resistance appearance and of the underlying resistance mechanisms, thus helping to optimise antibiotic therapy.

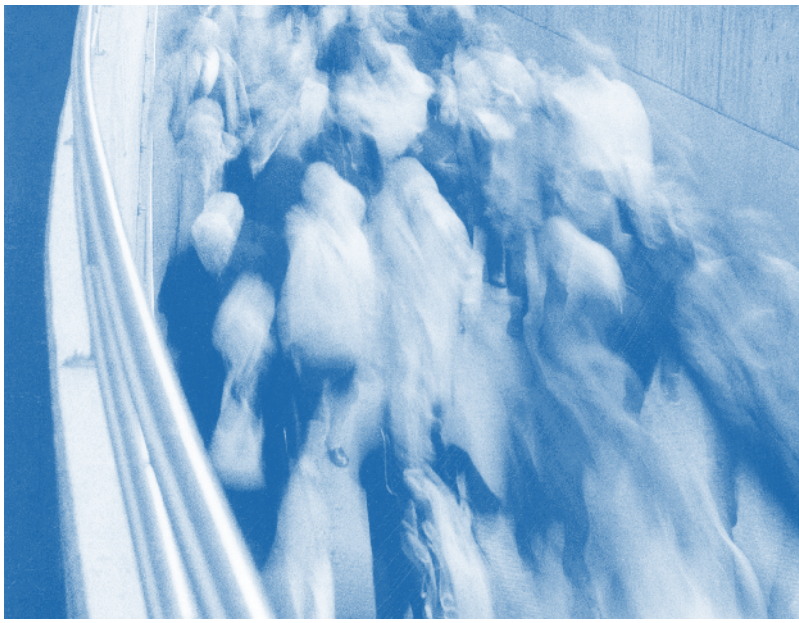
3.4 Recommendations

Strategic/political

New and promising approaches are emerging from basic research in academic institutes. However, the search for new antibacterial targets and lead compounds that the pharmaceutical industry might then develop as far as new therapeutic drugs requires significant financial support. Because it is not easy for an academic research group to obtain that kind of funding, a major role for public funds should be considered.

Implementation activities

The data collected with *Pseudomonas aeruginosa* have shown that virulence-modulating strategies are efficient to hinder the progression from colonisation to pneumonia, and thus to decrease the use of antibiotics and, indirectly, the emergence of resistance. That kind of strategy should be further investigated with other pathogens in clinical trials.



Society, law and economics

4. Society, law and economics

Summary
As compared to other European countries Switzerland exhibits relatively low levels of antibiotic consumption, and from a legal point of view, the Swiss legislation (relating to the fight against epidemics in general and antibiotic resistance in particular) is adapted overall to the public health needs in this field. However, across cantons and local areas, the use of antibiotics and the awareness and knowledge on antibiotics and antibiotic resistance are far from homogeneous. In addition, sources of information on the problem of antibiotic resistance are clearly unsatisfactory in Switzerland. At the national level, there is a lack of appropriate strategies for dealing with emerging epidemics or outbreaks of diseases threatening the community (as evidenced by the project on "Biological Terrorism and Crisis Management in Switzerland – Lessons Learned from the Anthrax Alert and Steps Ahead", (see J. Metzger project).
Therefore, appropriate policies affecting antibiotic consumption in the community have to take local determinants and their related impacts into account. It is mainly the responsibility of the regional authorities to promote local guidelines with proper incentives for an appropriate use of antibiotics. However, there is a great need for further policy actions and concerted measures on a national scale in order to reinforce and standardize locally implemented strategies. At the communication level, there is an urgent need in Switzerland for proper information on the topic. Campaigns should aim at increasing both knowledge and awareness of antibiotic resistance, since much of the practical advice on proper use makes more sense to people when they know something about the problem of resistance. The information campaigns have to consider the regional differences in proper use/misuse of antibiotics and awareness/knowledge of antibiotics and resistance.
Finally, in order to estimate the impact of resistance on antibiotic consumption, further improvement is needed in the collection, monitoring and diffusion of regional and local data on outpatient antibiotic consumption. The availability of a tested approach to investigate the impact of socioeconomic determinants of antibiotic use can be improved by the inclusion of additional data (the level of bacterial resistance and the incidence of infections, for example) at the regional and local levels.

J. Metzger

4.1 Objectives of NRP 49

In Switzerland there is little awareness of the growing problem raised by antibiotic resistance, particularly among politicians and the media. Despite this lack of awareness, however, experts agree that antibiotic resistance is and will be an important public health issue in the future. Identifying the social, legal, ethical and economic consequences of antibiotic resistance is the precondition to set up possible modifications of the rules governing the use of antibacterial drugs with a sufficient guarantee of acceptance. In fact, modifications of the use of antibiotics may have an impact on therapeutic freedom and on the rights of the individual vis-à-vis the interest of the community. Furthermore, it is necessary to investigate the consequences of resistance with a view to liability in cases of damage due to resistance. Therefore, the research foci of the NRP 49 programme in the area of society, law and economics were the following:

- Investigate how the Swiss population views the problem, including legal aspects of failed therapy due to resistance.
- Analyse ethical aspects, legal bases and the impact of a possible curtailment or modification of antibiotic use with a view to the economy, health freedom and the interests of the individual as opposed to the interests of the community.

To address these issues, seven projects were chosen for funding. They were meant to investigate antibiotic consumption and public perceptions of the antibiotic resistance problem, to analyse the standing of the legal situation in Switzerland and in the neighbouring countries, to examine the preparedness of Switzerland and the Swiss authorities to face bioterrorists attacks, in particular if resistant organisms are involved, and to set up health policy decisions in the long term and guidelines on the resistance problem. Unfortunately, the ethical aspects of antibiotic resistance could not be investigated. In

fact, no project proposals related to that topic were submitted in response to either the first or second call for proposals.

4.2 Outcomes of NRP 49

4.2.1 Antibiotic consumption

Given the association between antimicrobial usage and resistance, as well as the increasing heath care costs associated with this issue, public authorities all over the world are more and more concerned about the extensive use of antibiotics. The European Surveillance of Antimicrobial Consumption (ESAC) project, funded by the European Commission, is an international network of surveillance systems aiming to collect comparable and reliable data on antibiotic usage in Europe. Switzerland was the only European nation not providing such data, because the data were lacking! There was therefore a strong need to establish the antibiotic consumption rates in Switzerland. Since each canton has its peculiarities, it was also important to investigate the impact of the regional specificities.

M. Filippini **Project** **Economic analysis of outpatients' antibiotic consumption in Switzerland**

The project investigated outpatient antibiotic utilisation in Switzerland and compared it with use in other European countries. Swiss sales data were provided by IHA-IMS Health Market Research. Both total use in terms of defined daily doses per 1,000 inhabitants per day (DID) and sales per capita were considered. The analysis revealed that among European countries, Switzerland exhibits relatively low levels of per capita antibiotic consumption. However, within the country there are substantial differences in the use of antibiotics in the community across cantons and local areas. These differences were studied using econometric models. The results indicate that variations differences can be explained mainly by socio-economic, demographic and epidemiological factors, access to practices and antibiotic treatment (densities of physicians and pharmacies). Unexplained variations in local consumption can be interpreted as a rough measure of the welfare loss due to bacterial resistance (11% of the total spending). Self-dispensing practices improve access to antibiotic treatment but may also be responsible for higher levels of antibiotic use.

It should be pointed out that the empirical framework developed in this project has been applied in the study of outpatient antibiotic consumption in other European countries within the EU-funded European Surveillance of Antimicrobial Consumption Project (ESAC), which Switzerland could join as a participating country.

To conclude, appropriate policies affecting antibiotic consumption in the community must take into account local determinants and their related impact. It is mainly the responsibility of regional authorities to promote local guidelines or economic incentives to induce proper levels of antibiotic consumption.

G. Zanetti **Project** **Sentinel monitoring of antibiotic use in Switzerland**

Two sentinel networks for the assessment of antibiotic use were designed for public acute care hospitals (period 2004–2005) and the community (period 2002–2004), based on delivery data from either hospital or community pharmacies, respectively. The systems accurately reflected antibiotic use and allowed in-depth analyses and comparisons of the prescription patterns. The pilot projects can be extended to represent a larger proportion of hospitals and practitioners, thus gaining in accuracy. Given the relevance of this project for human medicine and the surveillance system of antibiotic resistance SEARCH, the outcomes of the project are referred to extensively in sections 2.1.2 and 2.1.3 above.

4.2.2 Awareness of the antibiotic resistance problem

Previous research in the United States and other European countries indicates that one of the major factors promoting overuse of antibiotics is lack of education, and this applies to both providers and patients. It is already known that patients' expectations have a significant influence on a doctor's decision to prescribe, even in cases where antibiotics are not recommended. On the other side, plenty of evidence also suggests that doctors overestimate patients' expectations. In Switzerland, there is not much available information on these issues or on whether patients comply strictly with the instructions for taking antibiotics as prescribed by the physician. There is thus a need to gain a better understanding of the behavioural factors that promote antibiotic overuse and to identify efficient communicative strategies that would make behavioural changes more likely. Actions that could decrease the volume of antibiotic use without affecting quality of medical care imply, for example, reducing inappropriate use of antibiotics. For this purpose, it is indispensable to gain an understanding of the Swiss population's knowledge on antibiotics as well as better insight into the complex doctor-patient interaction related to the prescription of antibiotics. The findings would contribute towards more effective design of information campaigns for both medical practitioners and the public at large.

P. Schulz

Project Towards judicious use of antibiotics by doctors and patients

In order to gain a better understanding of behavioural factors in patients and doctors that promote overuse of antibiotics, four different studies were conducted:

1) a survey of the knowledge, intention and behaviour of the Swiss population (in two waves),
2) content analysis of Swiss German newspaper coverage on antibiotic resistance,
3) comparative content analysis of Swiss and Italian patient package inserts, and
4) conversational analysis of 89 doctor-patient consultations.

Regarding the knowledge, intention and behaviour of the Swiss population, cultural differences exist regarding the three language groups about proper/judicious use of antibiotics and information/learning capabilities about antibiotic resistance. Indeed, the German-speaking population shows more judicious use of antibiotics, whereas use and misuse of antibiotics are higher in the Italian-speaking part and especially in the French-speaking part of the country. Residents in these two regions also show a higher appreciation for antibiotics as a breakthrough discovery of medical research. Even doctors' behaviour shows regional specificities. German-speaking doctors talk more about side effects and the danger of resistance, whereas French and Italian-speaking doctors give their patients more practical advice on dosage and treatment duration. In general, awareness/knowledge of antibiotics and antibiotic resistance is highest among the German-speaking, followed by the French-speaking, and lowest among the Italian-speaking Swiss residents.

The content analysis of Swiss German newspaper coverage of antibiotic resistance revealed that information sources in Switzerland on the problem of antibiotic resistance are unsatisfactory. Swiss German newspapers referred widely to antibiotic resistance in the past 3 years, but the information contents were incorrect. Thus, print media were not relevant in increasing peoples' awareness (and correctness) of the problem of antibiotic resistance. Moreover, with the exception of very few and not widely distributed leaflets, nothing could be found, for either practitioners for patients, on the problem of antibiotic resistance.

A comparative content analysis of 67 Swiss and 46 Italian Patient Package Inserts (PPI) of frequently prescribed antibiotics for upper respiratory infections was performed. Basic criteria of the analysis refer to 1) readability, 2) mention and explanation of the resistance phenomenon, 3) explicitness in the instructions concerning doses, therapy duration and the use of residual medicaments from past therapies, 4) accessibility, 5) relevance, 6) completeness and 7) applicability. Surprisingly, PPI very rarely mention the problem of antibiotic resistance, and they do not mention the difference between

viral and bacterial infection. The information provided in this regard is far from adequate. Furthermore, none of the PPI explained the resistance phenomenon as such, drew a connection between behaviour and this problem, provided information on how important is to finish the entire course of antibiotics, or provided information on what to do in case of allergic reactions or other side effects.
Finally, the conversational analysis of doctor-patient consultations led to constructive discussions with the doctors participating in the study on the doctors' understanding of their role in communicating prescription information and the efficacy of various methods used to disseminate information to patients.

4.2.3 Decisions on antibiotic treatment

Guidelines minimising the risk of development of antibiotic resistance (i.e. to preserve long-term antimicrobial efficacy) may result in convenient but/or less effective therapies for individual patients (i.e. ending up with increased morbidity, prolonged hospitalisation and/or increased mortality). Therefore, for long-term health policy decisions, it is important to weigh up the preferences of patients, health care professionals and society for acceptable risk of antibiotic resistance development for a given increase in morbidity, mortality and/or treatment inconvenience. Estimating population expectations would provide a rational basis for acceptance of future decisions/measures for reducing resistance.

D. Uehlinger

Project Individual decision on antibiotic treatment. A case for utility assessment
The objective of the project was to define patients', health care professionals' and society's preferences for the acceptable risk of antibiotic resistance development for a given increase in mortality, morbidity and/or inconvenience. Data analysis of the interviews is currently ongoing, and the results are still sparse and preliminary. As planned, the final results of the interviews will be used to weigh the possible outcomes of the simulation studies reported previously according to patients' preferences.

4.2.4 Best policy selection in Switzerland

Authorities responsible for decision-making on strategies to fight antibiotic resistance require a rational basis for the setting of population control and antibiotic usage rules to prevent appearance and/or spread of epidemics of bacterial resistance. But prediction and predictability of these epidemics may be poor due to "chaos" or variability in the number of contacts and infected persons. Therefore, mathematical studies can provide valuable indications for selecting the best strategies to face epidemics of bacterial resistance (both when the spread of the infection is predictable and to restore its predictability when not).

J. Shiner

Project Prediction and predictability of resistance to antibiotics: Studies based on coupled map lattices
For the elaboration of guidelines or the selection of strategies against increased antibiotic resistance, mathematical studies have shown to provide valuable support. In fact, when the time course of infections and/or changes in resistance are chaotic events, detailed prediction is impossible, except perhaps in the short-term. However, using mathematical models, it was shown that long-term prediction of statistical measures such as the mean or the standard deviation is not only possible but even good. Furthermore, the approach is not only true when a single population is involved but even when the infection disperses within multiple populations and the dispersal rate is too slow to merge populations into a single effective one.

4.2.5 Bioterrorism and antibiotic resistance in Switzerland

The anthrax attacks in the United States in the fall of 2001 set off a wave of more than 1,000 false anthrax alerts in Switzerland. The anthrax incidents increased the awareness of the danger raised by micro-organisms, in this particular case *Bacillus anthracis*. The Swiss authorities were not optimally prepared to respond to potential collectivity threats, since a number of issues at management level had never been clarified (e.g. government and leadership role). Because a bioterrorist event might also involve a resistant micro-organism, which would render the situation even more difficult, it seemed important to look at 1) the response to the anthrax alerts in Switzerland in the fall of 2001 in order to derive the lessons learned, and 2) Switzerland's present preparedness for bioterrorist incidents. These studies would be essential to the development of recommendations for enhancing Switzerland's preparedness for a future bioterrorist incident. The studies should consider the complexity in Switzerland generated by the involvement of both federal and cantonal authorities.

J. Metzger **Project** **Biological terrorism and crisis management in Switzerland – Lesson learned from the anthrax alert and steps ahead**

Switzerland's preparedness for bioterrorism has been considerably improved since autumn 2001. Still, this project developed recommendations for further improvements in the following areas: early warning, warning procedures, legal factors, crisis management groups, management processes, operational units, bioterrorism protection measures (location of a bioterrorist incident, transport of patients, use of medication, laboratory analysis), crisis communication strategy, training and exercises, research and international networking and the all-clear.

4.2.6 Legal aspects related to antibiotic resistance

There are an increasing number of infections for which antibiotics remain ineffective. The public health consequences of these antibiotic-resistant infections are severe enough to have encouraged several governmental agencies and professional associations to launch specific control programmes. Yet, few studies have so far been conducted on the legal challenges raised by this major public health problem. The legal issues linked to the present and future efforts to build a system of surveillance and control of antibiotic resistance in Switzerland need to be clarified with regard to a possible adaptation of the legal framework to the challenge that the resistance to antibiotics constitutes for public health, the protection of patients' rights and the practice of healthcare professionals.[25]

D. Sprumont **Project** **Legal implications of antibiotic resistance: Analysis of Swiss legislation and comparative law (D, F, UK)**

The Swiss legislation relating to the fight against epidemics in general and antibiotic resistance in particular was analysed in detail. In addition, a comparative law analysis of nearby countries was conducted. This was completed by a questionnaire survey of Swiss and European specialists on the appropriate measures to be taken for antibiotic resistance surveillance and control. One of the major findings was that the Swiss legislation is adapted overall to the public health needs in this field. However, despite the available resources, the findings strongly support the need for further policy action and concerted measures on a national scale to reinforce and standardize locally implemented strategies.

[25] The CD accompanying this report contains an additional contribution concerning the legal aspects: a summary of the Locher/Innopool report. In particular, the report provides an overview of the legal aspects relating to the role and responsibilities of the federal and cantonal authorities in the field of antibiotic resistance. The report was commissioned by NRP 49 as part of a feasibility study for the National Antibiotic Resistance Centre (NARC), a study that was conducted by the research institute gfs.bern Locher/Innopool

4.3 Situation at the end of NRP 49

We are now aware that in Switzerland there are clear and substantial differences across cantons and local areas in **consumption and use/misuse of antibiotics in the community** and in knowledge on antibiotics and antibiotic resistance. The empirical approach developed for the NRP 49 project on economic analysis has been applied in the study of outpatient antibiotic consumption in other European countries within the EU-funded European Surveillance of Antimicrobial Consumption project (ESAC). Switzerland is now a participating country in ESAC, an international network of national surveillance system aiming to collect reliable and comparable antibiotic consumption data for public health purposes in all European countries. However, this participation has to be consolidated in order to be pursued after the completion of NRP 49.

The concerned groups (i.e. the federal government, cantons, service providers, insurance companies, the pharmaceutical industry, politicians) are showing only limited interest in the issue of antibiotic resistance. In fact, **information sources** in Switzerland on the problem of antibiotic resistance are clearly unsatisfactory. Analysis of media coverage revealed that Swiss German newspapers referred to antibiotic resistance, but the content of the information was mostly inaccurate. Furthermore, most drug package inserts for antibiotics do not even mention the problem of antibiotic resistance nor do they inform the consumer how important it is to complete the entire antibiotic treatment course or what to do in case of allergic reactions or other side effects. Moreover, with the exception of very few and not widely distributed leaflets, no information could be found, for practitioners or for patients, on the problem of antibiotic resistance.

From a **legal point of view,** based on the legislation governing epidemics, food safety and health insurance, the federal government and the cantons already possess a wide and suitable range of legal instruments to implement the measures required to address the problem of antibiotic resistance. The division of responsibilities between the state and the cantons and the relationship between the authorities and service providers are defined clearly enough. However, political goodwill needs to be created to make use of these instruments. Additional legal measures are not indispensable but may prove to be useful to better identify the issue of antibiotic resistance.

4.4 Recommendations

Cantonal public health authorities

M. Filippini

Cantonal authorities should promote local guidelines with adequate incentives for appropriate use of antibiotics (see M. Filippini project) because:

- there are substantial differences across cantons and local areas in outpatient antibiotic use;
- higher per capita antibiotic consumption is correlated with the density of general practices and the dispensing status of practices;
- practice behaviour, therefore, can be influenced by the regulatory policy.

Federal public health authorities

D. Sprumont

The Federal health authorities should support further policy actions and concerted measures on a national scale to reinforce and standardise locally implemented strategies (see D. Sprumont project).

P. Schulz

In Switzerland, there is a clear need for further information campaigns regarding antibiotic resistance. These campaigns, however, should be targeted to specific groups of patients and should be delivered with the collaboration of general practitioners and pharmacists (see P. Schulz project).

J. Metzger

Federal and cantonal authorities (see J. Metzger project)

The lesson from the anthrax alerts shows that Switzerland's preparedness for bioterrorism has been considerably improved since autumn 2001. However, it is now up to the federal and cantonal authorities to put into action the recommendations of the report.

P. Schulz

Pharmaceutical industry (see P. Schulz project)

Package inserts of antibiotics should contain:

- clear instructions concerning antibiotic resistance;
- information in a more comprehensive form (i.e. FAQs module);
- information on the necessity to complete the entire course of antibiotics prescribed;
- information in case of side effects (for example, the instruction to contact the physician that prescribed the antibiotic).

5. Summary of the recommendations ensuing from NRP 49

Main recommendations	*Concerned parties*[26]	*Remarks*
General recommendation		
Establish a National Antibiotic Resistance Centre (NARC)	Federal health authorities (FOPH, FVO, FOAG) Cantonal health offices, Swiss Conference of Cantonal Ministers of Health	Should be sentinel-based and monitor antibiotic resistance and consumption in the different regions of Switzerland; should integrate the veterinary data; will be the national information and advice platform for all issues relevant to antibiotic resistance; should interact with EU and other countries. See section 7, Vision after NRP 49
Human medicine and surveillance		
Establish surveillance of antibiotic consumption and resistance in hospitals and long-term care facilities (LTCFs); implement new or improved infection control measures in LTCFs	Cantonal health authorities Hospitals and LTCFs	Use antibiotic resistance rate as a quality parameter for hospital and LTCF hygiene; track MRSA and other multiresistant pathogens in health settings
Veterinary medicine and food production		
Pursue the efforts to monitor antibiotic resistance and consumption	FVO, FOAG, Swissmedic	
Implement measures to minimize the use of veterinary antibiotics (e.g. by measures to foster animal health and well-being)	FVO, FOAG	Extensive information and policies will have to be provided to farmers and veterinarians
Advise milk producers not to use milk from antibiotic treated cows as animal feed; find alternative destinations for this milk	FVO, FOAG, ALP	Might be an economic issue
Define the antibiotic resistance qualitatively and quantitatively (e.g. the antibiotic gene copy number) as a food quality parameter; initiate discussions to define the limit of acceptability	FOPH, FVO, FOAG ALP	Concerns ready-to-eat food and starter and probiotic cultures. Should be compatible with EU directives

[26] FOPH: Federal Office of Public Health; FVO: Federal Veterinary Office; FOAG: Federal Office for Agriculture; FOE: Federal Office for the Environment; ALP: Agroscope Liebefeld-Posieux Research Station; EAWAG: Swiss Federal Institute of Aquatic Science and Technology; Swissmedic: the Swiss Agency for Therapeutic Products; SER: State Secretariat for Education and Research (within the Federal Department of Home Affairs); pharmaSuisse: Swiss Society of Pharmacists; FMH: FMH: Swiss Medical Association; SNF: Swiss National Science Foundation

Environment		
Promote research to analyse the effects on bacterial resistance induced by low concentrations of antibiotics in the environment. Start discussions to define the limit of acceptability of the antibiotic residual concentrations in groundwater used as drinking water	FOE, EAWAG	Should be compatible with EU directives
Promote further studies regarding the fate of antibiotic residual concentrations in groundwater, soils and manure. Promote research to develop more efficient methods to remove residual antibiotic compounds from wastewater	FOE, EAWAG	The objective is to correct the wastewater treatment inadequacies regarding elimination of antibiotic compounds
Encourage hospitals to treat their wastewater before discharging it into municipal sewers	FOE, FOPH, Hospitals	Hospitals are important point sources contributing to the spread of antibiotics into the aquatic environment
Molecular biology research		
Improve the funding to support the passage from the finding of new antibacterial targets to the development of new antibacterial compounds	SER, SNF Pharmaceutical industries	Promote start-up companies in the field of antibiotic resistance. The passage from academic basic research to the predevelopment of a potential drug is difficult and needs funding
Society and economics		
Develop information campaigns on antibiotic resistance with the collaboration of general practitioners, pharmacists and patient safety organisations	FOPH, Swissmedic FMH, pharmaSuisse	Should consider the cultural differences within the Swiss population
Promote local guidelines with adequate incentives for appropriate use of antibiotics	Cantonal health authorities	There are substantial differences across cantons and local areas in outpatient antibiotic use. Higher per capita antibiotic consumption is correlated with the density of general practices and the dispensing status of the physicians. Therefore, practice behaviour can be influenced by the regulatory policy
Provide better and comprehensive information on the antibiotic resistance issue in package inserts of antibiotics	Pharmaceutical industries, Interpharma, Swissmedic	

6. Concluding remarks

The National Research Programme "Antibiotic Resistance" (NRP 49) contributed significantly to a better understanding of the antibiotic resistance issue in Switzerland. Steps were undertaken for valuable implementation of the findings in all of the areas considered (e.g. public health, human medicine and infectiology, veterinary medicine, agriculture, food technology and food industry, bacteriology, pharmaceutical industry). The 27 research projects on antibiotic resistance conducted during the programme period made it possible, in particular, to:

- Establish SEARCH, a sentinel-based system for the monitoring of antibiotic resistance among pathogenic and commensal bacteria in human clinical samples, linked to antibiotic consumption data; SEARCH covers 60% of the annual hospitalisation days and 30% of the Swiss medical practitioners.
- Develop and implement new and sensitive analytical tools or strategies for the detection of bacterial resistance and antibiotics, for the estimation of antibiotic human consumption (which can be integrated into the SEARCH system) and for monitoring resistance from food animals or food products.
- Set up an important network of contacts at both the national and international level (i.e. with federal authorities, industry, research and diagnostic laboratories, international organisations) and to promote Switzerland as a member of international organisations in the domain of antibiotic resistance (i.e., EASAC, EARSS).
- Make important discoveries of new potential drug targets and of the mechanisms governing resistance, opening new opportunities for the management of serious bacterial infections.
- Recognise potential critical hazardous health situations, in particular for consumers, permitting the making of specific recommendations to authorities, politicians, industry, clinical laboratories, etc.

Thus, most of the objectives that were defined at the beginning of the programme were met. However, the social sciences were poorly represented despite specific calls for proposals addressed to the relevant academic institutes. In particular, ethics and economics aspects of resistance (for instance, the economic cost of resistance) remained uncovered. This apparent lack of interest among the social sciences experts is quite unfortunate.

The National Research Programme "Antibiotic Resistance" is to be considered an initial step in the management of antimicrobial resistance. We now dispose of established scientific knowledge and competence on the antibiotic resistance issue in all relevant areas. Switzerland is at last provided with a surveillance and alarm system detecting bacterial resistance in human clinical samples (SEARCH) and a monitoring strategy for bacteria isolated from animals for food consumption.

Nonetheless, a lot more has to be undertaken. Specialists, medical professionals and authorities are worried about the burden of antibiotic resistance, especially regarding its impact in the future. However, in Switzerland, the awareness of the problem is low and its consequences are underestimated. An essential action to address this situation would be to pursue the activities developed by NRP 49 (and above all the SEARCH related activities) through establishing a national antibiotic resistance centre (NARC).

7. Vision after NPR49: A National Antibiotic Resistance Centre (NARC)

Antibiotic resistance emergence and spread may be considered a global pandemic. The phenomenon is in a continuing evolution, and it is affecting countries at different rates. Although the resistance situation in Switzerland is not yet as worrying as in other European or non-European countries, it will likely deteriorate in the near future if the issue is not addressed efficiently. Its management requires constant monitoring activity, which has to be assured in Switzerland. Most European countries, including Switzerland's neighbouring countries Austria, Germany, Italy and France, have responded to the growing threat of antimicrobial resistance by setting up national surveillance systems and by co-operating internationally in the context of the European Antimicrobial Resistance Surveillance System (EARSS) and the European Surveillance on Antimicrobial Consumption (ESAC), in which also Switzerland now participates (thanks to NRP 49). STRAMA (the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance) in Sweden, DANMAP (The Danish Integrated Antimicrobial Resistance and Research Programme) in Denmark and NARMS (National Antimicrobial Resistance Monitoring System) in the United States are just three examples of a number of institutions that have been established to deal with the resistance problem. Most of them are financed by public money, and they co-operate closely with the national ministries of health and agriculture, which indicates the strong link between human and veterinary medicine in this area.
In addition, the recently established (2005) European Centre for Disease Prevention and Control (ECDC) in Stockholm is addressing antimicrobial resistance as a priority issue and will likely in the near future coordinate resistance surveillance, monitoring of drug consumption and interventions to prevent the emergence and spread of resistance.

The NRP 49 Steering Committee believes that after the end of the programme in 2007 the task of monitoring antibiotic resistance and consumption should be carried out by a national antibiotic resistance centre (NARC) built from the SEARCH project (Surveillance of Antibiotic Resistance in Switzerland) launched within NRP 49, which is already providing the first results. NRP 49 commissioned gfs.berne (a research institute in Bern)[27] to conduct a feasibility study of an antibiotic resistance centre. The purpose of the study was to define what demands the various stakeholders have regarding a national centre, what services that the centre should provide and how monitoring of antibiotic resistance could be financed after the conclusion of NRP 49 at the end of 2007. The feasibility study was conducted taking into account the current federal austerity measures. The main findings of the feasibility study are reported below.

Possible activities and priorities for NARC: Results of a survey by gfs-berne
The report by gfs.berne presents the results of a survey that gfs.berne conducted in 2005. This was a survey of 219 different experts and stakeholders on their demands regarding the services of an antibiotic resistance centre. The survey showed that there is great awareness of the problem of antibiotic resistance within the institutions to which the stakeholders belong. In comparison with other public health problems presented to the respondents in a list, the respondents classified antibiotic resistance as highly important today and even more important in 10 years' time. Antibiotic resistance, according to these stakeholders, is a more severe problem for Swiss public health policy than

[27] The research institute gfs.berne was tasked with planning the project, conducting and analysing various qualitative and quantitative surveys and providing a summary of the results. Dr. Heinz Locher Management- & Consulting Services, in co-operation with Innopool AG, Management Consulting, carried out a health-economic and business-economic analysis. The gfs.berne report is included on the accompanying CD gfs.berne. On the CD a broad excerpt from the Locher/Innopool report is also available Locher/Innopool: it provides an overview of the legal aspects relating to the role and responsibilities of the federal and cantonal authorities in the area of antibiotic resistance.

AIDS, allergies, influenza epidemics and Creutzfeldt-Jakob disease. It is interesting that the importance given to antibiotic resistance by the stakeholders is not reflected in high public awareness (on the contrary!). The stakeholders rated the idea of an antibiotic resistance centre as very positive: only 12 percent were against it, and 81 percent were completely or partially in favour.
The main task of the centre should be to analyse and link the data coming not only from the centre itself but also from other sources, and to provide the responsible actors with the results in a clear and understandable form. Activities that are already being conducted elsewhere (e.g. veterinary monitoring) should remain at their original place.
The tasks to be performed by a national centre can be classified in four groups, listed in order of decreasing desirability:

1. Surveillance: resistance and consumption data collection, statistical analysis and reporting. This also includes linking the system with the already established monitoring system in veterinary medicine.
2. Implementation: implementation of the results such as consulting, development of guidelines and training.
3. Applied research and execution of commissions provided by clients on a regular basis.
4. Market-oriented consulting activities: one-time commissions.

Most of the experts were also of the opinion that the NARC tasks are intrinsically of public or semi-public interest. The preferred organisational form was affiliation with a university, i.e. a semi-public organisational form.

According to the experts and the stakeholders, the NARC core tasks should be 'monitoring' (surveillance) and 'implementation'. Expansions of this core set activities ('applied research and commissions' and 'market-oriented consulting activities') are not of first priority and could be implemented in a second step.
Therefore, the minimum core set corresponds to continuation of the SEARCH programme, including the antibiotic consumption monitoring.

Financing NARC
The total annual budget to run SEARCH, with probable credit entries, was estimated as follows:

Total budget:	CHF 700,000
FOPH anticipated contribution as reference centre	CHF – 100,000
University of Bern contribution	CHF – 150,000
Total amount missing starting 2008:	CHF 450,000

Indeed, the FOPH, within the framework of contributions to the Swiss reference centres, has anticipated an amount of at least CHF 100,000, whereas the University of Bern together with the Inselspital (where SEARCH is presently located) will allocate approximately CHF 150,000, in addition to providing office spaces to SEARCH.[28]
The missing amount to balance the total NARC annual budget is hence CHF 450,000 in 2008 and thereafter.
Because the establishment of a centre such as NARC is well acknowledged among the experts and stakeholders, and because its independence from the private sector has to be preserved, it is important to secure the gap of CHF 450,000. The research institute gfs.bern was therefore also asked to explore different sources of financing. Among several alternatives, three different complementary scenarios seem the most promising:

[28] See enclosure UniBe_Inselspital_Letter.pdf

1) Hospitals pay contributions to the resistance monitoring in the framework of an integrated quality assessment process

The most realistic option is partial financing by hospitals, which pay contributions to the resistance monitoring in the framework of an integrated quality assessment process. Infections caused by micro-organisms that are directly related to hospitalisation (nosocomial infections) are directly connected with the service provision in hospitals, hence, according to Health Insurance Act Art. 16 on quality assessment, they have to be controlled by the hospitals. Monitoring, benchmarking with comparable hospitals and specific measures in the area of antibiotic resistance for individual hospitals might be developed in the framework of SEARCH, so that these services will become cost-effective thanks to quality improvement. This, then, would enable sustained financing by the hospitals themselves or by the Swiss Hospital Association H+. In other words, the antibiotic resistance rate within a medical institution would be considered a quality parameter, also related to the hospital hygiene condition.

This hospital-centred scenario is realistic and can be implemented without delay. The efforts towards a national system of quality assessment are supported by the FOPH and the Swiss Conference of Cantonal Ministers of Health (Clean Care Campaign). The FOPH and the Swiss Conference of Cantonal Ministers of Health undoubtedly consider the control of antibiotic resistance as part of these efforts. However, a strategy for a synergetic connection of resistance monitoring for the hospitals with the NARC project as a whole has to be defined. Clearly, NARC has to remain autonomous in order to assure the coverage of the community patients (as opposed to hospital patients) and so as not to endanger the co-operation with the laboratories and medical societies. In addition, the academic dimension has to be preserved so as to guarantee the multidisciplinary approach needed to address the resistance issue efficiently.

2) Direct financing by the cantons

The scenario above is intended to secure income to cover part of the costs of NARC, i.e. costs related to the surveillance within hospitals. Financing the other tasks foreseen for NARC (resistance surveillance and antibiotic consumption within the community patients, integration of the veterinary monitoring data, consulting, development of guidelines, training, etc.) might be ensured directly by the cantons. According to preliminary contacts established between a few representatives of NRP 49 and the Swiss Conference of Cantonal Ministers of Health, this scenario can be envisaged. Indeed, the cantons should be interested in controlling the antibiotic resistance situation, which, indirectly, would also contribute to better control of cantonal health expenses.

3) Contributions from sponsors

Sponsors can be used only as temporary additional sources of financing, for the efforts needed to find sponsors and the insecurity regarding amount and duration of their financial contributions would not allow long-term activity of the centre to be secured. The benefits for the potential sponsors have to be concrete and clear. Potential sponsors are the pharmaceutical and the generics-producing industries (one company has been approached and has expressed potential interest) or their associations (e.g. Interpharma, Intergenerika). However, the pharmaceutical industries do not have an interest in publicising problems with their own medications. In addition, today it is relatively difficult to obtain sponsoring: resources are limited and the duration short.

Conclusions

The Federal Council recognised the severity of the problems related to antibiotic resistance and responded by establishing the National Research Programme "Antibiotic Resistance" (NRP 49). In this context, SEARCH was established. SEARCH is a well connected and fully functioning antibiotic resistance monitoring system in Switzerland, covering both hospitalised and community patients. According to the NRP 49 Steering Committee and to most stakeholders and experts in the field, the establishment of a national antibiotic resistance centre (NARC) is vital to continue the antibiotic resistance and consumption monitoring in Switzerland as initiated by SEARCH. In addition, since bacterial resistance is a phenomenon that constantly evolves and that needs to be managed with diverse strategies, the presence of NARC would stimulate the scientific community to develop the strategies needed. Due to federal austerity measures, however, even continuation of SEARCH is by no means secure. In order to compensate for the reduced support of the federal authorities, a vast effort from health authorities and political actors on all levels is necessary. If SEARCH is discontinued, there will be information gaps and a loss of know-how, and a globally connected and unique monitoring system of antibiotic resistance would cease to exist. The risks related to that are unpredictable.

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