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1st SMS Meeting
4/5 September 2008
Bellinzona

1st Swiss Microbial Safety Meeting

Castelgrande Castle, Bellinzona

4-5 September 2008

Organisation

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Dr. Guido Vogel, MABRITEC, Basel

Welcome to Bellinzona!

The Meeting organisers welcome you all to this meeting.

The growing interest for biosafety in Switzerland is a response to the increasing social, economical and industrial concern connected to security in healthcare environments and to potential issues linked to biological incidents and accidents, as well as to epidemic, pandemic, or epizootic situations or bioterror.

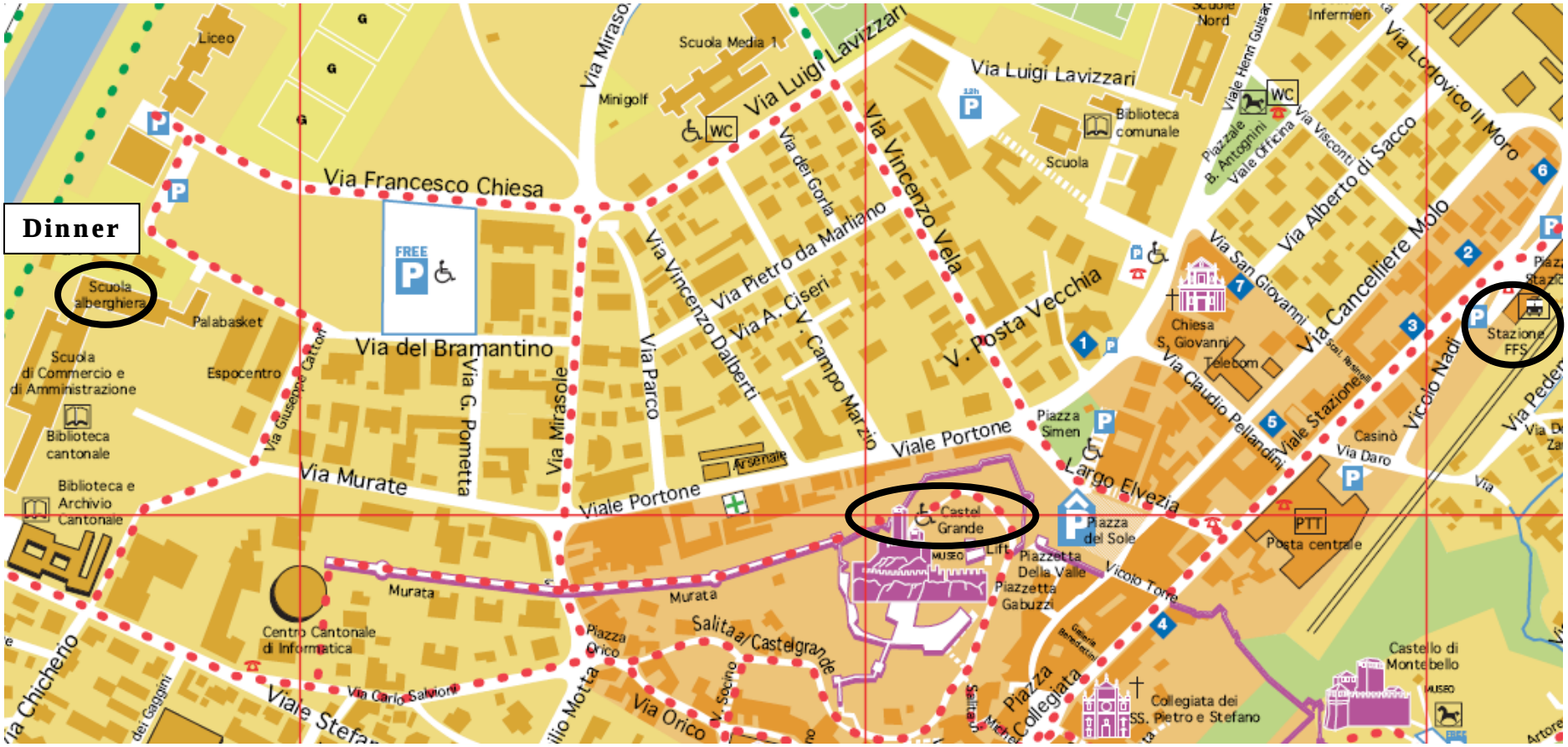
The meeting is organised under the auspices of the Swiss Society for Microbiology (SSM) and the Swiss Expert Committee for Biosafety (SECB). More than 100 participants from Switzerland as well as from institutes of other countries working in the field of biosafety attend this event. Medical, public health, research professionals in microbiology and other professionals will be able to exchange opinions and information on this topic. The meeting will also offer young researchers the opportunity to present their work, to network with senior scientists, and possibly to meet future employers.

The program includes important topics such as risk assessment, studies with highly pathogenic microorganisms, prevention of infection and contamination, as well as the response by health authorities to biosafety problems. Attendees will learn from experts how to best protect their communities from, and respond to biological events involving anthrax, smallpox, or other highly pathogenic microorganisms. New emerging methods will also be presented and discussed in a special session.

We wish you all a very successful meeting.

The SMS 2008 Meeting is 10 credits (hours) worth for FAMH professional training.

Bellinzona: how to get around in the centre



Meeting program

Thursday, 4 September 2008

09:00 **Registration**

10:10 **Welcome**
P. Pesenti, Member of the Government, Ct Ticino
O. Petrini

10:20 **Introduction**
M. Tonolla

10:30 **How dangerous are dangerous microorganisms?**
E. Peterhans

11:30 **Biosafety in Switzerland**
K. Summermatter

12:30 **Lunch break**

Session 1: Corporate Biosafety (Chair: I. Hunger-Glaser)

14:00 **Accidents and incidents in biocontainment laboratories: can they be avoided?**
C. Griot

14:30 **Biosafety in Production Units**
B. Wipf

15:00 **3-Step Risk Assessment of Human and Animal Cell Culture Activities**
U. Jenal

15:30 **Coffee break and poster session**

16:00 Biosafety in a university hospital
A. Foletti

16:30 Biosafety and experimental animals
M. Kuster

17:00 Transportation of infectious substances
J. Link

17:30 **A national Biosafety Curriculum**
D. Kümin

18:00 **Poster session**

19:30 **Dinner**

Friday, 5th September 2008

Session 2: Biological Threat (Chair: T. Rhomberg)

08:30 **Smallpox: should we care about a re-emergence?**
J.-C. Piffaretti

09:00 **Bioweapons and Biodefence**
M. Schütz

09:30 **Pandemic preparedness in Switzerland**
P. Durisch

10:00 **Coffee break and poster session**

Session 3: Tools and Methods (Chair: G. Vogel)

10:30 **New mass-based identification and screening methods for pathogenic microorganisms**
M. Welker

11:00 **Tubercolosis Research: (Bio)-Safety restraints from planning to publication**
S. Karlen

11:30 **Routine analytical procedures for monitoring biosafety compliance in laboratories, production facilities and the environment**
C. Beckmann

12:00 **Lunch break**

Session 4: Highly Pathogenic Viruses, Bacteria and Parasites (Chair: M. Engels)

13:30 **A New Home for Marburg Virus**
M. Eickmann

14:15 **Influenza Virus: biology and dangers**
Y. Thomas

14:45 **Anthrax - epidemiology, diagnostics, therapy, and prophylaxis: Current knowledge and new developments**
W. Beyer

15:15 ***Francisella tularensis*: new cases in human, wild and zoo animals. Where does the pathogen come from?**
P. Pilo

15:30 **Beyond Viagra®: New drugs for old diseases**
T. Seebeck

16:00 **Conclusions**
P. Meylan

16:15 **End of the meeting**

Abstracts

Keynote lectures

How dangerous are dangerous microorganisms?

Peterhans E
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Microorganisms may be viewed as dangerous, as useful, or as a nuisance. The way we categorize them depends on whether we, or our domestic animals, suffer detrimental effects (e.g. SARS, Ebola, influenza H5N1, African swine fever viruses), are only slightly disturbed (e.g. rhinoviruses) or profit from them (e.g. yeast turning grape juice into delicious wine).

In a historical perspective, dangerous viruses were viewed as beneficial as long as the unfortunate targets were those who competed for the same resources. The colonization of wide parts of the world by Europeans was aided greatly by a number of viruses that were more virulent for the indigenous peoples of the Americas, Australia and Africa than for Europeans. A well-known example is smallpox, which devastated native peoples in the Americas and Australia much more efficiently than it did in Europe. In return, however, European mortality in the tropics greatly exceeded that in Europe, due to diseases that were unknown in Europe, such as yellow fever.

A similar observation applies to many viruses crossing the species barrier from their "donor" hosts to what may be referred to as "recipient hosts". The term "emerging viruses" ignores that such viruses were "emerging" from their original hosts only because we, or our domestic animals, were entering the ecosystems in which such viruses had resided for millennia. Well-known examples are the African swine fever, myxomatosis in European rabbits (*Oryctolagus cuniculus*) and African horse sickness in horses, with warthogs, *Sylvilagus* spp. and certain species of zebra, respectively, being the chronically infected reservoir hosts.

Categorizing microorganisms as "dangerous" is understandable both from a medical and a veterinary viewpoint. Viewed through the eyes of the "donor" (or rather those of the evolutionary biologist), however, they represent a fitness advantage in the competition with the "recipients". Hence, dangerous viruses may have significantly contributed to biodiversity.

Biosafety in Switzerland

Summermatter K
Institute of Virology and Immunoprophylaxis (IVI), Mittelhäusern, Switzerland

A fundamental objective of laboratory biosafety is the containment of potentially harmful biological agents. The term "containment" is used to describe methods, facilities and equipment for safe managing of infectious materials in the laboratory environment where they are being handled or maintained. The purpose of containment is to minimize or eliminate exposure of laboratory workers, other persons, and the outside environment to potentially hazardous agents. Biosafety is achieved by implementing various degrees of laboratory control and containment, through laboratory design and access restrictions, personnel expertise and training, use of containment equipment, and safe methods of managing infectious materials.

National and international facilities are now facing a new challenge in safeguarding the public health from potential malicious use of dangerous biological agents or toxins. Therefore the laboratory biosecurity concept gains increasing attention worldwide. Complementary to biosafety laboratory, biosecurity focuses on the containment principles, technologies and practices that are implemented to prevent the unintentional exposure to biological agents and toxins, or their accidental release.

It has now been almost a decade since the Swiss legislation on biosafety, the Contained Use Ordinance (CO), the Ordinance on the Protection of the Employees against micro-organisms (OPEM) and the Ordinance on Deliberate Releases into the Environment (ODRE) came into force. Compared to international legislation in the area of biosafety, the Swiss ordinances still meet the highest standards in many aspects.

References:

WHO Laboratory biosafety manual, third edition, 2004:
http://www.who.int/csr/resources/publications/biosafety/Labbiosafety.pdf

Biosafety in Microbiological and Biomedical Laboratories, CDC/NIH, 2007:
http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm

Session 1

Accidents and incidents in biocontainment laboratories: can they be avoided?

Griot C, Summermatter K
Institute of Virology and Immunoprophylaxis, IVI, Swiss Federal Veterinary Office, Mittelhäusern, Switzerland

Animal diseases such as foot and mouth disease, avian influenza, classical swine fever and most recently bluetongue are a continuing threat to livestock. Outbreaks always have an enormous impact on the agriculture and on the economy of the affected country. Most countries within the European Union have biocontainment facilities that are OIE and/or EU reference laboratories for selected animal disease pathogens. These are highly specialized laboratories where work with known and unknown infectious agents is conducted without risk of their escape to the environment and without health risk to the laboratory staff. Most of these facilities are commissioned and financed by the local government, while few are part of (commercial) livestock vaccine production units. These facilities, however, have the potential to be responsible for disease outbreaks, for example if organisms are accidentally released into the environment. Fortunately, secure biocontainment facilities, in which these dangerous pathogens are handled, have had an excellent (albeit not perfect) biosecurity/biosafety record.

For safe operation, specific requirements need to be met. Besides technical aspects such as air filtration and waste water treatment, the biosecurity and biosafety of a facility is of outmost importance. For human pathogens this includes protection of both laboratory workers and environment; For animal pathogens the main emphasis is on preventing infectious agent release into the environment. In “aging” facilities, additional aspects deserve special attention to maintain safe operation levels.

Any accidental release from a biocontainment facility is of concern to the public and raises issues of public trust in both science and government. This is important not only to understand what went wrong and how to prevent it from happening again, but also to allow consideration of any more widely applicable issues that this incidents raise. In recent years, the emergence and re-emergence of new diseases which threaten public as well as animal health have been recognized. The facilities that will be handling these agents need to guarantee a safe operation, now and in the future with the appropriate financial and personal resources to allow preventive

maintenance and proper training. Furthermore, the international biosafety community has taken the initiative for the development of an international laboratory biosafety and biosecurity management standard. This new standard, overseen by the European Committee for Standardization (CEN), has been published (CWA 15793:2008 Laboratory biorisk management standard).

Biosafety in Production Units

Wipf B, Plaga A, Hanlon SP, Kupfer E
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Biotechnical production units use bioreactors ranging in size from 10L – 100 m^3 for the production of materials. The nature of the material can be as simple as ethanol or very complex as an antibody. Biosafety aspects can be on the one hand the prevention of contamination of the desired product of a *per se* unproblematic fermentation with some potentially hazardous agent or the manufacturing of a product using an organism classified in a risk class higher than 1. Especially the manufacturing of biological pharmaceuticals (proteins) using mammalian cell cultures needs extensive precautions to prevent the contamination of the cultures and the product with microorganisms or viruses. Critical steps in media preparation and downstream process are discussed. The technical equipment of a pilot plant used also for the cultivation of biosafety class 2 organisms is described. In this pilot plant, a microbiological reduction (biotransformation) of an intermediate could successfully replace an enantioselective reduction by a heavy metal catalyst. This reaction was developed using a biosafety class 2 organism in 100 L scale for the production of more than 10 kg of an intermediate in the synthesis of a compound for clinical trials. The details of the critical steps are shown that allow a safe operation of such biotransformations.

3-Step Risk Assessment of Human and Animal Cell Culture Activities

Jenal U, Stroot P
Jenal & Partners Biosafety Consulting, Rheinfelden, Switzerland

A new draft guidance document for the risk assessment of human and animal cells and cell culture activities was developed by Jenal & Partners Biosafety Consulting on behalf of the Biosafety Section of the Office for Waste, Water, Energy and Air of the Canton of Zurich.

The goal of the new guidance was to provide a scientifically sound risk assessment approach that would meet the requirements of safe biosafety practices, support users and authorities in their risk evaluation and get wide acceptance from experts.

The newly proposed risk assessment for cell culture activities consists of 3 steps: (1) the assignment of cells to a risk group according to their characteristics; (2) the assignment of the type of activity (transformation, virus production ...) with these cells to a provisional risk class; and (3) the determination of the definitive risk class from considering whether control measures (authentication, contamination) were to be put in place during the assessed activity.

The risk assessment of cell cultures is very specific and appears much more difficult than the risk assessment of many other biological agents or materials. Reasons for this are the complexity of the cell metabolism and interactions, the diversity of the cell lines, their origin and the transformations they have undergone, the impact of the culture conditions on their characteristics, their relatively poor traceability, the difficulties and limitations of the testing, the importance of the work practices and the environment.

The guidance presented here is based on the scientific bases for the risk assessment of cell lines and cell culture activities. It considers the guidelines and practices in place in different countries and organisations, and analyses their pitfalls.

Biosafety in a university hospital

Foletti A
Biosafety and Security Coordinator at the University Hospital of Lausanne (CHUV)

The name hospital comes from Latin *hospes* (host), which is also the root for the words *hotel*, *hostel*, and *hospitality*. By definition open to everybody, a university hospital has generally three missions: the first and leading one are the health cares, then come the teaching and finally the research.

And biosafety? Among the multiple services that compose the hospital, three are particularly relevant for biosafety:

1) Health care services, with focus on the patients and their treatments, are confronted with the difficult problem of nosocomial infections. They are under the supervision of the infectious control unit, which may also be considerer as the origin of the actual biosafety.
2) Diagnostic laboratories which, with the progressive analysis automation, tend to evolve towards semi-industrial processes and industrial production lines. Increasingly concerned by questions related to traceability, cost reduction, normalization, biosafety is generally integrated to the quality management.
3) Research laboratories, where the keywords are discovery and innovation and where the genetically modified organisms are source of hope but also at the origin of the still unresolved questions concerning their use and environmental dissemination.

These three different units have their own (corporate) culture, as well as targets and problems to solve. Diversity is of course beautiful and stimulating but may give rise to some incongruity if two different cultures are juxtaposed. Setting up and maintaining biosafety in a hospital not only require a good background in biology and some specific technical notions but also needs good communication, negotiation and management skills. All these aspects are necessary for the continuous fine tuning of the right equilibrium and compromise, which are essential for the harmonious cohabitations of the three services.

Biosafety and experimental animals

Kuster M,
Corporate Health and Biosafety Manager, Novartis International AG, CH-4002 Basel

Animals are a fixed item in the every-day work of many people in numerous occupations. The work with and around animals encompasses two aspects: biological safety and "process safety", leading to injuries and illness.

This presentation should provide an overview over the present state of the art of prevention and treatment of animal related occupational injuries and illnesses.

The first part of the presentation deals with animal handling related occupational injuries. Bites and scratches are recorded at a low frequency due to the training and experience of those involved in animal work. However, some bites may involve a high risk to develop treatable infections. Two infections, rabies and Herpes B, however rare in occurrence, deserve special attention due to the severity of the consequences.

The second part of the presentation describes occupational illnesses related to handling of animals. In the first section, animal related occupational infections (zoonoses) are reviewed. These might be rare, but as some of the animals come from the wild, they might carry some specific diseases. Prevention measures include veterinary medicine surveillance and, if the disease is artificially introduced, precautions according to the risk group of the agents.

The second section tackles the issue of laboratory animal allergy (LAA). Over the last few years, important insight into the patho-physiological mechanisms of LAA and how to deal with the issue with engineering measures came into the relevant literature. The presentation will also try to show why keeping the allergen levels to rodents below 5 ng/m^3 might be a good start, despite the fact that the levels of non-reactivity of allergens vary substantially.

Handling of animals is often carried out by using latex gloves and the rationale for or against their use is also discussed.

Transportation of infectious substances

Link J
Federal Expert Commission for Biosafety, Berne Switzerland

When not correctly packaged, biological material containing pathogenic and genetically modified organisms may pose a risk for people involved in its transportation and may also endanger the environment in the event of unintended release due to broken, leaking or improperly packaged material. For the purpose of transportation, some pathogenic and genetically modified organisms are therefore classed as dangerous goods and are regulated by international dangerous goods regulations. Under these regulations, pathogenic organisms are referred to as infectious substances and are divided into two categories. These categories are only indirectly related to the commonly used risk group concept. Category A comprises infectious substances capable of causing permanent disability or life-threatening or fatal disease in otherwise healthy humans and animals. In general, viruses and bacteria of risk groups 3 and 4 are assigned to this category. Category B contains substances that do not fall into category A, and is the more frequently used transport category. Because of the differences between the hazards posed by category A and category B infectious substances, there are differences in the packaging, labelling and documentation requirements for the two categories. While category A infectious substances may only be transported by licensed carriers, category B infectious substances can be shipped through normal postal services.

There are some exemptions from dangerous goods regulations. For instance, because of the low level of hazard they present, environmental samples and human and animal specimens where there is only a minimal likelihood that pathogens are present, are not considered as dangerous goods.

Useful Links:

Practical explanation of the transport, import and export of substances consisting of or containing pathogenic or genetically modified (micro)organisms, provided by the Federal Expert Commission for Biosafety: http://www.efbs.admin.ch/en/transport/index.html

Guidance on regulations for the transport of infectious substances 2007-2008, WHO: http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2007_2cc.pdf

A National Biosafety Curriculum

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[2]Federal Department of Home Affairs (DHA), Federal Office of Public Health (FOPH), Seilerstrasse 8, 3011 Bern
[3]Swiss National Accident Insurance Fund (SUVA), Occupational Safety, Rösslimattstrasse 39, 6002 Luzern
[4]Federal Expert Commission for Biosafety (FECB), Worblentalstrasse 68, 3063 Ittigen
[5]State Laboratory of the Canton Basel-Stadt, Chemical and Biological Safety, Kannenfeldstrasse 2, 4056 Basel
[6]Ecole Polytechnique Fédéral de Lausanne, EPFL SV BS, 1015 Lausanne

Good microbiological practice, biosafety officers (BSOs) with sufficient knowledge and skills and a biorisk management system are the three main pillars that ensure that biosafety and biosecurity are addressed and managed properly in biorisk facilities. The BSO plays a pivotal role when it comes to setting up and implementing the management system including – to name just the most important elements – risk assessment and management, safeguard, training and controlling its implementation and application. In Switzerland, the Containment Ordinance and the Ordinance on Occupational Safety in Biotechnology stipulate that each facility must assign at least one person to oversee the biological safety. In order to fulfil the job, this person must have a sufficient professional background and knowledge in safety issues, but no further details in relation to the person's background and training are given in the legislation.

Here, we propose a biosafety curriculum that covers all necessary aspects of biosafety and biosecurity in relation to the respective needs at the different levels of biosafety. We outline the curricular timetable, subjects to be covered as well as propose courses that go into more specific details regarding the individual needs of BSOs. Furthermore, we would like to demonstrate the incorporation of the Swiss Biosafety Curriculum into the European Curriculum Initiative currently being elucidated.

Session 2

Smallpox: should we care about a re-emergence?

Piffaretti JC, Convert M
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The last natural smallpox infection was identified in 1977 in Somalia and the last fatal case was reported in 1978 in Birmingham, England, as a laboratory-acquired case. Systematic vaccination was stopped worldwide at the beginning of the 80ies, in Switzerland in 1972. Today, two smallpox virus stocks are officially known to the WHO. One is kept at the CDC in Atlanta, U.S.A., the other at Vector in Koltsovo, Russia. These stocks are held only for research purposes. However, concern has been rising that additional stocks may be present in unidentified laboratories, either as forgotten items in old viral collections or to generate stockpiles to use as weapons or bioterrorism agents. This is why a number of countries, including Switzerland, are preparing smallpox contingency plans.

If smallpox should recur somewhere in the world, this would be considered a serious threat to public health. The extent of the event would depend on various factors, among which: i) the clinical and laboratory diagnostic capacities; ii) the residual immunity level of the target population; iii) the amount of the vaccine doses available (most are first generation vaccines with relevant side effects); iv) the availability of efficient anti-viral drugs (presently in development but difficult to evaluate). One crucial factor is the effective reproductive rate R (i.e., the average number of secondary cases infected by each primary case). Recently, R has been estimated to range between 3.5 and 6, which would cause a rather rapid epidemic rise before the public health interventions would contain the event. The establishment and maintenance of rapid diagnostic capacities together with vaccination are still the most important measures to control a potential smallpox resurgence. This constitutes a difficult problem to solve for public-health decision-makers confronted with an unlikely event, but still with severe consequences in case of occurrence.

Bioweapons and Biodefence

Schütz M
Spiez Laboratory, Spiez, Switzerland

Bioweapons are microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes. It is not the biological agent itself, but the intention to use it (or the use) for hostile purposes, that makes a weapon or a warfare agent out of it.

Progress in molecular and cell biology, genetics, microbiology, and other life science disciplines results in incredible benefits. However, the risk of misuse is increasing and poses a challenge to public health and national security. All stakeholders in life science need to be aware of the dual-use character of their work. Responsible behaviour (e.g. through compliance with codes of conduct) is essential and a very important element of biodefence.

Besides awareness raising in the scientific community, another important element of biodefence is to build-up capacities and capabilities for rapid and reliable detection of biological agents. In this respect, the new maximum containment laboratory in Spiez is a good example and will be discussed.

Pandemic Preparedness in Switzerland

Durisch P
Pandemic Preparedness Unit, Federal Office of Public Health, Bern, Switzerland

Since 2003, the H5N1 virus continues to spread amongst wild birds and domestic poultry in Asia, Africa and Europe. Isolated human cases are regularly confirmed by WHO in Asia and Africa. However, the risk of infection for human beings is extremely weak, and the known cases are practically always linked to direct contact with contaminated poultry or its secretions. Currently, we are in the alert phase 3 out of the 6 defined by WHO.

The risk of adaptation of the avian virus remains present. The Director-General of WHO reminded last May about three global crises looming on the horizon: food security, climate change and pandemic influenza. It is not time to let down the guard, and each state should be best prepared to face this menace.

The Swiss Influenza pandemic plan (www.bag.admin.ch/pandemic) issued by the FOPH describes the measures developed to prevent the introduction and transmission of a pandemic virus in Switzerland and to limit its consequences on persons, the economy and the essential services of the country. Simultaneously, this document serves as a reference for the cantons, hospitals and businesses to prepare their own operational plans. An evaluation carried out by WHO Europe in October 2007 showed that Switzerland is amongst the best prepared countries in Europe. The Swiss Influenza pandemic plan will be once again updated in 2008.

Presently, three major challenges can be underlined:

1. The recently increasing emerging phenomenon of resistance to oseltamivir, which urges to carefully rethink the strategy of utilisation of antiviral drugs;
2. The organisation of a mass vaccination campaign with the H5N1 pre-pandemic vaccine (of which 8 million doses are stockpiled by Switzerland), with a study undergoing to gain experience with this product;
3. The distribution and coordination of tasks between the Confederation and the cantons, in particular around communication.

Session 3

New mass-based identification and screening methods for pathogenic microorganisms

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Identification of pathogenic microorganisms in the clinical routine diagnostics is currently based primarily on biochemical methods probing the metabolic capacities of an isolate. A major drawback of this approach is the need to cultivate an isolate on a series of different culture media for at least six hours before a result is available. Further, a pre-selection for the correct test series has to be made based on the experience of the analyst. A completely different approach to identify microorganisms is based on mass spectrometry of intact cells. Matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has been shown to have the power to discriminate species or even strain in a wide array of microbial taxa, including Archaea, Eubacteria, and Protista based on mass fingerprints (from 2,000 to 20,000 Da). For a number of species the majority of recorded mass signals represent abundant proteins such as ribosomal proteins. Thus, the mass fingerprints have a truly taxonomic value and a reliable identification is possible by comparing mass fingerprints of an unknown specimen to mass fingerprints of designated reference strains. A database of reference mass fingerprints is the core of SARAMIS™ (Spectral Archive And Microbial Identification System) developed by AnagnosTec. To identify an unknown specimen, SARAMIS™ compares its mass fingerprint to SuperSpectra™ that consolidate mass spectral information of multiple strains and samples of particular species. The system has been tested with success in clinical routine in several laboratories. For example, approximately 500 isolates from urine samples were analysed, 97% of which were identified correctly. The remaining 3% either gave no result or no mass fingerprint of sufficient quality could be obtained, thus indicating that no false positive results occurred. Mass-based microbial identification methods are therefore ready for the routine application in clinical diagnostics.

Tuberculosis Research: (Bio)-safety restraints from planning to publication

Karlen S
Faculty of Life Sciences, Swiss Federal Institute of Technology, Lausanne.

Working with the aeropathogen *Mycobacterium tuberculosis* (TB) might be hazardous, especially in a research environment where highly concentrated bacterial cultures may be produced. TB belongs to risk group 3 and as such, with the exception of some clinical samples, must be handled in a biosafety level 3 (BSL3) environment.

BSL3 requires specific safety means both in terms of equipment (e.g. aerosol-proofed rotors and centrifuges, respirators, inoculators) and in terms of infrastructures (e.g. sealed laboratory spaces, air filtration, water decontamination). Here, we review some of the tools we have implemented or developed at EPFL to meet the safety standards required to work with TB, with a specific emphasis on water, air and surface decontamination. Our experience with VHP (vaporized hydrogen peroxide) will be described.

Routine analytical procedures for monitoring biosafety compliance in laboratories, production facilities and the environment

Beckmann C[1], Alt M[1], Vogel G[2], Vögeli U[1], Brodmann P[1], Bagutti C[1]
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[2] Mabritec AG, Socinstrasse 57, 4002 Basel, Switzerland

The use of pathogenic and genetically modified organisms requires appropriate containment measures to ensure public and environmental safety. As an enforcement agency for biological safety guidelines (Containment Ordinance, Release Ordinance) we establish versatile methods for sampling laboratory surfaces (e.g. centrifuges, work benches) during biosafety inspections and for detecting and quantifying specific microbial contaminations. The methods developed in our lab comprise also tools to follow an accidental release of organisms into the environment as well as along potential escape paths. Additionally, a monitoring system has been established to survey the appearance and dissemination of genetically modified plants into Switzerland based on the screening of pollen.

The range of methods developed in our laboratory and significant for monitoring pathogenic and genetically-modified organisms comprise:

- Extraction of DNA and RNA from swabs or samples taken from pollen baskets, soil, sewage or working clothes
- Detection of specific microbial or plant DNA and RNA using real time PCR
- Detection of live organisms in samples by infectivity tests (viruses) or in-culture-quantitative PCR (bacteria);
- Identification of bacteria by MALDI-TOF MS analysis.

Session 4

A New Home for Marburg Virus

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Marburg virus is a member of the family *filoviridae*, which also includes the genus Ebola virus. Marburg virus was first recognized in 1967, when outbreaks of haemorrhagic fever occurred simultaneously in laboratories in Marburg and Frankfurt, Germany and in Belgrade, Yugoslavia. The first people infected had been exposed to African green monkeys or their tissues. Since 1967, members of the Institute of virology are investigating the nature of the virus. The need of BSL4 facilities within Europe was underlined by the recent Marburg virus infection of a tourist, who travelled to Uganda, Africa, and died of haemorrhagic fever after returning to Leiden, Netherlands, in July 2008.

After forty years of research and diagnostics a new building was designed and constructed to host genetic engineering of viruses. Before and during the construction stage biosafety was the main issue for the construction team. First of all requirements had to be defined. For example the leak tightness of the construction had to be calculated and special technical equipment was designed and assembled. After two years of construction and validation the new BSL4 laboratory was opened in December 2007. 11.4 million Euros were spent for the building with six floors and approximately 160 m^2 lab area. Fourteen researchers and two engineers are authorized to enter the building. Research on Marburg virus, Ebola virus, Nipah virus and highly pathogenic Arenaviridae is the main task, and the preparedness for diagnostics of hemorrhagic fever viruses is an additional responsibility of the lab.

Influenza virus : biology and dangers

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Influenza viruses circulate both in animal and humans. Animal viruses, particularly those infecting avian species, exhibit different types of pathogenic behaviour according to the species infected. Thus the currently circulating highly pathogenic H5N1 virus can easily kill chicken, while it leads to an asymptomatic shedding in other species. Until 2008, the H5N1 virus has evolved as an avian adapted virus that failed to cross species barrier in an efficient way. However as an ever evolving virus, influenza can accumulate point mutations or acquire new genes following reassortment. This could lead to the acquisition of new tropisms and provide the virus with the ability to be transmissible across the human kind. The specificity for the animal world is mainly related to the receptor affinity limiting the virus in its ability to infect human. In less than 6 years, 9 different clades and 8 subclades have been observed. Some have already disappeared while other acquired the ability to infect humans and birds. At this time, none of these clades seems to be associated with a higher mortality or a higher risk of transmission in humans.

Among the different tools available to fight H5N1 viruses, countries have stockpiled antiviral drugs or vaccines. The recent circulation of an influenza A (H1N1) virus resistant to oseltamivir highlights the ability of this virus to generate unexpected mutants in absence of persisting drug pressure. This resistance was related to only one mutation and did not seem to have impaired the virus with his ability to be transmissible. It is known that the risk does exist that resistant H5N1 viruses emerge under treatment; we thus have to keep in mind that any antiviral drugs strategy needs to consider the dangers related to the biology of this virus. Another important feature of risk assessment is avian influenza diagnosis.

Anthrax - epidemiology, diagnostics, therapy, and prophylaxis: Current knowledge and new developments

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Bacillus anthracis is the etiological agent of Anthrax, a potentially fatal disease of wildlife, livestock, and humans. While rather simple in clinical samples, the identification of *B. anthracis* from environmental and bioterrorism related samples still requires well-trained laboratories. Environmental samples will generally harbour large quantities of competing *Bacillus* spp., among them representatives of the *B. cereus sensu lato* group, near relatives of *B. anthracis*. These materials always bear the danger of false positive or even false negative results. Molecular fingerprinting methods like SNR analysis or MLVA with up to 31 VNTR-markers now allow for molecular-epidemiological and also forensic investigations of outbreaks and help to distinguish between *B. anthracis* and its near relatives isolated from Anthrax like diseases. Currently approved antibiotic treatments of Anthrax do not address the damaging action of the toxins, and hence will not help after the onset of toxin related organ failures. Moreover, multiresistant strains probably would escape from treatment. New therapeutic approaches, therefore, should comprise antitoxic and antibacterial activities as well and should be effective also against multiresistant strains. Different from life spore vaccines, acellular vaccines used in humans do not prevent the replication of the organisms. New developments in vaccine research are therefore directed to multicomponent vaccines, eliciting an antitoxic as well as an antibacterial immunity. This can be achieved by using different antigens from the toxin complex, the vegetative cell and the spore, complexed with new adjuvants or by taking advantage of new vaccine delivery systems. Contributions from the anthrax laboratory in Hohenheim to all those fields will be presented.

Francisella tularensis: New cases in humans, wild and zoo animals: Where does the pathogen come from?

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Francisella tularensis is the causative agent of tularemia. Re/emergence of this zoonotic disease in European countries poses public health issues. Knowledge of the epidemiology of natural distribution of strains will aid medical authorities to take appropriate measures in the event of natural outbreaks as well as in case of the suspicion of a deliberate release of the causative agent. To this end, we have genetically characterized Swiss strains of *F. tularensis* isolated between 1996 and 2008 from animals and humans and performed antibiotic susceptibility analysis. Swiss strains were found to belong to *F. tularensis* subsp. *holarctica* and genetically closely related with strains from Spain and France. All strains showed a chromosomal deletion denoted RD23, recently reported as specific to strains from France and the Iberian Peninsula. All Swiss strains were found to be susceptible to antibiotics currently used for treatment of tularemia, *i.e.*, aminoglycosides, ciprofloxacin, tetracycline, and additionally to erythromycin. These results suggest that highly related clones of a specific *F. tularensis* subpopulation are naturally more widely dispersed in western parts of continental Europe than previously thought.

Beyond Viagra®: New drugs for old diseases

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Protozoal diseases such as African sleeping sickness, Chagas disease, Leishmaniasis or Malaria threaten a large part of humankind and are important causes for illness, death and economic misery throughout the world. With no vaccination available and great problems with prevention, chemotherapy is often the last and only resort. Tragically, chemotherapy for all these diseases is at a dismal state, for a variety of reasons.

Cyclic nucleotide specific phosphodiesterases (PDEs) are crucial enzymes in biological signal transduction. The human genome codes for eleven families of PDEs. All are being explored as drug targets for treating conditions from erectile dysfunction to cardiovascular problems and impairment of cognitive functions. Recent work with parasitic protozoa has demonstrated that these organisms also contain PDEs that are very similar to their human counterparts, both in their domain organization and in the three-dimensional structure of their catalytic domains. In *Trypanosoma brucei*, the causative agent of African sleeping sickness, PDEs were genetically validated as drug targets by demonstrating that genetic deletion of the corresponding genes, or strong reduction of enzyme levels by RNA interference, is lethal for the parasite, both in cell culture and in the mouse model.

These findings indicate that the extensive know-how accumulated by the pharmaceutical industry while developing inhibitors for the various human PDEs might also be applicable to parasite PDEs. High-throughout screening of compound libraries and *in-silico* screening of virtual libraries have confirmed the validity of this concept. PDE-inhibitors might potentially constitute a novel generation of anti-parasitic drugs.

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Posters

Biosecurity controls of *Bacillus thuringiensis* subsp. i*sraelensis* in the natural wetland reserve Bolle di Magadino

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Bacillus thuringiensis subsp. *israelensis (Bti)*, is an effective and efficient insecticide against mosquito larvae. The monitoring of its impact on the ecosystem is currently carried out in a Swiss wetland reserve, the Bolle di Magadino where, since 1988, the *Bti* product Vectobac-G® is successfully used against the mosquito *Aedes vexans*. During the summer, this insect is generally present at high densities and repeated *Bti* treatments are needed. The genes *cry* and *cyt* coding for the insecticidal proteins of *Bti* are located on a large plasmid. A method based on recovery by cultivation, specific *cry4* genes amplification and ribotyping was developed for the detection of viable *Bti* strains in soil, sediment and water. Analyses of soil samples were performed during a whole year. In two of three sites invesetigated, an increase of *Bti* spores was observed after insecticide treatment, followed by a progressive decrease (about 80% after 60 days).

Mosquitocidal proteins were detected by an ELISA test in selected soil and sediment sites. This quantification test was combined with biotests against *Aedes aegypti* larvae to determine their residual toxicity in the environment. The results showed that, although these toxins were present at relatively high concentrations (6,244 ng/g dry substance) in the wetland reserve, they did not show any activity against mosquito larvae.

We are currently working on the development of more rapid methods for the direct quantification of *Bti* spores in soil, based on DNA extraction without culturing, followed by real-time PCR of the *cry4* endotoxin genes. Moreover, Matrix Assisted Laser Desorption Ionisation – Time-of-Flight mass spectrometry (MALDI-TOF MS) analysis of strains and toxins from the *B. cereus* group is underway to enable: *i)* a rapid detection after cultivation, *ii)* the search of specific biomarkers for *Bti*.

Fast screening methods in drinking water microbiology based on flow cytometry

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Throughout the world the hygienic quality of drinking water and recreational water is based on the analysis of two microbiological parameters: the heterotrophic plate count (HPC) and the search for the faecal indicator bacterium *Escherichia coli*. Both methods were developed originally more than a hundred years ago and have so far served their purpose fairly well. Although they were improved over the years they still have the disadvantage of being slow (*E. coli* and HPC) and insensitive (HPC). Testing for specific pathogenic bacteria requires usually even more time and effort. Also the many recently developed molecular methods have a number of disadvantages. Despite the multitude of analytical techniques presently available there is an urgent need for methods that allow a fast, reliable and cheap assessment of the hygienic state of a water sample within 1-2 hours. Flow cytometry has the potential to fill this gap because it allows detecting cells quickly after staining with fluorescent dyes. We have investigated several possible applications of flow cytometry for the fast detection of total cells, their viability, as well as for the screening for specific pathogenic microbes after fast immuno-enrichment and immuno-staining. Our work shows that flow cytometry has a large potential for fast and easy detection and quantification of microbial hygiene parameters. Flow cytometric determination of total and viable bacterial cell numbers can already now supplement (or on the long-term even replace) the established heterotrophic plate count method. The results reported here also indicate that many different techniques for the fast screening of pathogens can be developed based on immuno-magnetic enrichment and immuno-staining procedures, which will allow for the fast screening for target organisms in raw and drinking water.

Differentiation of bacteria, spores and “white powders” by MALDI-TOF MS fingerprints

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Worldwide there is an evident danger for the use of biological hazardous agents as weapons of mass destruction. The potential spectrum of bioterrorism ranges from hoaxes to classical biological warfare agents, which could produce mass casualties. Therefore, the reliable and fast identification of bacteria, spores as well as “white powders” is a challenging task. MALDI-TOF mass spectrometry fingerprinting has been shown to be suitable for the identification of microorganisms without any prior assessment. Here we present a MALDI-TOF MS based system which allows identification of bacteria as well as spores and which is able to discriminate hoaxes from real biological threats.

Bacteria, spores and “white powders” were processed using a short inactivation/extraction protocol. Mass spectra were acquired with a benchtop instrument in the mass range from 2,000 to 20,000 Dalton. Based on the acquired profile spectra reference data sets were created containing species-related information. These databases were used for analysis by different dedicated software algorithms, i.e. pattern matching, weighted pattern matching, principle component analysis and correlation analysis. Even different *Francisella tularensis* subtypes of the same species could be distinguished with the described method. Furthermore, mass spectra of spores as well as “white powders” are distinguishable because of their mass spectrometric pattern. Spores from different species of the *Bacillus cereus* group were analyzed. Small acid soluble proteins expressed in spores could be detected which allowed a discrimination of these species. Furthermore, the analysis of “white powders” (e.g. flour) demonstrated the applicability of this system for different threat scenarios.

Rapid identification of *Legionella* Spp. by MALDI-TOF MS based protein mass fingerprinting

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MALDI-TOF MS (matrix assisted laser desorption ionization – time of flight mass spectrometry) is becoming a popular tool for the identification and classification of bacterial and fungal species since commercial database applications are available for diagnostic and research purposes.

Legionnaires' disease (LD) is a severe form of pneumonia caused by *Legionella* spp. These bacteria are naturally present in water and soil in association with amoebae and other protozoa that act as reservoirs for their survival and as vectors for their spread via bioaerosols. The identification of *Legionella* spp. which was previously based on serological tests is now performed mainly by sequencing of the *mip* gene (macrophage infectivity potentiator).

The aim of this study was to use intact cell MALDI-TOF MS (ICMS) for the identification of *Legionella* spp. For this purpose, SuperSpectra™ were created by choosing specific biomarkers shared by different strains of the same *Legionella* species isolated from different environments. A set of *Legionella* reference strains and naturally occurring strains representing 22 different species were analyzed by ICMS in combination with the SARAMIS™ (spectral archive and microbial identification system) application from Anagnostec. The amount and the quality of specific biomarkers for each *Legionella* species necessary for their unambiguous characterization and identification were determined. Choosing appropriate sets of biomarkers it was possible to create specific SuperSpectra™ recognizing the more frequently isolated *Legionella* species. These SuperSpectra™ were tested for their ability to identify naturally occurring *Legionella* strains isolated from water samples, cooling towers, potting soils and patient's specimen collected by the National Reference Center for Legionella in Bellinzona and previously identified by standard methods (mip-sequencing).

Most strains isolated from the environment could be identified by MALDI-TOF thanks to the new SuperSpectra™. The identification by MALDI-TOF is very quick and easy to perform and also has the advantage of being time- and cost-saving in respect to sequence-based identification.

Classification and identification of bacteria strains by MALDI-TOF MS using the SARAMIS™ database

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Identification of bacteria by MALDI-TOF MS is an emerging new technology. This technique provides specific biomarker profiles that can be used for identification at the genus, species or even subspecies level. The purpose of this study was to investigate the robustness/reliability of the SARAMIS™ database that allows the identification of bacteria analysed with MALDI-TOF MS. In addition, 100 strains of the genus *Yersinia* were classified.

To test the robustness/reliability of the data base, selected bacterial strains were analysed with MALDI-TOF MS under varying cultivation conditions and identified with SARAMIS™. The examination of the influence of tri-fluor-acetic acid (TFA)-inactivation was an integral part of this study. TFA-inactivation changes the composition of the peptides of the different bacteria strains. There are indications that the cultivation conditions also influence the composition of some bacteria strains. This has to be considered in the identification process. The super spectra needed for a reliable identification require mass spectra from varying cultivation conditions as well as from TFA-inactivated bacteria strains.

Yersinia strains were cultivated on agar plates and analysed with MALDI-TOF MS. The generated mass spectra were depicted as dendrograms (family trees) in the SARAMIS™ database. The classification of *Yersinia* strains shows that in most cases there are different groups corresponding to the different species. The two most important sub-groups of the species *Yersinia enterocolitica* are biotype 1 and 4. The species *Yersinia frederiksenii* can be divided into three groups. *Yersinia pestis* and *Yersinia pseudotuberculosis* each form a group on their own. The measured difference between these two groups is 1%.

Rapid detection and enumeration of *Giardia lamblia* cysts

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Giardia lamblia is an important waterborne pathogen and the most common intestinal parasite of humans worldwide. Giardia cysts are reported to be strongly resistant to disinfection, including chlorination, and difficult to remove by standard filtration as well as being characterised by low infection doses, which can be as low as 1-10 cysts. The fecal-oral transmission leads to contamination in the environment and, so far, reliable quantitative rapid-screenings are not available for various matrices such as tap waters, surface-waters and wastewater. The necessity to establish methods that enable reliable rapid detection of a single cyst in 10-100 liter of drinking water has been clearly expressed.

We have developed a method that consists of filtration, resuspension, immunomagnetic separation (IMS), and flow cytometric (FCM) detection. The time requirements lie below 100 min. Key features of the system are the error insusceptible procedure and the automation potential of the method.

Recovery rates of 97 ± 8.4% were observed for tap water samples at spiking levels of 100 to 10.000 cysts per liter. The detection and determination limits were found to be around 20 and 40 cysts per liter, respectively. When processing 100 liter of tap water at 100 cysts seeding level, recovery rates of above 70 % were seen.

It was possible to detect around 10^4 cysts per liter in wastewater samples. These data were confirmed by immunofluorescence microscopy.

Phylogenetic analysis of clinical and biocontrol strains of *Pantoea agglomerans* to address biosafety concerns

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Pantoea agglomerans strains have recently been registered for agricultural application in the United States and in New Zealand for biological control of fire blight. This destructive bacterial disease of apples and pears raged in Switzerland in 2007. However, registration in Europe is hindered because P. agglomerans is currently listed as a biosafety level 2 (BL2) organism due to clinical isolates reported as opportunistic human pathogens. The aim of this work was to understand whether or not clinical isolates of P. agglomerans have undergone a discrete evolution that may imply specialization toward human pathogenicity and to look for molecular markers enabling the selection of safe biocontrol strains. The taxonomy of a numbber of strains gathered from culture collections designated as “Pantoea agglomerans” (or recorded under the old species name “Enterobacter agglomerans”) was assessed by sequencing of two housekeeping genes and by PCR amplification of biocontrol-relevant and P. agglomerans specific genes. Surprisingly, only about one third of the strains investigated belonged to P. agglomerans (sensu stricto), while other could be identified as Enterobacter spp., suggesting that the countless taxonomical rearrangements that this genus has undergone in the last decades resulted in the misassignment of many isolates into P. agglomerans. In P. agglomerans (sensu stricto) both sequencing and fAFLP data show that no discrete evolution occurred between biocontrol and clinical strains. It is possible that clinical isolates acquired pathogenicity factors on plasmids or other mobile elements, but markers potentially pointing to pathogenicity yet remain to be found. Furthermore, only one of four Koch’s postulates (isolation from a diseased host) has been demonstrated for *P. agglomerans* (*sensu stricto*). If no more evidence of the pathogenicity of *P. agglomerans* can be collected, it might be necessary to reconsider the classification of this species as a BL 2 organism.

Methicillin resistant *Staphylococcus aureus* (MRSA) population study: prevalence of MRSA in long-term care facilities in southern Switzerland

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Methicillin resistant *Staphylococcus aureus* (MRSA) are a cause of health related problems in most hospitals, but the extent to which long-term care facilities represent a reservoir for MRSA is unknown. The aim of this study was to evaluate MRSA prevalence in long-term care facilities (nursing homes for elderly and disabled individuals) in the region of Ticino (Switzerland).

The study protocol was approved by the local ethical commission and performed between January and February 2008. The sampling was carried out by selecting facilities representative for dimension and geographic distribution (n=19). 900 individuals were enrolled in the study (22% of the total population living in long-term care facilities). Microbiological samples were collected through nasal and perineal swabs (wound swabs when appropriate) and transported to the laboratory within 24 h. Swabs were pooled and MRSA were cultured on selective plates. Demographic data as well as infection risk factors were collected for each participant. Statistical data analysis was performed using standard descriptive methods as well as logistic regression techniques. Genetic characterization of MRSA strains was performed used spa-typing.

The overall prevalence of MRSA in the long-term care facilities was 6.1% (ranging from 0 to 30%) and was lower than expected. this is most likely due to health workers compliance to the local guidelines which do not include isolation of the MRSA positive individuals.

Arbovirus transmitted by mosquitoes in southern Switzerland: a potential risk?

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Commercial trade, travellers and climatic global changes are facilitating the introduction and establishment of exotic vectors of pathogens in the temperate zones. According to the European Network on Imported Infectious Disease Surveillance (TropNetEurop), some cases of emerging Arbovirus diseases (West Nile fever, Chikungunya) were reported in European countries during the last years. Several mosquito species detected in canton Ticino are potential vectors of pathogenic Arbovirus (arthropod-borne viruses), a large group of viruses that are spread by blood-sucking insects. For this reason, assessing the degree of colonisation by viruses of the mosquitoes present in our region is crucial.

We assessed the presence of Arbovirus in different species of mosquitoes collected in Ticino, with special emphasis on Phlebovirus (Rift Valley Fever virus, Sandfly fever virus, Toscana virus and others), Alphaviruses (Sindbis virus and Chikungunya virus), and Flavivirus (Yellow fever virus, Dengue viruses and West Nile virus). Viral RNA was extracted from mosquitoes (adults and eggs) collected between 2007 and 2008, transcribed in cDNA and detected by a multiplex PCR followed by specific nested-PCR. The nested PCR products were sequenced and analyzed phylogenetically.

A positive amplification was obtained only for Flavivirus in female adults of the species *Aedes vexans* and *Aedes cinereus*/*geminus* or in *Aedes albopictus* eggs. Sequences were related to those of Kamiti River and cell fusing agent viruses that have been described as "invertebrate host only" Flaviviruses. Among the different species collected in Ticino, *Aedes albopictus*, the Asian tiger mosquito, is particularly interesting because it is considered the competent vector for the transmission of the Chikungunya virus. The real-time RT-PCR based on the gene E1 established to detect CHIKV in mosquitoes (adults and eggs) and in human blood samples demonstrated the absence of CHIKV in the mosquito samples collected.

The Arboviruses we could detect in some of them belong to a group of Flavivirus not known to be pathogenic for humans. Given the significance of some of the disease agents they may carry, it appears that close monitoring of the presence of Arboviruses in mosquitoes in Ticino must be continued.

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