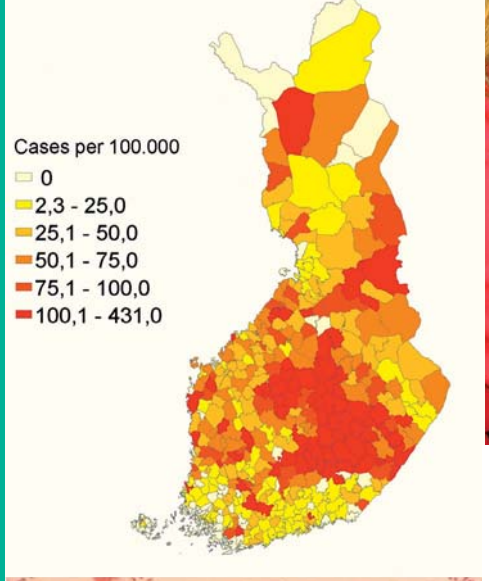

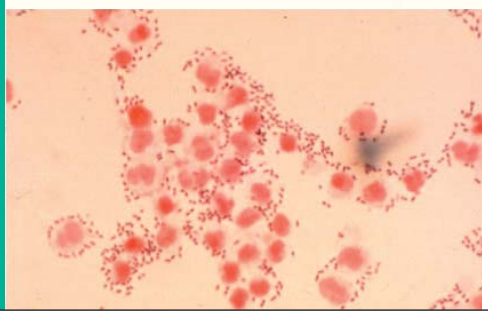

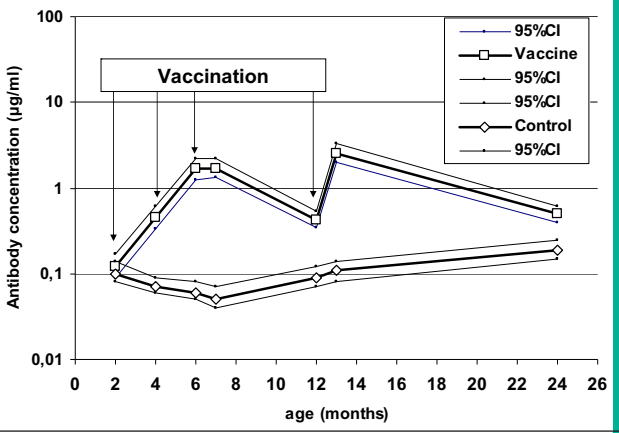

Tapani Hovi • Pentti Huovinen • Terhi Kilpi • Petri Ruutu (Eds.)

National Public Health Institute

Infectious Disease Surveillance, Control and Research 2000–2007

Background Material for the International Evaluation

Publications of
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Tapani Hovi - Pentti Huovinen – Terhi Kilpi - Petri Ruutu (eds.)

National Public Health Institute

Department of Bacterial and Inflammatory Diseases
Department of Infectious Disease Epidemiology
Department of Vaccines
Department of Viral Diseases and Immunology
Department of Child and Adolescent Health

Background Material for the International Evaluation
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Kansanterveyslaitos
Bakteeri- ja tulehdustautien osasto
Infektioepidemiologian osasto
Rokoteosasto
Virustautien ja immunologian osasto
Lasten ja nuorten terveyden osasto

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CONTENT

Some abbreviations

AEFI	Adverse events following immunization
AOM	Acute otitis media
ARIVAC	Acute Respiratory Tract Infection vaccine trial
BATO	Department of Bacterial and Inflammatory Diseases (Turku and Helsinki)
CAP	community-acquired pneumonia
CD	communicable diseases
CSF	Cerebrospinal fluid
CTR	*Chlamydia trachomatis*
DC	Dendritic cells
DG	Director General
Dpt	Department
DSN	Disease Specific Surveillance Networks
ECDC	European Centre for Disease Control (Stockholm, Sweden)
EHEC	Enterohaemorrhagic *Escherichia coli*
EIA	Enzyme immunoassay
ELVIRA	Research Programme on Nutrition, Foods and Health
EPIET	European Programme of Intervention Epidemiology Training
ESBL	Extended spectrum beta-lactamase
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
ESEN	European Seroepidemiological Network
EU	European Union
Evira	Food Safety Authority
FinOHTA	Finnish Office for Health Technology Assessment
FinOM	Finnish Otitis Media vaccine trial
FiRe	Finnish Study Group for Antimicrobial Resistance surveillance network
HCV	Hepatitis C virus
Hib	*Haemophilus influenzae* capsule type b
HPV	Human papillomavirus
hr	High risk
HILMO	Hospital Discharge Register
IHR	International Health Regulations
ID	Infectious disease(s)
IDU	Injecting drug user
INFE	Department of Infectious Disease Epidemiology (Helsinki)
KELA	National Social Insurance Institution
KRAR	National Advisory Committee on Vaccination
KTL	National Public Health Institute (In Finnish: Kansanterveyslaitos)
LNTO	Department for Children's and Adolescent's Health (Oulu)
LTHSC	Low Threshold Health Service Centres
MEF	Middle ear fluid
METO	former Department of Microbial Ecology and Inflammatory Diseases (Turku)
MIBO	former Department of Microbiology (Helsinki and Oulu)
MIKSTRA	Programme for strategies for antimicrobial use in the community in Finland
MSAH	Ministry of Social Affairs and Health
NAM	National Agency for Medicines
NGO	Non-govermental organizations
NIDR	National Infectious Disease Register
NIP	National Immunization Programme

NPA	Nasopharynx
NTHi	Non-typable *Haemophilus influenzae*
PFGE	Pulsed-field gel electrophoresis
PCV	pneumococcal conjugate vaccine
PPV	Pneumococcal polysaccharide vaccine
Prn	Pertactin
PS	Polysaccharide
ROKO	Department for Vaccines (Helsinki)
SOP	Standard Operation Procedure
STD	sexually transmitted diseases
STM	Ministry of Social Affairs and Health, MSAH
TB	Tuberculosis
TBE	Tick-borne encephalitis
T1D	Type 1 diabetes
URI	Upper respiratory infections
UTI	Urinary tract infections
VAP	Vascular Adhesion Protein-1
VIMO	Department of Viral Diseases and Immunology (Helsinki)
VRE	Vancomycin-resistant enterococcus
WG	Working group
YE	*Yersinia enterocolitica*
YTOS	Department for Environmental Health (Kuopio)

PREAMBLE

In the early 1990s the Science and Technology Policy Council in Finland encouraged the Ministries to evaluate research institutions in their jurisdiction. In accordance to this policy, the Medical Research Council of the Academy of Finland carried out an evaluation of the research activities of KTL in 1994–1995, in response to a proposal put to it by the Finnish National Public Health Institute (KTL) and the Ministry of Social Affairs and Health (STM). The objective of this evaluation was to provide information on the public health functions, strategic importance, scientific merit and value for money of the scientific work undertaken and to make proposals for future work.

The international Evaluation Panel, chaired by Dr. David Evered of the UK Medical Research Council, prepared an evaluation Report to the Academy in October 1995. For the evaluation, KTL prepared a report describing the work in the Institute. The Evaluation Panel worked via internal meetings, discussions with important stakeholders of KTL, and through site visits to the three divisions of KTL. On the basis of their evaluation, the Panel made 35 major recommendations for further development of the organization, management and work of the Institute.

Over the past 10 years, most of the recommendations made by the Panel have been implemented: the organization of KTL has been changed, several areas of research and public health work have been directed towards new priorities, and more emphasis has been put on the public health impact of the work of KTL. In addition, a renewed strategy was prepared for the Institute in 2001 during a thorough process involving the whole organization. At the end of 2003, a new Director General was appointed to KTL.

Based on these developments, and on changes in the environment, time is ripe for a new evaluation of KTL. The purpose of such an evaluation would be to evaluate the effectiveness of the work and assess the scientific and societal impact of the Institute.

KTL IN BRIEF

Strategy and functions

The mission of KTL is to protect and promote the health of the Finnish people. As a research and expert institute belonging to the Ministry of Social Affairs and Health, KTL is responsible for providing decision-makers, professionals and citizens with the best possible health-related information for their choices. A general strategy for the Institute was prepared in 2001, while detailed objectives for the work are agreed upon annually with the Ministry.

The three main areas of work in KTL have traditionally been: 1) infectious diseases and immunizations, 2) chronic diseases and health promotion, and 3) environmental health. In all these areas, both research and public health functions are carried out. Activities of the Institute include basic research, ranging from the detailed analysis of the molecular mechanisms of pathogenesis to large scale epidemiological and preventive studies and research into factors influencing health.

KTL monitors public health, diseases and their determinants through surveys and registers. Research and expert information is transferred into action by developing health-promoting and preventive measures and by advising and collaborating with various stakeholders. National vaccine

service, many centralized laboratory functions and forensic medicine investigations are some of KTL's service functions.

Several of KTL's functions are based on laws, such as surveillance of infectious diseases and protection from communicable diseases by vaccinations. In the prevention of chronic diseases KTL works in close collaboration with various Non-Governmental Organizations. A strong presence in the media is a way to reach the people. The ultimate goal is to reduce the human suffering and economic cost caused by illness and to help people enhance their quality of life.

Organization, personnel and budget

KTL's main facilities are located in Helsinki and three other facilities in Kuopio, Oulu and Turku. The Institute has 11 departments, each of which is built of various laboratories and units.

Ultimate responsibility of leading and managing the whole Institute rests on the Director General of KTL. He is assisted by the Deputy Director General, the Administrative Director and the Steering Group, consisting of the Directors of Departments. The Director General is also advised by a Scientific Council of KTL, where representatives of most important stakeholders are present.

At the end of 2006, KTL had a staff of 980 persons, of whom 450 were scientists or experts. Women make up 73% of the staff. In addition to the permanent or temporary staff, KTL is also a working place for non-paid students or scientists who pursue their studies and research together with the staff of KTL.
The total expenditure of KTL was 66 million euros in 2006, and the operating expenses were 56 million euros when the acquisition of vaccines is excluded. Most part (62%) of the operational funding comes from the national budget, 30% from external sources like the Academy of Finland, the European Union, US National Institutes of Health, or various Foundations supporting scientific research. The rest 8% of KTLs budget is covered through income from chargeable services and from miscellaneous other funding.

EVALUATION PROCESS

Scope and purpose of evaluation

The objective of the review is to provide an evaluation of the work of KTL for the Director General of the Institute as well as for the Ministry of Social Affairs and Health. The evaluation should examine the functions, strategic importance, scientific merits and value for money of the scientific and expert work undertaken, and to make proposals for future work.

The evaluation should address the following main issues:

- **a.** Appropriateness and adequacy of the research, expert functions and services
- **b.** Output and quality of research activities
- **c.** National relevance and effectiveness of the activities
- **d.** National and international co-operation
- **e.** Resource allocation
- **f.** Research fund raising
- **g.** Development needs, especially regarding processes and organization

The main purpose of the evaluation is to guide the development of the Institute, based on observations on the developments in the past, on the situation analysis of the current status and on the plans for the future. Thus the results of the evaluation will be used mainly by KTL, helping the Director General in the development of the Institute. The evaluation results will also be communicated to the Ministry of Social Affairs and Health, so that they can use them for the strategic management of KTL.

Entities to be evaluated

The first round of detailed evaluations consists of four separate, partly parallel evaluations covering the main functional areas of KTL:

a. Environmental health (YTOS)
b. Chronic disease prevention and health promotion (ETEO, TTO, MAO)
c. Infectious diseases (INFE, ROKO, BATO, VIMO)
d. Molecular medicine (MLO) – the evaluation of this area will depend on whether the results of the planned evaluation conducted by the Ministry of Education will provide sufficient information for the purposes of KTL.

After the first round has been completed, the entire Institute will be evaluated. This evaluation will focus merely on the general strategy, function and management of the Institute, with less emphasis on the evaluation of individual research and expert functions.

Steps in the evaluation

After the Ministry of Social Affairs and Health has approved this evaluation plan, preparation is launched at KTL by inviting the members for the Evaluation Panels and by collecting background information for them. A Panel of 4–8 external experts will be invited by the Director General of KTL, after consultation with the Ministry of Social Affairs and Health. The Chair of the Scientific Council of KTL will also be consulted.

Approximately half of the members of each Panel will be from abroad, the other half from Finland. Members will be selected so that the panel represents relevant knowledge and experience of both scientific and public health aspects in addition to having an understanding of the needs and expectations of the community.

Members will be invited to Helsinki to take part in the first meeting of each Panel, where the terms of reference will be examined and methods of evaluation agreed upon. During the meeting, representatives of KTL (Director General, Directors of the relevant Departments) and representatives of the Ministry of Social Affairs and Health will give their initial presentations.

The second step of the evaluation is focused on desk research, during which the Panel will examine the documentation provided to them. During this phase the Panel may collect additional information by questionnaires and letters from relevant stakeholders.

The third step of the evaluation will consist of site visits to KTL and the Departments in question. During the visit, Panel members will have an opportunity to interview KTL staff and discuss with

the representatives of key customers and collaborators (in the Ministries, universities, other organizations, health care providers, NGOs etc.).

After the discussions, desk research and site visits, the Panel will prepare a Report to the Director General of KTL addressing the questions listed above and giving its conclusions and recommendations for future development of the Institute.

Information sources for the evaluation

KTL will provide the Panels following information:

Published documents concerning the whole Institute

a. Strategy of the Institute 2001 (available in Finnish, will be translated)
b. Annual Report 2006
c. Kansanterveyslaitoksen toimintakertomus ja tilinpäätöslaskelmat 2006 (available only in Finnish)
d. Evaluation of the National Public Health Institute of Finland. Report of the Evaluation Panel 1995

A Report prepared by the Director General for the Evaluation Panel, summarizing 1) a brief history and account of the mission, roles and responsibilities of the Insitute, and 2) his views about the changes in the environment, public health priorities and needs of different stakeholders, and 3) his views for the future development of the Institute.

A Report prepared by the Director of each relevant Department involved in the evaluation, summarizing 1) a report on progress in research over period 2000-2006 and research plans for the period 2006-2010, 2) the arrangement for governance and management, and 3) allocation of staff and resources, and 4) his/her plans for the future development of the Department.

Each Department involved in the evaluation will also provide the Panel a self evaluation of 1) the appropriateness of its work to the national public health needs, 3) its role in the dissemination of research results and knowledge and technology transfer, 3) a description of the interfaces between the Department and the key players in Finland and abroad.

KTL will also provide appropriate information about population health in Finland, the Finnish health care system and about roles and responsibilities of other players in public health field in Finland.

Schedule

The first round of detailed evaluations will take place in the years 2006–2008. Eight to ten months will be reserved for each of the four evaluations, four months for convening the Panel and collecting the background information, two months for the evaluation itself, and two to four months for preparing the Report. The provisional schedule will be as follows:

e. Environmental health 6/2006 – 2/2007
f. Chronic disease prevention and health promotion 9/2007 – 6/2008
g. Infectious diseases 1/2007-10/2007

h. Molecular medicine, probably 1/2007 – 10/2007 – as said above, the evaluation of this area will, however, depends on the results of the evaluation conducted by the Ministry of Education.

The evaluation of the entire KTL will take place in 2009, so that the final Report will be ready in 12/2009.

1. INTRODUCTION

1.1. Statutory role of KTL in surveillance and prevention of infectious diseases

1.1.1. Statutory role

In 1988, the National Board of Health was dissolved, and its´ normative and policy functions relating to infectious diseases were transferred to the Ministry of Social Affairs and Health (MSAH) or the so called sectoral research institutions under the ministry, one of which is the National Public Health Institute (KTL).

The Communicable Disease Act of 1986, with subsequent revisions, determines the role of KTL as follows: KTL functions as the national expert organisation in the control of communicable diseases (CD). The institution maintains a National Infectious Disease Registry, which consists of mandatory notifications from treating physicians and microbiological laboratories, as well as microbial strains. Laboratory tests and other laboratory activities needed for the control of communicable diseases are carried out at KTL and other designated laboratories. The State Provincial Offices of Finland have to consult KTL prior to granting a license to a laboratory to carry out microbiological testing. KTL and the State Provincial Offices have the right to acquire all relevant information pertaining to the activities of a microbiological laboratory.

The Communicable Disease Decree defines in more detail the mandates and obligations of KTL as follows:

1) monitor the implementation of control measures against CD and make initiatives to the MSAH on measures to prevent CD;
2) carry out scientific research on CD and develop laboratory methods needed in the control of CD;
3) implement national level communication on CD;
4) give expert consultation to those responsible for CD control on the municipal and health care district level;
5) organise training aiming at the control of CD;
6) communicate about the current epidemiological situation to the health care districts, laboratories and municipal health care centres, as well as provide information on the current CD situation to the MSAH, state provincial offices, national defence organisation, border guard and to the international exchange of information.

The Health Protection Act, The Food Act, The Decree on the Investigation of Food-borne Outbreaks and other statutes and technical guidelines define that KTL maintains a notification system on all suspected food- or waterborne outbreaks. The Decree on Zoonosis Centre defines KTL as one of the two components of the newly established zoonoosis centre.

The content of the National Immunization Programme (NIP), ie. vaccines to be included, vaccination schedules and target groups for vaccination, are laid down by decree of the Ministry of Social Affairs and Health. This programme consists of a pediatric vaccination programme, a booster programme and a tick-borne encephalitis (TBE) and a flu vaccination programme. KTL, as an

expert institution in the control of communicable diseases, is responsible for several aspects of implementation and further development of the programme.

International Health Regulations 2005 (IHR 2005) became Finnish law in 2007 and defines KTL as the agency implementing the obligations of the IHR in Finland. In the evolving collaboration in the surveillance and control of infectious diseases within the EU, KTL has been nominated as the national delegate or focal point in numerous tasks of wide-ranging nature.

KTL experts are intensely involved, in support of the MSAH, in developing the statutory basis for surveillance and control of infectious diseases

1.1.2. Outline of practical activities

The wide-ranging mandates of the statutes, as described above, are implemented in numerous processes within KTL and in interaction between KTL and health care and other authorities and experts on national, regional and local level which are described in more detail in subsequent chapters.

The overall role of the KTL is of expert and consultant nature. The proper authorities on various levels of the health care system are the MSAH, the state provincial office health authority and the municipal health care centre. The expert interaction between KTL and MSAH is complemented by working groups, such as the Expert Group on CD and the National Advisory Group on Vaccinations, nominated by the MSAH. The health care district infectious disease specialist team, working in 20 central hospitals, also have consultant role. KTL interacts intensely with all these levels in surveillance and control. KTL also provides a wide range of training to the regional and local collaborators in topics aiming at strengthening the surveillance and control activities.

The National Infectious Disease Register (NIDR), consisting of data collected from the clinical microbiology laboratories, attending physicians and reference laboratories, as well as microbial strains (statutorily since 2004) collected from the laboratories, constitutes the backbone of infectious disease surveillance (see specific paragraph). Other infectious disease surveillance systems complementary to the NIDR are the nosocomial infections project (see specific paragraph), resistance surveillance network (FiRe, see specific paragraph), and the sexually transmitted infections sentinel surveillance network (STD sentinel surveillance, see specific paragraph)

As the primary recipient of the notification on suspected food- or waterborne outbreaks from the municipal level, KTL has a key position in consulting or implementing outbreak investigations (see specific paragraph). For more comprehensive syndromic surveillance of eg. respiratory infections, including influenza, KTL has started the development of a sentinel syndromic surveillance system. As a natural extension of its experience in investigation and control of outbreaks and epidemics, KTL occupied a key role in the preparedness planning and coordination of action in the activities related to various biothreats (see specific paragraph)

KTL gives expert advice on further development of NIP, supervises the effectiveness and safety of the programme, purchases and delivers the vaccines as stipulated in the Communicable Diseases Act and decree, controls the quality of vaccines and observes the coverage of vaccination and communicates the recommended immunization practices to the local health centres that are responsible for administration of vaccines included in NIP. The role of KTL in developing and maintaining the national vaccination programme is explained in more detail the specific paragraphs.

The expert role of KTL in maintaining the national licensure system for clinical microbiological laboratories is explained in a specific paragraph**.** It serves to ensure that all the clinical microbiological laboratories participate in external quality assurance for accurate and reliable diagnostics and optimal patient care.

The data derived from the ongoing surveillance activities are used, both internally and in collaboration of external collaborators, for 'spin-off' research aimed at creating information supporting the control of infectious diseases.

1.2. Departments and units

KTL units dedicated to surveillance, prevention and research of infectious diseases are clustered in a number departments ("the Communicable Diseases (CD) -cluster) for administrative purposes and for functional coordination. History, geography and search for new synergy in functions have contributed to the varying number, names and patterns of functions of individual departments. Starting from six departments in 2000, a combination of three previous departments (Specific Bacterial Pathogens, Virology and the Department in Oulu) existed under the name of Department of Microbiology (MIBO) in 2001-2004, together with the Departments of Infectious Disease Epidemiology (INFE), Department for Vaccines (ROKO) and the Department of Microbial Ecology and Inflammatory Diseases (METO) (formerly Dpt in Turku).

From the beginning of 2005 three Helsinki-based bacteriological laboratories of MIBO were administratively joined with METO in Turku, and the department changed its name to Department of Bacterial and Inflammatory Diseases (BATO). MIBO also changed the name to Dpt of Viral Diseases and Immunology (VIMO), and the above losses were balanced with imports of small units from both INFE and ROKO, as well as that of the Laboratory for Immunobiology from outside the CD-cluster.

Finally, from the beginning of 2007, the VIMO units located in Oulu were separated to be a new independent department, Dpt for Children's and Adolescent's Health (LNTO) aiming in future principally at coordinating broad scope expert advice to Healthy Baby Clinics and school health care systems.

While the current names of the departments could reflect strictly divided responsibilities in the functions, the truth is not black and white: Bacteriology continues to comprise a significant part of the research programme of VIMO and both bacteriology and virology remain in the activities of LNTO. Moreover, microbiological laboratories also exist in both INFE and ROKO, and the programmes of these two latter departments have several contact points.

Likewise, the border between the CD-cluster and other KTL-departments is easily crossed in practical functions, e.g. in investigations of water-born outbreaks, the KTL Department for Environmental health (YTOS, in Kuopio) is responsible for microbiological testing of the environmental specimens and give technical advise on the measures to control the outbreak.

In spite of the lively reorganization activities at the department level, the key functions of individual laboratories or other units, especially those relevant to public health functions, have remained relatively stable or developed in a logical way according to new demands, and thus can be considered to represent continuity. Major changes include final ceasing of own vaccine production and its delivery at KTL in the early 2000s' and some of the above reorganizations in 2005 partly

due to retirement of three senior scientists. The existing units show a range in history, size and pattern of functions, with the latter extending from exclusively public health functions derived from laws and decrees to more or less freely selected research projects. Unit heads report to director of the corresponding department. Major changes in the programme of a unit, including major grants from e.g. EU, require the permission given by Director General of KTL (DG).

All directors of departments in KTL report to DG. There is no official administrative coordination specifically for the CD-cluster. There are certain long-term cross-department working groups, such as the KTL Advisory Group for vaccinations, Advisory Group for National Infectious Disease Register, and the KTL WG for Preparedness for Influenza Pandemics etc, and substantial ad hoc collaboration in both public health functions and research. Because of the general transparency of activities, overlaps in functions can be avoided in this "freely floating organization", but possible forgotten or newly emerging topics in the general mission on infectious diseases may be missed in the absence of regular comprehensive oversight.

Current relevant KTL departments and units, their abbreviations, and the respective persons in charge, are listed in the following.

Department of Bacterial and Inflammatory Diseases (BATO; Director Pentti Huovinen)
- Anaerobe Reference Laboratory (ANBA; Head Eija Könönen)
- Antimicrobial Research Laboratory (MILL; Head Antti Hakanen)
- Cell Traffic Laboratory (SOLI; Head Marko Salmi)
- Enteric Bacteria Laboratory (SUBA; Head Anja Siitonen)
- Hospital Bacteria Laboratory (SABA; Head Jaana Vuopio-Varkila)
- Microbial Ecology Laboratory (MIEL; Head Jari Jalava)
- Microbial Immunology Laboratory (MIMM; Head Kaisa Granfors)
- Mycobacterial Reference Laboratory (MYBA; Head Merja Marjamäki)
- Pertussis Laboratory (PERT; Head Qiushui He)
- Respiratory Bacteria Laboratory (HEBA; Head Anni Virolainen-Julkunen)

Department of Infectious Disease Epidemiology (INFE; Director Petri Ruutu)
- Biological Threats Unit (BUY; Head Mika Salminen)
- HIV Unit (HIV; Head Mika Salminen)
- Surveillance and Epidemiologic Investigations (TART; Head Petri Ruutu)
(- Finnish Hospital Infection Programme (SIRO; PI Outi Lyytikäinen))
(- Outbreak Surveillance and Investigation (PI Markku Kuusi))

Department of Vaccines (ROKO; Director Terhi Kilpi)
- Clinical Unit (ROKL; Head Terhi Kilpi)
- Vaccine Immunology Laboratory (ROIM; Head Helena Käyhty)
- Vaccine Research Clinics (ROTK; Head Arto Palmu)
- Vaccine Safety Unit (ROTU; Head Tea Nieminen)
- Vaccine Supply Unit (ROHU; Head Rose-Marie Ölander)

Department of Viral Diseases and Immunology (VIMO; Director Tapani Hovi; from 1 September 2007 on: Ilkka Julkunen)
- Enterovirus Laboratory (ENVI; Head Merja Roivainen)
- Immunobiology Laboratory (IMBL; Head Outi Vaarala)
- Infection Immunology Laboratory (INIM; Head Ilkka Julkunen)
- Infection Pathogenesis Laboratory (IPAT; Head Mirja Puolakkainen)

- Influenza Laboratory (INFL; Head Reijo Pyhälä)
- Respiratory Viruses Laboratory (HEVI; Head Thedi Ziegler)
- Viral Vaccines Laboratory (VIRL; Head Irja Davidkin)

Department of Child and Adolescent Health (LNTO; Director Anneli Pouta)
- Prenatal Serology Laboratory (NESE; Head Heljä-Marja Surcel)
- Adolescent Sexual Health Unit (NUSE; Head Matti Lehtinen)
- Respiratory Infection Unit (HETI; Head Maija Leinonen)

1.3. Follow up of recommendations of the previous evaluation in 1995

The major recommendations of the evaluation panel in 1995 are listed below, each followed by a comment on subsequent development of the topic:

1) "The current research strategy, the major objective of which is to improve the diagnosis, control and prevention of infections, has led to development of programmes in which the public health surveillance and research activities are well integrated with effective internal and external collaboration, and these should be strengthened and developed. A greater degree of focus should be achieved through discontinuation of projects which are of low priority and do not contribute to the overall Divisional strategy." The panel also identified some projects of designated low priority and proposed to discontinue them as soon as possible.

Comment: While none of the listed major projects was immediately discontinued, their future was carefully considered by the superiors within the institute. Some of the listed projects have continued to receive substantial external resources while others have been modified to better fit to the general mission of the institute.

2) The assumption of an increasing range of public health responsibilities by this Division merits greater investment but this should be met by the reallocation of resources released from the discontinuation of activities of low priority.

Comment: This assumption has become to reality in increased work load due to various public health functions, especially those connected to European Union collaboration, and new emerging infectious diseases. The relative proportion of KTL resources allocated to the CD cluster has not increased and the recommended project discontinuations were not executed. However, some resources liberated from unnecessary storage space rents and by retirement of senior scientists have been available for reallocation to improve the focus on public health functions.

3) Further investment in the development of improved diagnostic methods should be more clearly justified by public health and research needs

Comment: This was a bit confusing major comment because in detailed comments the panel recommended further work to improve diagnosis of pneumococcal diseases and the only other detailed comment on methods development, with wording like in this major one, was on a project where the goal already was as recommended. Anyhow, subsequent methods development has tried to follow the recommended principles.

4) The Division should be reconfigured in the light of this review to concentrate expertise in smaller number of larger Departments. Particular attention should be paid to the need to ensure that the

existing expertise in bacteriology is used to best effect and to strengthen immunology (particularly in cellular immunology) within KTL.

Comment: See above Chapter 1.2. for reorganizations. A special evaluation on bacteriology revealed that while KTL bacteriology is dispersed in four cities - according to decentralization principles of the Finnish national policy - the work is functionally divided between the different groups. A single observed minimal overlap in activities has been mended e.g. by creating a shared database. As for immunology, several groups in the Cluster have a strong research programme on various aspects of immunology.

5) The future role of the Laboratory (Department) in Oulu should be reviewed by the proposed Director General´s strategy group in the light of this evaluation.

Comment: This recommendation was followed. The Oulu laboratories continued their successful research and surveillance programmes, but from 2001 to 2006 connected to other microbiological units in Helsinki ("Department of Microbiology" in 2001 - 2004, and ""Department of Viral Diseases and Immunology" in 2005 - 2006). A major change in the long term mission of the Oulu units took place recently and from 2007 on they form a new independent department, Dpt for Children's and Adolescent's Health (LNTO) (see above Chapter 1.2.).

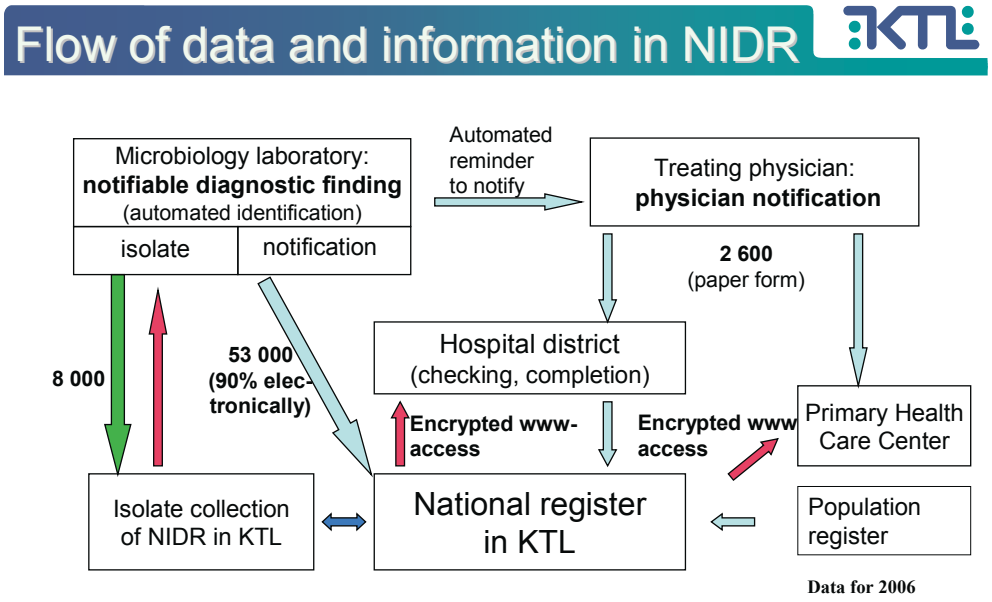
2. SURVEILLANCE AND PREVENTION OF INFECTIOUS DISEASES INCLUDING EXPERT FUNCTIONS

2.1. National Infectious Disease Register (NIDR)

Project leader: Petri Ruutu, MD, PhD

2.1.1. Data collection and processing

Since 1994, the clinical microbiology laboratories in Finland have a mandatory duty to notify (Figure: Flow of data and information in NIDR) diagnostic findings on approximately 70 specified microbes or microbe groups, as well as all microbiological findings from blood and cerebrospinal fluid (CSF). In addition, the laboratory has to remind in its report to the treating physician about the obligation to notify the diseases which are mandatorily notifiable also by physicians. The data are sent either electronically or on paper forms. The proportion of laboratory notifications sent electronically in encrypted format through the internet has gradually grown to 90% and the timeliness improved, with a current median delay from sample date to NIDR data base of 8 days. The NIDR maintains and provides to the commercial laboratory software providers a full taxonomic list of all notifiable microbes, and the microbe specific criteria of notification, including sample type and method.



The treating physician notifies 30 diseases, all microbiologically proven with the exception of some cases of tuberculosis. The notification is sent to the hospital district which checks it and sends it to KTL for data entry. The considerable advantage in timeliness from laboratory notification directly to the NIDR data base, as compared with conventional physician notification, is depicted by the

much longer median delay of physician notification, approximately 50 days from the date of the sample verifying the infection.

The data derived by the national reference laboratories, mostly located at KTL, are to a large extent notified to the central NIDR data base. A development process over the last five year has led to integration of the data handling systems within KTL in such a way that most of the reference laboratory data, which include test results on verification of identification, susceptibility test and epidemiological typing results are sent electronically to the central NIDR. On the other hand, the KTL reference laboratories receive from the NIDR data in automated processes which facilitate their laboratory function in surveillance, and serve to increase the coverage of strains which is well over 90% of notified cases. The main IT tool for interaction between the NIDR main data base and the laboratory data bases is shared by several laboratories, and has led to rationalization of the laboratory processes, including elimination of redundant parallel processes in laboratory testing in several laboratories. The microbial strain collection is presented in Table 1.

The notifications on one case from different sources are frequently multiple and arrive at different times. They are merged automatically into a case by predefined computer algorithms in the NIDR database using the national personal identity code or, in case this is missing, using birth date, name, sex, and the municipality in which the case is treated, as well as a time frame specified for each disease, in order to avoid duplication. Missing or inconsistent information is identified by automatic alerts, and requests for corrections sent to the notifiers. The NIDR receives annually 50 000 - 60 000 laboratory notifications from clinical microbiological laboratories, approximately 4 000 notifications from the reference laboratories at KTL and approximately 2 000 - 2 500 notifications from attending physicians. The NIDR microbial strain collection receives annually approximately 8000 isolates and/or samples from clinical microbiology laboratories (Figure: Flow of data and information in NIDR).

Country of birth, most recent nationality, the place of residence and the date of possible death are automatically extracted from the population information system using the national personal identity code. The earliest date of a diagnostic laboratory sample among the notifications of a case is recorded as the epidemiological date for a case.

In a limited number of diseases, additional high quality case data are acquired in standardized processes on the prior vaccination status of vaccine preventable diseases or on exposure types or sites, using additional structured forms or telephone queries.

2.1.2. Access to and exploitation of the NIDR data

NIDR data are exploited in the public domain in the extent which protection of personal identity and data safety regulations allow, and with full data content using restricted access applications to regional and local health authorities, who are in charge of infectious disease surveillance and control in their respective areas.

Access to the NIDR data base is provided to the hospital district and primary health care infectious disease teams, each for all data on cases in their own area, through internet using high level encryption. Training is regularly carried out for these target groups in optimal use of the application and to ensure high level of data safety procedures.

The once weekly updated public statistical www service of the NIDR includes a wide range of diseases under surveillance. The dynamic web application allows versatile analysis using time,

geographic area, age band and sex. The data can be presented in different ways by the application, and downloaded for independent use. The web service is available in Finnish, Swedish and English.

Once weekly the NIDR sends an automated weekly report of viral findings to a listing of microbiologists and infectious disease specialists.

An annual report is produced with analytic comments on trends and epidemics. The annual report is available until 2004 both in printed and electronic (web) format, since 2005 in electronic format in the KTL web service. The production of the annual report entails careful review of the data, using the different sources of notification, and the microbial strains sent to the reference laboratory, to check the quality of data for the reported disease, and additional checks or requests for further data are made with the original notifiers for some diseases.

In addition to statistical and analytic reports from NIDR, as described above, each laboratory submitting strains to the NIDR strain collection received feedback on the strains they have sent, either on-line or every six months depending on the objectives of the feedback.

The NIDR data are used in various research projects as explained in the paragraphs on spin-off research from surveillance.

2.2. Reference laboratories and their general functions

Tapani Hovi, MD, PhD, Jaana Vuopio-Varkila, MD, PhD, Anni Virolainen-Julkunen, MD, PhD

The mandate for KTL to carry out reference laboratory actions is based on the communicable disease law from 1986 which determines that laboratory tests and other laboratory activities needed for the control of communicable disease are carried out at KTL and other designated laboratories. In addition, the communicable disease decree mandates KTL to carry out scientifically based measures against CD and develop laboratory methods needed in the control of CD.

As described above, a national microbial strain collection acts as part of the National Infections Disease Register (NIDR) and the mandatory laboratory notification system (see 2.1). The NIDR microbial strain collection was established in 1995 on voluntary means, and since 2004 it has been mandated in the communicable disease decree. At present, it consists of microbial isolates and samples covering 25 specified bacterial or viral diseases (Table 1)**.** Furthermore, by agreement between laboratories, some other strains are sent regularly to the laboratories for clinical, epidemiological or scientific purposes.

Table 1. National Infectious Disease Register
Microbial Strain Collection

Strain or microbial specimen	Annual no of strains or specimens collected	Reason for collection	Reference lab at KTL	Feedback to clinical laboratories	Link to EU and WHO
Bacteria	in 2006				
H. influenzae (blood and CSF)	*32*	Impact of vaccination, serotype distribution	LNTO/HETI	Serotype, betalactamase production 2x/year	IBIS
L. monocytogenes (blood and CSF)	*37*	Phenotypic and molecular epidemiology	BATO/SUBA	Serotype	Listeria-net PulseNet
N. meningitidis (blood and CSF)	*63*	Need of vaccination, national and international epidemiology	BATO/SABA; ROKO/ROIM	Serogroup, phenotype 2x/year	IBIS
S. agalactiae (blood and CSF)	*214*	Background data for future vaccines	BATO/SABA		
S. pneumoniae (blood and CSF)	*731*	Resistance situation, serotype distribution, genotype in selective cases	BATO/SABA, MILL, HEBA; LNTO/HETI	Serotype, penicillin susceptibility 2x/year	EARSS, Arctic Investigations Programme
S. pyogenes (blood and CSF)	*163*	Molecular epidemiology, background data for future vaccines	BATO/SABA, MILL	Sero- and genotype 2x/year, susceptibility	Strep-EURO
B. pertussis	*25*	Impact of vaccination	BATO/PERT	Sero- and genotype 2x/year	
C. diphtheriae	*1*	Verification, epidemiology	BATO/SABA	Verification, toxin	DIPNET
Legionella	*3*	Epidemiology	BATO/ANBA	Species, serotype	EWGLINET
M. Tuberculosis Atypical mycobacteria	*266 388*	Species identification, resistance situation, genotype	BATO/MYBA	Susceptibility, genotype in certain cases	EuroTB
Enterococcus, VRE	*96*	Resistance situation, molecular epidemiology	BATO/SABA	Resistance, genotype	EARSS
S. aureus, MRSA/VRSA	*1702*	Resistance situation, molecular epidemiology	BATO/SABA	Resistance, genotype	EARSS
E. coli EHEC	*45*	Phenotypic and molecular epidemiology	BATO/SUBA	Verification, serotype	Enter-net PulseNet
Salmonella	*2598*	Resistance situation, phenotypic and molecular epidemiology	BATO/SUBA	Species, serotype	Enter-net PulseNet

Shigella	*124*	Resistance situation, phenotypic and molecular epidemiology	BATO/SUBA	Species, serotype	Enter-net PulseNet
Vibrio cholerae	*3*	Verification	BATO/SUBA	Species, serotype, toxin	
*Yersinia sp.**	*253*	Phenotypic and molecular epidemiology	BATO/SUBA	Species, sero- and biotype	
*Campylobacter sp.**	*367*	Epidemiology	BATO/SUBA	Species	
*Clostridium difficile**	*0*		BATO/ANBA		
*ESBL**	*324*	Species identification, resistance situation, molecular epidemiology	BATO/SABA, MIEL	Phenotype, genotype	
Viruses	**in 2006**				
Polioviruses	3**	Verification, wild vs vaccine strain, epidemiology	VIMO/ENVI	Verification	WHO Polio Labnet
Enteroviruses (faeces)	68	Discrimination from polioviruses	VIMO/ENVI	Verification	WHO Polio Labnet
HIV	243 specimens/191 cases/109 typed	Primary resistance and subtype distribution	INFE/HIV	Resistance profile and subtype	EuroHIV, EHR
Hepatitis A	17	Genotype distribution, epidemiology	VIMO/VIRL		
Mumps virus	12	Vaccination	VIMO/VIRL	Verification	
Measles virus	3	Vaccination	VIMO/VIRL	Verification	WHO MR RL Network
Rubella virus	4	Vaccination	VIMO/VIRL	Verification	WHO MR RL Network
SARS - coronavirus	0	Epidemiology	VIMO/INFL	Verification	
Parasites	**in 2006**				
Plasmodium	1828/30***	Prevention guidelines	(HUSLAB)	Verification, species	

Total number of isolates/samples received annually into reference laboratories at KTL: 8300

*collection currently not based on law

** one sewage sample is included

***number of samples received and analysed/number of positive findings

2.2.1. National reference laboratories in KTL and outside KTL

Five departments in KTL accommodate national reference laboratories. The KTL reference laboratories cover only bacterial and viral diseases. The parasite and fungal reference functions are based at Helsinki University Central Hospital Laboratory (HUSLAB). In addition, the reference laboratory for hemorrhagic viral diseases is based at Helsinki University, Haartman Institute.

The organisational division of the laboratories within the departments has changed during the past years. Regardless of this, the division of reference functions among the designated laboratories has more or less remained unchanged during the last ten years. KTL holds the WHO National Influenza Centre, WHO Collaborating Centre for Poliovirus Surveillance and Enterovirus Research, and the National Reference Laboratory in the WHO Measles/Rubella laboratory network.
For most KTL reference laboratories the scope of functions covers 1) verification of bacterial/viral species for the clinical laboratories, 2) provision of typing services for CD surveillance and outbreak investigation, 3) follow up of recent developments in the diagnostics and typing methodology, 4) development and evaluation of new laboratory techniques, 5) validation of commercial tests, 6) provision of technical support and expertise to clinical laboratories and 7) participation in training of laboratory and ID personnel. The research activities of the laboratories are integrated with the reference laboratory functions in most instances.

In the Enterovirus Laboratory, the methods for virus isolation and identification are accredited due to the international standard EN ISO/IEC 17025 since 2004. Since the establishment of KTL guidelines on good laboratory practises in 2006, much activity has focussed on the development of standard operation procedures (SOP) for various laboratory methods and functions. All laboratories participate in national (Labquality) or international (NEQAS, WHO) external quality assessment surveys as part of their routine activities.

Many of the laboratory technologies and instruments are shared between the laboratories. An example for this is the DNA-laboratory facility at the KTL in Helsinki which serves four units of the Department of Bacterial and Inflammatory Diseases and one from the Viral and Inflammatory Diseases. The services and products provided by the "Media Preparation Unit" of KTL are also jointly exploited by the laboratories.

The majority of the laboratories provide their services free of charge with the exception of the Mycobacterial Laboratory, HIV-unit and Prenatal Serology Laboratory. The reference functions are mostly covered by KTL budget, but also consume substantially extramural funding, some of it originally earmarked for research purposes.

2.2.2. Statements for licencing clinical microbiological laboratories for infectious disease diagnostics

Project leader: Anni Virolainen-Julkunen, MD, PhD

Description

In Finland, over 600 laboratories investigate human clinical specimens for diagnostics of infectious diseases. Most of these laboratories are small, carrying out a limited number of tests at general or occupational health care centres. However, around 30 laboratories perform a wide variety of demanding testing for diagnostics of infectious diseases in regional, central and university hospitals.

These have recently been at particular focus when evaluating the overall performance of the clinical microbiological laboratories for licensing purposes.

The State Provincial Offices enforce the law and monitor the clinical microbiological laboratories but before granting a license to any individual laboratory, are obliged to request a statement from KTL. This statement is either in favour or in denial for the license, depending on how well the laboratory is able to meet the requirements named in law and the directions published by KTL. The basic requirements include appropriate and sufficient equipments and professional staff in relation to the function and test variability of the laboratory. In addition, the laboratory has to participate in external quality assurance.

Since the licensing procedure has been implemented, the availability of external quality assurance and the participation of the clinical laboratories in it have increased remarkably. The licensing procedure has enforced the local and regional authorities to be active in recruitment of professional staff to the microbiological laboratories.

Major achievements

1) KTL gives more than 600 statements within a three year period, about 200 statements per year.

2) During the years 2000-2007, 103 site visits have been performed.

Key publications

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Siitonen A. Kliinisen mikrobiologian tutkimukset: mitä, missä ja paljonko? In Finnish. (Clinical microbiology studies: what, where and how much? Moodi 2005;1:22-3.

Strandén P, Riihelä K, Karjalainen K-M, Siitonen A. Mikrobiologian laboratorioiden toimiluvat. In Finnish. (Licences of microbiology laboratories) Moodi 2005;4:129-32.

2.3. Programmes for surveillance and control

2.3.1. Outbreak investigations and control

Project leader: Markku Kuusi MD, PhD

Description

Since 1997, municipal authorities should notify to the Department of Infectious Disease Epidemiology (INFE) at KTL outbreaks that are suspected to be transmitted through food or water.

The criteria for notification are as follows:
1) outbreak in an institutional setting,
2) commercially distributed food suspected,
3) restaurant-associated outbreak,

4) more than five persons ill,
5) botulism suspected (even a single case).

Family outbreaks are notified only if one of the above mentioned criteria is fulfilled. INFE receives the notifications by fax and relays the notification immediately to Finnish Food Safety Authority (Evira), authorities of the respective Health Care District and Province, and the Enteric Bacteria Laboratory and Department of Environmental Health at KTL.

Annually KTL receives from 60 to 120 notifications. The majority of notifying municipalities are contacted for additional information and advice for microbiological and/or epidemiological investigations. In some outbreaks KTL takes a more prominent role, e.g. helps with the data collection and analysis. Annually in 2-5 outbreaks that are large, regional, national, or international, KTL coordinates the investigation. Close collaboration with municipal, regional, and other national authorities is essential.

Major achievements

1) Training courses and technology transfer. Municipal authorities have the main responsibility for outbreak investigations in their area. However, they have little methodological training for conducting these activities and often little experience. To improve the quality of investigations, annual one-week outbreak investigation courses have been organized since 1998. KTL has been the main organizer of these courses and has also been responsible for a substantial part of teaching. More than 200 veterinarians, physicians, health inspectors, and infection control nurses have attended these courses. In addition, since 2005 annual two-day courses have been organized for health inspectors and infection control nurses by Mikkeli University of Applied Sciences. Epidemiologists of KTL have had the main responsibility of teaching on these courses. The course programme consists of lectures, group works, and practical exercises with Epi Info software.

2) Collaboration. Many outbreak investigations since 1997 have required close collaboration between local, regional and national health and environmental authorities. The training courses have been essential in networking with these persons. Close collaboration with reference laboratories, both human and veterinary, has been essential, because typing results, including molecular typing of strains from humans and foods/environmental samples have become increasingly important in outbreak investigations. In waterborne outbreaks, collaboration with other departments in KTL has been important, and diagnostics for investigation of noroviruses and *Campylobacter* sp. from water samples has been developed. Annually KTL has evaluated all reported food- and waterborne outbreaks together with Evira and participated in writing the annual outbreak report. KTL has participated in the investigation of several international outbreaks.

3) New scientific findings. Outbreak investigations conducted by KTL have resulted in new scientific findings. Examples of this are e.g. the role of environmental contamination in the transmission of norovirus infections, new vehicles associated with *Yersinia pseudotuberculosis* infections, and butter as vehicle for *Listeria* infections. Innovative methods in outbreak investigations, like the internet for data collection have been used. Research has been made on reactive arthritis after outbreaks caused by *Y. pseudotuberculosis* and *Campylobacter jejuni*. Findings on the vehicles transmitting *Y. pseudotuberculosis* have led to new recommendations on food handling practices issued by the Finnish Food Safety Authority.

4) KTL has developed a wide range of recommendations, guidelines and fact sheets, available in KTL web service, for implementing control in various suspected and verified outbreak situations (list in Appendix). This has been done in collaboration with regional infectious disease teams as

well as veterinary and environmental experts, as relevant, to ensure effective implementation in the field.

Key publications

Lyytikainen O, Autio T, Maijala R, Ruutu P, Honkanen-Buzalski T, Miettinen M, Hatakka M, Mikkola J, Anttila VJ, Johansson T, Rantala L, Aalto T, Korkeala H, Siitonen A. An outbreak of *Listeria monocytogenes* serotype 3a infections from butter in Finland. J Infect Dis. 2000;181:1838-41.

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Kuusi M, Klemets P, Miettinen I, Laaksonen I, Sarkkinen H, Hänninen ML, Rautelin H, Kela E, Nuorti JP. An outbreak of *Campylobacter* infections from a non-chlorinated community water supply. J Epidemiol Comm Health 2004;58:273-7.

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Jalava K, Hakkinen M, Valkonen M, Nakari UM, Palo T, Hallanvuo S, Ollgren J, Siitonen A, Nuorti JP. An outbreak of gastrointestinal illness and erythema nodosum from grated carrots contaminated with *Yersinia pseudotuberculosis*. J Infect Dis 2006;194:1209-16.

2.3.2. Hospital Infection Programme

Project leader: Outi Lyytikäinen, MD, PhD

Description

The Finnish Hospital Infection Programme (SIRO) started at the end of 1997 as a collaboration project between the KTL and four selected hospitals. Two ongoing surveillance modules were developed, including hospital-wide surveillance for nosocomial bloodstream infections (from September 1998) and surgical site infections in selected surgical procedures (from January 1999: hip and knee prosthesis, femur fractures, and coronary surgery; from January 2003: abdominal hysterectomies, appendectomies, breast surgery and cesarean sections). During February-March 2005, the first national prevalence survey on health care-associated infections was conducted in Finnish acute care hospitals.

The aim of the programme is to prevent health care associated infections by standardizing surveillance methods and creating a national database with which hospitals can anonymously compare their own infection rates. The other activities are training/courses, nosocomial outbreak investigations, common infection control guidelines, participating in antimicrobial resistance surveillance and preparedness plans, and research.

The representatives of the participating hospitals in the programme are infection control nurses and physicians, surgeons, and microbiologists. The programme is coordinated by the team working at KTL: infectious disease specialist/epidemiologist, infection control nurse, and data manager/information technician. Background support is given by the advisory board and steering group. The participation in the programme is voluntary. The hospitals can choose the surveillance module in which they participate. The programme is based on collaboration and confidentiality. No external comparison of the individual hospitals is possible. Joint meetings with the participating hospitals are arranged annually. Feedback is given through the project website. Hospitals have

access to their own data. All participating hospitals have access to the aggregated data. Reports on the website are generated on-line according to the users' search criteria such as hospital, time period, ward, and surgical procedure.

Major achievements

1) The programme began together with four so-called pilot hospitals. Annually, one to three new hospitals have started conducting prospective surveillance. Currently, there are 10 to 15 hospitals providing surveillance data to the national database, depending on the surveillance module and surgical procedure group under surveillance. In 2005, the first national prevalence survey on health care associated infections was conducted in 30 Finnish acute care hospitals; all 5 university and 15 central hospitals took part in the voluntary survey.

2) The programme has arranged more than ten courses or training days on the following topics, some have been repeated on request: hospital epidemiology including surveillance and outbreak investigations, multi-resistant bacteria, communication, surveillance of antimicrobial resistance and usage, infection control during renovation and construction, and nosocomial prevalence survey.

3) Outbreak investigations have been reported both domestically and internationally, and some of them have lead to national guidelines and changes in infection control practices, such as scabies and influenza.

4) Collaboration in preparedness plans and personal protective equipments with occupational health authorities.

5) Research topics have been based on prospectively collected surveillance data and its validation. So far, the studies have primarily focused on surgical site infections after orthopaedic surgery and paediatric nosocomial infections. One cost analysis of a MRSA outbreak was performed in collaboration with health economists and clinicians.

Sending data to EU-funded projects: European Antimicrobial Resistance Surveillance System (EARSS): http://www.earss.rivm.nl/; Hospital in Europe Link for Infection Control through Surveillance (HELICS), currently Improving Patient Safety in Europe (IPSE): http://helics.univ-lyon1.fr/

Key publications

Lyytikäinen O, Lumio J, Sarkkinen H, Kolho E, Kostiala A, Ruutu P and the Hospital Infection Surveillance Team. Nosocomial bloodstream infections in Finnish hospitals in 1999-2000. Clin Infect Dis 2002;35:e14-9.

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Huotari K, Lyytikäinen O and the Hospital Infection Surveillance Team. Impact of postdischarge surveillance on surgical site infection rates in orthopedic surgery. Infect Control Hosp Epidemiol 2006;27:1324-9.

Huotari K, Agthe N, Lyytikäinen O. Validation of surgical site infection surveillance in orthopedic procedures. Am J Infect Control 2007;35:216-21.

2.3.3. Surveillance and control of antimicrobial resistance

Since early 1990s, KTL has served as the national reference laboratory for health care-associated infections. Bacterial resistance is one of the main areas of reference functions. During the last years much effort has been devoted to verification and typing of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and also extended spectrum beta-lactamase producing (ESBL) *E.coli* and *Klebsiella pneumoniae*. The isolates are in most cases referred to KTL from clinical microbiological laboratories as pure cultures. In addition, KTL assists local health care authorities and other health care professionals by performing molecular typing in various outbreak investigations concerning a wide range of microbial species (such as *Pseudomonas aeruginosa*, *Serratia* and *Acinetobacter* species, coagulase-negative staphylococci, *Candida* species, *Streptococcus pyogenes*). The methodology applied covers from conventional microbiology tests and antimicrobial susceptibility panels to PCR-based verification of species-specific genes (*nuc*, 16SRNA), antimicrobial resistance genes (*mec*A, SCC*mec* complex, *van*-genes), virulence genes (Panton-Valentine leukocidin), pulsed-field gel electrophoresis (PFGE), sequence based typing (spa-typing for *S.aureus*, *emm*-typing for beta-haemolytic streptococci) and MLST (multilocus sequence typing).

Since 1995, all Finnish clinical microbiology laboratories have reported all isolates, including clinical cases and asymptomatic carriage, of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), penicillin-resistant (PRP) and intermediately resistant pneumococci (PIP) and multidrug-resistant tuberculosis (MDR Tbc) to the National Infectious Disease Register (NIDR). Data collected with each notification include date of isolation, date of birth, sex, type of specimen, and place of treatment. The corresponding isolates are collected to the National Microbial Strain Collection and characterized in the appropriate KTL reference laboratory. Surveillance of multiresistant bacteria is based on combined analysis of data on laboratory notifications and microbiological typing results.

Methicillin-resistant Staphylococcus aureus (MRSA)

Project leader: Jaana Vuopio-Varkila, MD, PhD; Anni Virolainen-Julkunen, MD, PhD (in 2002-2005)

Description

Since 1992, microbiology laboratories have sent all MRSA isolates, including clinical cases and asymptomatic carriage, to the KTL Hospital Bacteria Laboratory. All isolates are verified for methicillin-resistance by disk diffusion test, oxacillin MIC-test and *mec*A-PCR, performed either by KTL or the primary clinical microbiology laboratory. At KTL, the isolate is tested for correct species identification by *nuc*-PCR and typed by pulsed-field gel electrophoresis (PFGE). Spa-typing, SCC*mec*- analysis and MLST (multilocus sequence typing) are performed, when needed, and for all epidemic MRSA strains. The increase of community-acquired MRSA strains, provoked the establishment of Panton-Valentine Leukocidin-PCR-test, which is currently performed for all MRSA strains isolated from abscesses, blood or other sterile sites.

In the case of MRSA, test result is reported back to the clinical microbiology laboratory, the hospital hygiene nurse on site and in certain instances also to the infection control units of the health district. The test result is also recorded to the National Infectious Disease Register. At current, the MRSA strain collection consists of over 7000 strains; including all Finnish MRSA strains since 1992, a representative set of European MRSA clones and a collection of Nordic MRSA-isolates. Periodically, additional information (patient /staff member, clinical/screening specimen, hospital contact aboard/outbreak) have been collected from MRSA positive persons by sending a questionnaire to infection control nurses.

KTL has participated in the EU-Harmony project on MRSA typing, and is a member of the European SeqNet.org network and European Study Group on Epidemiological Markers (ESGEM/ESCMID) and the Nordic MRSA group.

Major achievements

1) Since 1995, the annual number of all MRSA isolates notified to the NIDR has increased steadily. Molecular typing has revealed numerous outbreaks of MRSA strains, some of which have been have been successfully controlled in health care facilities either locally or regionally. Using population-based study design and linking data from the National Hospital Discharge Register we showed that three strain types were associated with community acquisition, suggesting that community-acquired MRSA may also arise de novo.

2) In 1997-2002, the increase in MRSA notifications was greatest in elderly and outside Helsinki and Uusimaa hospital district. Isolates from long-term facilities accounted for more than half of the notifications to the NIDR in 2001. We also performed a survey on laboratory detection of MRSA in Finnish clinical microbiology laboratories. The previous national guidelines for the control of MRSA were updated by an expert group to cover also long-term facilities and laboratory diagnostics.

3) In 2004 for the first time, the worsening of MRSA situation was seen in invasive isolates, and it was mostly related to the spread of two internationally recognized MRSA clones. A two-day practical training course was organized to all clinical microbiology laboratories, and consequently, all laboratories started to perform *mec*A-PCR test for MRSA verification locally.

4) Experts from KTL have been involved in updating the national guidelines on prevention of MRSA in health care facilities to cover also long-term care facilities in 2004. These guidelines cover also microbiological diagnostics of MRSA.

5) The national nomenclature for epidemic MRSA strains was renewed in 2005 to better assist surveillance activities, local outbreak investigations and international comparisons. A two day-laboratory course on laboratory diagnostics of MRSA was arranged in 2005. Assistance in investigation of outbreaks in various health care settings in collaboration with health care professionals or the hospital infection programme has been given. In collaboration with the FiRe-Network, several laboratory rounds on antimicrobial susceptibility testing of MRSA and VRE have been arranged during years 2000-2004.

Participation in EU-funded projects Harmony:
http://www.phls.co.uk/International/Harmony/Harmony.htm and
EARSS: http://www.earss.rivm.nl/

Key publications

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Extended spectrum beta-lactamase producing bacteria

Project leaders: Jari Jalava, PhD and Antti Hakanen, MD, PhD

Description

Extended-Spectrum Beta-Lactamase (ESBL) producing *Escherichia coli* and *Klebsiella* spp. isolates are spreading all over the world and becoming an increasing problem, regarding both treatment, diagnostics and hospital hygiene. Especially strains harbouring CTX-M-type extended-spectrum beta-lactamases are rapidly spreading in many European countries, including Finland. In addition to being highly-resistant to third generation cephalosporins, these CTX-M strains are very often multi-resistant. ESBL producing bacteria have traditionally been isolated from hospitalized patients but nowadays they are more frequently found also in community acquired infections. Of the urinary tract isolates from the community, already 1,5- 7 % can be ESBL producers.

Major achievements

1) Molecular methods for detection and characterization of the most important ESBL genes are in use.

2) A strain collection and a database of ESBL producing *E. coli* and *Klebsiella* species have been created. At the moment the collection consist of 1036 clinical isolates from Finnish clinical microbiology laboratories.

3) First survey of the prevalence of different ESBL genes in clinical *E. coli* and *Klebsiella* strains in Finland has been conducted in collaboration with the FiRe-Network.

4) A study of the molecular epidemiology of ESBL producing *E. coli* and *Klebsiella pneumoniae* strains collected from Helsinki and Uusimaa and Northern Ostrobothnia, has been conducted.

Key publications

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Zoonotic and other food-borne bacteria

Project leaders: Antti Hakanen, MD, PhD and Anja Siitonen, PhD

The antimicrobial susceptibility of human *Salmonella*, *Campylobacter*, *Shigella*, verotoxin-producing *E. coli* (VTEC), *Yersinia* and *Plesiomonas shigelloides* isolates of domestic and foreign origin has been surveyed continually and tested by minimum inhibitory concentration (MIC) and/or disk-diffusion method to a large set of antimicrobials in order to detect 1) trends in antimicrobial resistance and epidemiological changes in resistance patterns, 2) multi-resistant strains invading Finland, 3) reduction of susceptibility to various fluoroquinolones, especially to ciprofloxacin, 4) emergence of strains resistant to cephalosporins of third generation or imipenems, and 5) to be able, if needed, to advise of the antimicrobial treatment of the patients.

Major achievements

1) From 2000 through 2004, the annual proportion of the *Salmonella* strains with reduced susceptibility to ciprofloxacin varied between 3 and 15% among domestic strains but increased from 23 to 39% ($P=0.001$) among all foreign isolates and from 4 to 73% ($P<0.001$) among those from Spain, and remained at a constantly high level (52-66%) among isolates from Thailand. We have described a new quinolone resistance phenomenon in Salmonella isolates. This is an important finding since such isolates might easily be misclassified as quinolone-susceptible in clinical laboratories

2) Among of almost 11 000 *Salmonella* strains tested between 2000 and 2004, the percentage of multi-resistant strains remained relatively constant: resistance to at least three drugs was about 16%. Fortunately, the *Salmonella* types endemic to Finland, especially *Salmonella* Typhimurium definite phage type DT1, *Salmonella* Infantis and *Salmonella* Agona that have their reservoir in Finnish production animals, have remained sensitive to all antimicrobials tested.

3) Among *Shigella* strains, the proportion of trimethoprim-resistant strains is increased from 0% to nearly 80% during 1988 - 2 005 and that of nalidixic acid-resistant strains from 0% to 20% since 1995. The first strains fully resistant also to ciprofloxacin emerged during 2004 - 2005. The possibility of ciprofloxacin resistance should be taken into consideration when treating patients returned from Asia, especially from China and Indiaor patients with shigellosis caused by *Shigella flexneri*.

4) Among *Yersinia* strains isolated from Finns, *Yersinia enterocolitica* bioserotype 4/O:3 strains with virulence plasmid and *Yersinia enterocolitica*-like strains without virulence plasmid show

varying resistance against 12 antimicrobials tested. In contrast, *Yersinia enterocolitica* biotype IA strains without virulence plasmid are sensitive to the same set of antimicrobials.

Key publications

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Hakanen AJ, Kotilainen P, Pitkanen S, Huikko S, Siitonen A, Huovinen P. Reduction in fluoroquinolone susceptibility among non-typhoidal strains of *Salmonella enterica* isolated from Finnish patients. J Antimicrob Chemother. 2006;57:569-72.

Haukka K, Siitonen A. Emerging resistance to newer antimicrobial agents among *Shigella* isolated from Finnish foreign travelers. Epidemiol Infect 2007; doi:10.1017/S0950268807008862:1-7.

Anaerobic bacteria and gut microbiota

Project leaders: Eija Könönen, DDM, PhD, and Silja Mentula, PhD

Description

Antimicrobial resistance among anaerobic bacteria has increased significantly during the last 20 years, having an impact on antimicrobial therapy options when treating mixed infections at various body sites. Therefore, screening of antimicrobial susceptibility among clinically relevant bacterial groups in different study populations is of clinical importance.

Antimicrobial agents select resistant organisms and disturb the balance of the commensal gut microbiota allowing harmful bacteria to multiply and resistant bacteria to emerge and spread, which in turn leads to reduction in drug efficacy. Antibiotic-associated diarrhea and the increase of antibiotic-resistant strains can be inhibited using a beta-lactamase enzyme targeted to degrade penicillin group antimicrobial remains in the gut before they affect the microbiota.

Major achievements

1) KTL has participated in European susceptibility surveys organized by the European Study Group on Antimicrobial Resistance of Anaerobic Bacteria (ESGARAB) with susceptibility data on *Propionibacterium acnes*, gram-positive anaerobic cocci, and the *Bacteroides fragilis* group organisms.

2) KTL has run studies on penicillin resistance among anaerobic commensal bacteria of the oral microbiota but also antimicrobial susceptibilities of anaerobic organisms, isolated from various infectious specimens, to antimicrobials potentially used to treat anaerobic infections.

3) In studies performed in collaboration with Ipsat Therapies Ltd. (Helsinki, Finland) on ampicillin-induced changes among the gut microbiota in beagle dogs and humans, orally administered targeted beta-lactamase inhibited the emergence of resistance and preserved the healthy microbiota, whereas without beta-lactamase administration ampicillin selected numerous genetically different multi-resistant strains.

Key publications

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Oprica C, Nord CE; ESCMID Study Group on Antimicrobial Resistance in Anaerobic Bacteria (Kalenic S, Chmelar D, Lundgren B, Könönen E, Rautio M, Rodloff A, Bezirtzoglou E, Nagy E, Menozzi MG, Brazier J, Endtz H, Muller F, Kolman J, Hedberg M, Emtestam L, Lund B). European surveillance study on the antibiotic susceptibility of *Propionibacterium acnes*. Clin Microbiol Infect 2005;11:204-13.

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Vancomycin-resistant enterococci

Project leader: Jaana Vuopio-Varkila, MD, PhD

Since 1995, all glycopeptide-resistant enterococci (VRE) are sent to KTL for species verification, MIC- and *van*-gene determination. All strains are also typed by PFGE. In collaboration with health care professionals and clinical microbiology laboratories, national surveillance and outbreak investigation on VRE is conducted. Since 1995, seven different epidemic and numerous sporadic VRE strains have been detected. In 2005 and 2006, 96 and 38 new VRE cases, respectively, were identified and typed.

The test result is reported back to the clinical microbiology laboratory, the hospital hygiene nurse on site and in certain instances also to the infection control units of the health district. The test result is also recorded to the National Infectious Disease Register.

Clostridium difficile

Project leaders: Silja Mentula, PhD and Eija Könönen, DDM, PhD

Toxin-producing strains of *Clostridium difficile*, which is an anaerobic, spore-forming organism, cause antibiotic-related diarrhea mainly in health care settings. During the last years, new variants of *C. difficile*, especially PCR-ribotype 027, have been reported from several European countries in

connection with outbreaks and increased disease severity. In this context, European Centre for Disease Prevention and Control (ECDC) and ESCMID Study Group on *Clostridium difficile* (ESGCD) have put efforts on building network activities in EU member states.

From 2006 onwards, KTL has assessed the diagnostic preparedness for *C. difficile* in Finnish microbiology laboratories and started to set up typing systems, PCR-ribotyping (the reference method in Europe) and pulsed-field gel electrophoresis. Arrangements for clarifying the current situation in Finland are in progress.

Key publications

Lyytikäinen O, Turunen H, Rasinperä M, Könönen E, Vuento R, Keskimäki I. Clostridium difficile - infektiot lisääntyneet iäkkäillä. In Finnish. (Clostridium difficile Infection in Patients Discharged from Finnish Health Care Facilities, 1996-2004) Suom Lääkäril (Finn Med J) 2007, in press.

FiRe-surveillance network (Finnish Study Group for Antimicrobial Resistance)

Project leaders: Pentti Huovinen, MD, PhD and Antti Hakanen, MD, PhD

Description

FiRe - Finnish Study Group for Antimicrobial Resistance is a coalition of the Finnish clinical microbiology laboratories and the bacteriology units of the National Public Health Institute (KTL). FiRe was founded in 1992 and one of it's primary goals was to standardise the antimicrobial susceptibility testing methodology in the country. In 1996, the NCCLS standard method was accepted as the basis for the standard methodology to be recommended in Finland. Since then, most of the laboratories have adopted this methodology to their diagnostic routine. In principle, this method (FiRe standard method) equals to the CLSI (formerly NCCLS) disk diffusion method. The interpretative breakpoints for susceptibility and resistance published by the CLSI are used with only a few exceptions and the breakpoints are updated annually.

FiRe has accepted as its' primary task to produce reliable and comparable information on the antimicrobial resistance among pathogenic bacteria isolated from the clinical specimens submitted to the FiRe laboratories both from the hospitals and the health care centres in Finland. The comparability of the results obtained by the FiRe standard method is assessed by comparing the inhibition zone diameter distributions of patient and control bacterial strains between laboratories. In addition to these comparisons, the proper performance of the FiRe laboratories when testing for difficult-to-detect type of resistance is tested by special surveys. The susceptibility data produced by the laboratories is collected annually for the Finres report.

Today practically all of the major Finnish clinical microbiology laboratories participate in FiRe. Problems and needs arising are discussed twice a year in meetings of the laboratory representatives. In these meetings, the points to be developed are also agreed. Among the representatives of the FiRe laboratories, a five-member board is elected for three years to supervise the activities of the group.

Major achievements

1) *The annual FINRES report* includes antimicrobial resistance statistics of the most common, clinically important bacteria in Finland. The data has been collected from the Finnish clinical microbiology laboratories (FiRe laboratories) where it has been produced by testing bacterial strains isolated from clinical specimens by the routine antimicrobial susceptibility testing methods.

2) Nationwide data collection started in 1997, when the vast majority of the FiRe laboratories had adopted a common disk diffusion susceptitility testing method, which was agreed upon in 1996 and is based on the CLSI (formerly NCCLS) standard. The FINRES 2005 report is published in www.finres.fi.

3) Large clinical materials have been collected, analyzed and published in collaboration of KTL and FiRe laboratories, including pneumococci and group A streptococci.

Key publications

Pihlajamäki M, Kotilainen P, Kaurila T, Klaukka T, Palva E, Huovinen P and the Finnish Study Group for Antimicrobial Resistance. Macrolide-resistant Streptococcus pneumoniae and antimicrobial consumption. Clin Infect Dis 2001;33:483-8.

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Rantala M, Huovinen P, Huikko S, Jalava J and the Finnish Study Group for Antimicrobial Research (FiRe -network). Prevalence and molecular genetics of macrolide resistance among clinical Streptococcus pneumoniae strains in Finland. Antimicrob Agents Chemother 2005;49: 4180-4.

Bergman M, Huikko S, Huovinen P, Paakkari P, Seppala H, and the Finnish Study Group for Antimicrobial Resistance (FiRe Network). Macrolide and azithromycin use are linked to increased macrolide resistance in Streptococcus pneumoniae. Antimicrob Agents Chemother 2006;50:3646-50.

MIKSTRA-programme; Strategies for antimicrobial use in Finland

Project leader: Pentti Huovinen, MD, PhD

Description

During the past 60-70 years antimicrobials have played a decisive role in the fight against serious diseases. Increasing bacterial resistance everywhere in the world has caused a mounting concern about the potential loss of effect of these 'miracle pills' and has led to criticism of current treatment practices. In Finland, a country of 5.2 million in-habitants, some 2.5 million courses of antimicrobials are prescribed annually in outpatient care. About four out of five prescriptions are for respiratory tract infections; of these 20%-50% are probably of questionable benefit.

MIKSTRA is a joint programme that is administered by several Finnish organisations, designed to optimise diagnostic and treatment practices for common infections in primary care. The aim is to preserve the effectiveness of existing antimicrobials while ensuring patient safety. The programme started in 1998, the first surveillance period was 1998-2002 and the programme will continue with further surveillance programmed to 2008.

There are five interlocking projects within MIKSTRA:

1. Monitoring changes in the diagnosis and treatment of six common outpatient infections (otitis media, sinusitis, tonsillitis, acute bronchitis, skin infections and urinary tract infections).
2. Analysing the costs of these infections for the patient, health care and society before and after launching the guidelines;
3. Studying patients' and physicians' attitudes towards antimicrobials and treatment decisions during the programme;
4. Studying the effect of different educational approaches in the implementation of current care guidelines, including cost-benefit analysis;
5. A cost-benefit analysis of the entire MIKSTRA programme.

MIKSTRA health centres: The programme is implemented through a network of 30 primary health care centres. These are of various sizes and evenly distributed throughout the country, with a population base of 820 000 and some 350-400 general practitioners among the personnel.

Every year during the first study period 1998-2002, consultation data (diagnosis, treatment, sick leave etc.) were collected for one week in each participating centre on all patients with infections. Patient and physician attitude surveys were done regularly. The MIKSTRA health centres were randomised to receive different educational packages for a set of three current care guidelines and another three later. Related health-education material was prepared and distributed to patients and the population. Using the national registers on drug sales, sick-leaves, adverse drug-reactions and hospital discharges the study area was compared to the rest of the country.

In addition to the network of 30 health centres, following organisations are participating:

- National Public Health Institute (KTL) – *Programme leader organization*
- Social Insurance Institution (KELA)
- National Agency for Medicines (Lääkelaitos)
- Research and Development Centre for Welfare and Health (STAKES)
- Finnish Office for Health Care Technology Assessment (FinOHTA)
- The Finnish Medical Society Duodecim

Research groups from the Universities of Helsinki, Tampere, Turku and Oulu are also collaborating.

MIKSTRA is first and foremost a public health programme, but the scientific approach goes hand in hand with the practical implementation. The programme will hopefully guide antimicrobial prescribing in Finnish outpatient care in a more prudent direction. At the same time, implementation tools for guidelines and good clinical practices will be developed. Such tools could be transferable to other public health programmes as well.

Major achievements

1) The use of major antibacterial agents in the community has decreased by 15 %, i.e. about 500000 courses less antibacterial agents were used in 2005 compared to 1995.

2) Prescription habits in the MIKSTRA health centres have changed in 1998-2002 to expected direction guided by the current care guidelines.

Key publications

Rautakorpi U-M, Klaukka T, Honkanen P, Mäkelä M, Nikkarinen T, Palva E, Roine R, Sarkkinen H, Huovinen P, and the MIKSTRA Collaborative Study Group. Antibiotic use by indication: a basis for active antibiotic policy in the community. Scand J Infect Dis 2001;33:920-6.

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2.3.4. Monitoring of maternal infections

Project leader: Heljä-Marja Surcel, PhD

Description

Antenatal health monitoring of pregnant women is an important preventive measure. KTL has the mandate and obligation to implement national screening for infectious diseases during pregnancy. According to the Communicable Disease Decree, all pregnant women should be screened during the first trimester of pregnancy for HIV, hepatitis B and syphilis. The screening yields nationwide information about the prevalence of these infections.

The Prenatal Serology Laboratory is accredited and provides tests for these diseases, for each of which the newborn can be protected with specific drugs or by vaccination. The screening programme covers almost all of the pregnant women in Finland, with a refusal rate of about 2 per cent. During 2006, 16 new cases of HIV, 86 of Hepatitis B and 16 cases of syphilis were identified among 59 659 samples.

Future challenge involves maintenance of the leading position as a testing laboratory. A centralization of the screening programme secures that nationwide epidemiologic information of infectious diseases included in the screening programme is efficiently collected. At the same time, KTL can gather reliable data for prevalence of other preventable infections or other factors that can potentially risk the health of the pregnant mother or the child.

Major achievements

1) An unique collection of the prenatal serum as the Finnish Maternity Cohort serum bank was organized as a nationwide effort by KTL in 1983 and new blood samples are continuously added into the serum bank (approximately. 63 000 samples / year). Representing the whole population, the Finnish Maternity Cohort serum bank is irreplaceably valuable in the scientific research that is done at KTL with the aim of maintaining population health and preventing diseases. The preservation of a sample includes a signed consent of the Mother-to-be and is based on the law on KTL. The preserved specimen is available also for medical examinations involving the health of the mother or the child. The scientific use of the Finnish Maternity Cohort serum bank is monitored by an advisory committee.

2) Research projects are focused on studying epidemiology and causality of certain viral and bacterial infections with genital cancers or with diabetes. Seroepidemiologic data obtained using Finnish Maternity Cohort serum bank has been crucial in epidemiologic and effectiveness studies on human human papillomavirus vaccination Phase III and Phase IV design.

Key publications

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Sädeharju K, Knip M, Virtanen SM, Savilahti E, Tauriainen S, Koskela P, Åkerblom HK, Hyöty H, Finnish TRIGR Atudy Group. Maternal antibodies in breast milk protect the child from enterovirus infections. Pediatrics 2007;119:941-6.

2.3.5. Sexually transmitted infections

Project leaders: Eija Hiltunen-Back, MD, PhD and Petri Ruutu, MD, PhD

Description

NIDR collects data on the notifiable sexually transmitted infections, *Chlamydia trachomatis* infection, gonorrhoea, syphilis and HIV-infection. Gonorrhoea, syphilis and HIV are notified by both physicians and microbiological laboratories, *Chlamydia trachomatis* infections are reported only by laboratories. Genital herpes infections and genital warts are not reportable diseases.

The sexually transmitted infections sentinel surveillance network, established jointly by KTL and clinics, consists of 5 sexually transmitted disease outpatient clinics, 3 primary health care centres, 2 university student health care centres and 2 gynaecological departments in different parts of the country. The aim of the network is to obtain detailed epidemiological data on sexually transmitted infections including genital herpes and warts. A self-administered 22-point questionnaire is used to collect data on risk behaviour, previous sexually transmitted infections and use of contraceptives.

Detailed partner information is included and allows profiling the source partners. In addition to patients with various sexually transmitted infections, data is also collected from attendees in whom no sexually transmitted infection was confirmed. The network covers microbiologically verified chlamydia, gonorrhoea, syphilis, genital herpes and HIV infection and mainly clinically diagnosed genital warts. The data is entered at each site, and collected from the clinics annually.

Major achievements

1) Since 1995 the incidence of *C. trachomatis* infection has been increasing. The National Infectious Diseases Register data was analyzed for gender, age and domicile of the patients in order to disclose the groups with highest increase in the incidence. Data from the sentinel surveillance network disclosed a significant increase in the proportion of cases with a high number of annual sex partners in young women.

2) Due to a rapid increase in the incidence of syphilis an analysis of all cases reported to National Infectious Diseases Register was performed by collecting additional detailed data. The focus was on the source partners, source of the infection and partner notification activities. A local epidemic in Tampere with 45 patients was identified through the sentinel network and investigated. Information on the risks of unprotected sex in the countries of transmission, mostly Russia and Estonia and on the symptoms of syphilis was given to health-care providers and the public.

3) Sentinel surveillance network data on sexually transmitted infections, including genital warts and herpes, provides important additional information and forms a good epidemiological tool to supplement the notification data collected in the National Infectious Diseases Register. Trends in sex and risk taking behaviour with specific sexually transmitted infections can be analysed and used in planning interventions and preventive measures. Each clinic can use their own data as a tool for their daily work. Last but not least, the clinics form a network that work in close contact using uniform diagnostic and treatment practices.

4) Co-operation with European surveillance of sexually transmitted infections (ESSTI). The ESSTI network is a working collaboration between sexually transmitted infections surveillance heads and reference microbiologists of 25 European countries.

Key publications

Hiltunen-Back E, Haikala O, Kautiainen H, Paavonen J, Reunala T. A nationwide sentinel clinic survey of Chlamydia trachomatis infection in Finland. Sex Transm Dis 2001;28:252-8.

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2.3.6. Surveillance and prevention of HIV and other blood-borne viral infections

Project leader: Mika Salminen, PhD

Description

HIV-infection and AIDS are notifiable diseases in Finland. Surveillance data is available since the early 1980s and personal identifiers are confidentially used throughout the system. Hepatitis B and C infections are likewise notifiable, but data is only available since 1995.

The annual rate of HIV-infection in Finland was until the mid-1990s at a very low level, even compared to other Nordic countries. This has changed in the last 5 years so that the annual incidence is at almost the same level as in Sweden. Sexual transmission has increased as a slow trend for the last 5 years. In 2006 close to 200 new cases were reported.

In addition to the passive diagnostic testing based surveillance system, KTL conducts regular unlinked-anonymous HIV & hepatitis C testing surveys among injecting drug users (IDU) through a sentinel surveillance network established with Low Threshold Health Service Centres (LTHSC) for IDU.

The almost universal coverage of maternity and neonatal services and a centralised and well managed blood-banking system enable a high level of vigilance in these groups.

KTL is an active adviser for the MSAH in HIV/AIDS issues and maintains a close contact to the major NGO:s working in the field.

Major achievements

1) Development and maintenance of nationally relevant and WHO/EU compatible HIV/AIDS surveillance schemes with components of both passive and active surveillance. Passive surveillance shows that increases in HIV transmission rates are equally distributed among sexual transmission groups of men having sex with men, heterosexual transmission and cases due to immigrants coming from high prevalence areas. Travel associated HIV-infection is common in the group of heterosexually acquired infections among native Finns. An anonymous survey conducted in 2006, employing mail - out oral fluid collection devices and a risk-factor questionnaire showed an estimated HIV prevalence of 4.6% among MSM, much higher than the estimated prevalence among the general population.

2) An HIV-outbreak among IDUs that was quickly detected in 1998 through the national surveillance system has largely been contained. After a peak in 1999 of close to 100 IDU cases, annually reported cases have declined to 6 reported cases in 2006. This is strongly associated with a major effort towards targeted prevention, which has been executed through a multiplayer network of actors.

3) Development of intervention in the IDU low threshold health promotion and service centres together with the MSAH, STAKES and the A-clinic foundation in 1996-7. This network has grown to more than 30 sites in over 20 municipalities throughout Finland and serves approximately 10.000 users annually (out of an estimated 14.000 - 19.000). In 2005 more than 1.9 million needles and syringes were exchanged through the network. IDU low threshold health promotion services and injection equipment exchange were made statutory elements of the responsibilities of municipal health care in 2004.

4) Development of new methods and testing schemes that enable low-threshold testing and sampling based unlinked studies using rapid fingerpick based tests and oral fluid. Diagnostic testing

at the LTHSC and prisons successfully employs rapid testing schemes supported by the KTL. Unlinked surveys consistently point to an HIV-prevalence of 1-2% among the target group of IDU with no rise over the years.

5) Hepatitis C prevalence among IDU follows a similar declining but slower trend, although the prevalence is still high, approximately 50% in a study conducted in 2005. Passive surveillance points to declining incidence of hepatitis C during the last 5 years. Hepatitis B and A outbreaks among IDU have not been detected in the last 5 years following immunization campaigns within the LTHSC. The vaccines are covered by the national programme for this risk group and their close contacts.

6) Development of and maintenance of sequencing based surveillance for drug resistance and genetic subtyping for in-depth epidemiological monitoring of HIV.

Key publications

Liitsola K, Ristola M, Holmstrom P, Salminen M, Brummer-Korvenkontio H, Simola S, Suni J and Leinikki P. An outbreak of the circulating recombinant form AE-CM240 HIV-1 in the Finnish injection drug user population. AIDS 2000;14:2613-5.

Zetterberg V, Ustina V, Liitsola K, Zilmer K, Kalikova N, Sevastianova K, Brummer-Korvenkontio H, Leinikki P and Salminen MO. Two viral strains and a possible novel recombinant are responsible for the explosive injecting drug use-associated HIV type 1 epidemic in Estonia. AIDS Res Hum Retroviruses 2004;20:1148-56.

Wensing, A.M., et al. Prevalence of Drug-Resistant HIV-1 Variants in Untreated Individuals in Europe: Implications for Clinical Management. J Infect Dis 2005;192:958-66.

Smolskaya T, Liitsola K, Zetterberg V, Golovanova E, Kevlova N, Konovalova N, Sevastianova K, Brummer-Korvenkontio H. and Salminen MO. HIV Epidemiology in the Northwestern Federal District of Russia: Dominance of HIV Type 1 Subtype A. AIDS Res Hum Retroviruses 2006;22:1074-80.

Kivela P, Krol A, Simola S, Vaattovaara M, Tuomola P, Brummer-Korvenkontio H and Ristola M. HIV outbreak among injecting drug users in the Helsinki region: social and geographical pockets. Eur J Public Health 2007;17:381-6.

2.3.7. Invasive bacterial infections

Project leader: Outi Lyytikäinen, MD, PhD

Description

All Finnish clinical microbiology laboratories notify all bacterial isolations from blood and cerebrospinal fluid (CSF) to the National Infectious Disease Register (NIDR). Most laboratory reporting is done electronically. With each notification, the following information is transmitted: date and type of specimen, date of birth, sex, and place of treatment. Using this information and a time interval of three months, possible multiple positive culture results or notifications of the same person are merged as a single case.

In the studies conducted before year 2004, national identity codes for each person with invasive infections were retrospectively collected from the primary diagnostic laboratory either in electronic format or on paper. To obtain information on comorbidities and underlying conditions for patients, was linked the database to national population-based health care registries using the national

identity code: the Cancer Registry, NIDR (HIV infection), the National Social Insurance Institution (KELA), and Hospital Discharge Register (HILMO). To determine the proportion of infections that were health care-associated, we identified preceding hospitalizations for all persons with certain infections from HILMO.

Major achievements

1) To identify opportunities for prevention, national surveillance data of group B streptococcus (GBS) during 1995-2000 were analyzed and birth histories of early-onset neonatal cases reviewed in hospitals participating in SIRO during 1999-2000. The incidence of early-onset GBS disease in Finland is relatively low, but geographic variation exists and current prevention practices are suboptimal. In 2006, the national guidelines for prevention of perinatal GBS were published, which may lead to the reduction in the incidence. Cost analysis of different prevention strategies for policy-makers is ongoing in collaboration with the Finnish Office for Health technology Assessment (FinOHTA).

2) Laboratory-based surveillance data of candidemia from the NIDR were analyzed and cases of candidemia reviewed in one tertiary care hospital during 1995-1999 in Finland. The rate of candidemia increased in Finland, but is still substantially lower than in the United States. No shift to non-C. albicans species could be detected.

3) Analysis of the data from the national, population-based laboratory surveillance of bloodstream infections (BSI) in Finland was performed. Blood-culturing rates were determined from data from clinical microbiology laboratories and trends in rates were evaluated using Poisson regression. The annual blood-culturing rate increased by one-third during the study period but the number of BSI detected per blood cultures remained unchanged. Regional BSI incidence was significantly associated with blood-culturing rates. The increase in BSI rates may have been due to more frequent blood culturing but was not associated with changes in the reporting system or etiology of BSI.

4) In Finland, a country with a low prevalence of methicillin resistance among invasive infections, the increase in annual incidence of *Staphylococcus aureus* bloodstream infections (SABSI) among elderly persons resulted in an increase in annual rate of mortality associated with SABSI.

5) The characteristics, risk factors and outcome of patients with nosocomial pneumococcal bacteremia (NPB) were investigated in a large population-based study. Overall, 10% of pneumococcal bacteremias were health care-associated. Patients with NPB were significantly more likely to have severe underlying conditions and twice as likely to die as patients with community-associated pneumococcal bacteremia. Pneumococcal serotypes included in the pneumococcal polysaccharide vaccine (PPV23) and 7-valent conjugate vaccine caused 72% and 46% of NPBs, respectively. The high prevalence of underlying conditions for which PPV23 is recommended among NPB patients emphasizes the importance of strengthening immunization efforts. Childhood conjugate vaccination might provide additional indirect protection for these patients at high risk of illness and death.

Key publications

Lyytikäinen O, Nuorti P, Halmesmäki E, Carlson P, Uotila J, Vuento R, Ranta T, Sarkkinen H, Ämmälä M, Kostiala-Thompson A, Järvenpää A-L. Invasive group B streptococcal infections in Finland: a population-based study. Emerg Infect Dis 2003;9:469-73.

Poikonen E, Lyytikäinen O, Anttila V-J, Ruutu P. Candidemia in Finland, 1995-1999. Emerg Infect Dis 2003;9:985-90.

Lyytikäinen O, Ruotsalainen E, Järvinen A, Valtonen V, Ruutu P. Trends and outcome of nosocomial and community-acquired bloodstream infections due to *Staphylococcus aureus* in Finland, 1995-2001. Eur J Clin Microbiol Infect Dis 2005; 24:399-404.

Skogberg K, Lyytikäinen O, Ruutu P, Ollgren J, Nuorti JP. Increase in bloodstream infections in Finland, 1995-2002. Epidemiol Infect 2007:5:1-7.

Lyytikäinen O, Klemets P, Ruutu P, Kaijalainen T, Rantala M, Ollgren J, Nuorti P. Defining the population-based burden of nosocomial pneumococcal bacteremia. Arch Intern Med 2007;167:1635-40.

2.3.8. Legionellosis

Project leader: Silja Mentula, PhD

Description

Since 1987, the Anaerobe Reference Laboratory has set up and maintained the reference laboratory methodology for Legionella, including species identification, and serotyping, sequence-based typing, and DNA-fingerprinting by AFLP-PCR of Legionella pneumophila isolates. Methodology serves both surveillance and outbreak investigations. All functions have been designed in collaboration or in accordance to the recommendations of the European Working Group for Legionella Infections (EWGLI).

Key publications

Skogberg K, Nuorti P, Saxen H, Kusnetsov J, Mentula S, Fellman V, Mäki-Petäys N, Jousimies-Somer H. A newborn with domestically acquired legionnaires disease confirmed by molecular typing. Clin Infect Dis 2002;35:e82-85.

2.3.9. Surveillance for poliovirus and other enteroviruses

Project leaders: Tapani Hovi, MD PhD, and Merja Roivainen, PhD

Description

This is in principle a permanent activity carried out by KTL including

1) identity confirmation and further characterization of poliovirus strains and any faecal enterovirus strain, isolated by any laboratory in Finland ("Enterovirus surveillance"),

2) monitoring putative poliovirus circulation in the Finnish population by sewage screening ("Environmental surveillance"), and

3) monitoring of herd immunity by serosurveys.

The global wild poliovirus eradication programme has been delayed, and intensive poliovirus surveillance is most likely needed for many years to come. Apart from this National Polio Laboratory activity, KTL is also serving the WHO Polio Laboratory Network as one of the European Regional Reference Laboratories responsible for characterization of poliovirus isolates from 12 European countries and as one of the 7 Global Specialized Laboratories supporting the programme by sequence analysis, methods evaluation and research. KTL Enterovirus Laboratory is accredited for poliovirus isolation, identification and subtyping by WHO while methods for

enterovirus isolation and identification are accredited due to the international standard EN ISO/IEC 17025:2005. Resources are mainly from KTL budget but a significant support also from WHO

Major achievements

1) Key expert advice to the Ministry of Health in creating national polio surveillance policy for the era after certification of polio-free European 2002 and for containment of poliovirus strains. Documentation of absence of signs of poliovirus circulation in Finland is carried out by regular monitoring of about 20% of population by environmental surveillance supplemented by enterovirus surveillance. Validation of the environmental surveillance method is done by "spiking experiments" and mathematical modelling.

2) Persistent high quality performance in the WHO Polio Labnet, reflected by relatively short through-put times of primary samples and referred strains, repeatedly excellent performance in international and national external quality assurance tests, and repeated accreditation by WHO. ISO accreditation by FINAS was received since 2005. Organization of annual EQA tests in enterovirus isolation for primary virus diagnostic laboratories in Finland.

3) Redesignation as a WHO Collaborating Centre for Poliovirus Surveillance and Enterovirus Research obtained in 2004 (First nomination in 1993). Special expert advice to WHO in applying environmental surveillance for poliovirus surveillance in different epidemiological situations. Writing of most chapters and primary editing for publication "WHO Guidelines for Environmental Surveillance of Poliovirus Circulation". Technology transfer (environmental surveillance) to Egypt, Georgia, Turkey, and Indonesia.

4) Characterization of strains reacting aberrantly in the standardized intratypic poliovirus differentiation tests. Discovery of three separate episodes of vaccine derived polioviruses in European sewage waters and expert advice to WHO/EURO in attempts to identify the individuals excreting these strains. No clinical cases could be linked to these episodes but in two out of three cases the virus strains were shown to be fully neurovirulent. Design, launching, performance and evaluation of environmental surveillance programme in Egypt since 2000 (collaboration with WHO/EMRO, Egyptean polio laboratory and CDC, USA) revealing widespread wild poliovirus circulation and resulting in changes in national polio control policy eventually eliminating the circulation.

Key publications

Valtanen S, Roivainen M, Piirainen L, Stenvik M, Hovi T. Poliovirus specific intestinal antibody responses coincide with decline of poliovirus excretion. J Infect Dis 2000;182:1-5.

Hovi T, Senvik M, Salonen H, Kangas A. Poliovirus surveillance by examining sewage specimens. Quantitative recovery of virus after introduction into sewerage at more upstream location. Epidemiol Infect 2001;127:101-6.

Savolainen C, Hovi T. Caveat: poliovirus may be hiding under other labels. Lancet 2003;361:1145-6.

Blomqvist S, Savolainen C, Laine P, Hirttiö P, Lamminsalo E, Penttilä E, Jöks S, Roivainen M, Hovi T. Characterization of a highly evolved vaccine derived poliovirus 3 isolated from sewage in Estonia. J Virol 2004; 78:4876-83.

Hovi T, Blomqvist S, Nasr E et al. Environmental surveillance of wild poliovirus circulation in Egypt - balancing between detection sensitivity and workload. J Virol Meth 2005; 26:127-34.

2.3.10. Influenza and other respiratory viral infections

Project leaders: Reijo Pyhälä, PhD and Thedi Ziegler, PhD

Description

Over a period of 18 years, KTL has conducted surveillance of respiratory viruses in certain segments of the Finnish population, particularly in small children and in army conscripts. Routinely, clinical samples have been tested for adenoviruses, influenza A and B, parainfluenza viruses, and respiratory syncytial viruses. A long-term epidemiological analysis of this material is currently being performed. Since 2005, KTL has served as the Finnish reference laboratory of the European Influenza Surveillance Scheme (EISS) and reports influenza and RSV findings on a weekly base, and provides training and support to laboratories in Estonia and in Bosnia and Herzegovina that are designed to become WHO National Influenza Centres. KTL participates in clinical studies of respiratory infections in children.

Major achievements

1) KTL has acted as a WHO National Influenza Centre since 2000. The regular functions and extra surveillance and research activities include (1) isolation of 100-200 influenza virus strains per epidemic season from specimens representing the whole area of Finland, antigenic typing (hemagglutination inhibition test), more detailed antigenic characterization and sequence analysis of hemagglutination 1 and neuramididase genes; shipments of representative isolates to the WHO World Influenza Centre, Mill Hill, London; (2) maintenance of a collection of ca. 4100 samples of influenza virus strains isolated in Finland in 1968-2007 and annual phylogenetic analyses of current strains in relation to selected reference strains of the collection and to vaccine strains. These analyses have enabled, e.g., to find new virus variants that have heralded an early outbreak in the following autumn; this has aided in advancing vaccination campaigns; (3) regular mailing of an e-mail on isolated strains and their characteristics to the WHO and ca. 20 foreign laboratories participating in influenza surveillance in Europe and the USA, editing of a regularly issued internet document and annual reports on influenza outbreaks and epidemic viruses in nation-wide trade magazines for citizens and physicians; (4) standardized virological samples and monitoring of upper respiratory tract infections with consistent methods have enabled to determine comparable morbidity figures and to analyse the influence of antigenic drift on the intensity of influenza outbreaks among conscripts in the Finnish Defence Forces; and (5) vaccination induced antibody response and vaccination efficacy and effectiveness have been analysed in several target groups (dialysis and cardiac patients, healthy military conscripts) during influenza A and B outbreaks, e.g., under circumstances of incomplete antigenic drift and in relation to antibody cross-reactivity and appearance of drift variants as a consequence of vaccination in a semi-closed population.

2) KTL maintains a collection of over 10,000 samples of respiratory excretions. From many patients, particularly from army conscripts, paired acute- and convalescent-phase sera are available.Selected samples of this collection are currently being studied for the presence of the recently identified "novel" respiratory viruses, i.e., human metapneumovirus and bocavirus. In addition to respiratory viruses, KTL has screened respiratory samples for the presence of *Mycoplasma pneumoniae* and determined the optimal type of clinical specimen for the laboratory diagnosis of *Mycoplasma pneumoniae* infections. The collection of respiratory samples is used for the development and validation of new laboratory techniques.

3) During the SARS epidemic in 2003, KTL prepared for possible cases of SARS in Finland and prepared diagnostic methods. In collaboration with other experts certain immunological aspects of SARS coronavirus infection of human macrophages and dendritic cells were characterized.

4) KTL participates in preparations for an eventual influenza pandemic by developing and maintaining diagnostic methods, preparing for work under biosafety level-3 conditions, preparing the national pandemic preparedness plan.

Key publications

*Pyhälä R, Ikonen N, Santanen R, Haanpää M, Visakorpi R, Jäppinen P, Valle M.*_Vaccination-induced HI antibody response to intraepidemic influenza A (H3N2) virus variants of the 1996-1997 epidemic season. J Med Virol 2001;65:584-9.

*Ikonen N, Pyhälä R, Axelin T, Kleemola M, Korpela H.*_Reappearance of influenza B/Victoria/2/87-lineage viruses: epidemic activity, genetic diversity and vaccination efficacy in the Finnish Defence Forces. Epidemiol Infect 2005;133:263-71.

Ikonen N, Pyhälä R, Toivonen M, Korpela H. Influenza A/Fujian/411/02(H3N2)-lineage viruses in Finland: genetic diversity, epidemic activity and vaccination-induced antibody response. Arch Virol 2006;151:241-54.

Ziegler T, Matikainen S, Ronkko E, Osterlund P, Sillanpää M, Siren J, Fagerlund R, Immonen M, Melen K, Julkunen I. Severe acute respiratory syndrome coronavirus fails to activate cytokine-mediated innate immune responses in cultured human monocyte-derived dendritic cells. J Virol 2005;79:1380-5.

Heikkinen T, Silvennoinen H, Peltola V, Ziegler T, Vainionpää R, Vuorinen T, Kainulainen L, Puhakka T, Jartti T, Toikka P, Lehtinen P, Routi T, Juven T. Burden of influenza in children in the community. J Infect Dis 2004;15:1369-73.

2.3.11. Measles, mumps and rubella

Project leader: Irja Davidkin, PhD

Description

KTL is responsible for confirmation of suspected measles, mumps and rubella cases, especially in vaccinated persons, and for monitoring the virus strains occurring in Finland. KTL has participated in two EU-projects which focus on the surveillance of measles: ELSM (Enhanced Laboratory Surveillance of Measles, 2002-2005) and EUVAC.NET (A Surveillance Community Network for Vaccine preventable Infectious Diseases) 2000-2003, and 2005- continues.

The MMR vaccine-induced immunity has been followed intensively in a study cohort since 1982. The high vaccination coverage maintained since 1987 and the MMR disease-free period since the mid of 1990s have provided the possibility to monitor the immunity (humoral and cellular) induced by vaccinations only. The population immunity studies are needed to evaluate the effectiveness of vaccination programme and identify possible susceptible age groups. Samples from the Finnish Maternity Cohort and the serum bank collected from residual sera were used for population immunity studies. KTL participated in EU collaboration ESEN1 and 2 (European Sero-Epidemiology Network) projects, 2000-2005.

In the future, the long-term follow-up of antibodies and cellular immunity in the cohort continues (collecting 25-year follow-up samples from the cohort in autumn 2007), as well as population immunity studies, and an intensive surveillance of MMR diseases. These studies are vital for monitoring the success of the present two-dose MMR vaccination and for assessing a need for changes.

Major achievements

1) The intensive study of suspected MMR diseases showed that less than 5% of clinical measles, mumps or rubella suspicions were correct, especially in vaccinated individuals. The results stress the importance of laboratory confirmation of all suspected MMR cases for reliable incidence data, particularly in the elimination phase.

2) After the elimination of indigenous MMR diseases by the mid of 1990s, a few annual imported cases have been confirmed and their transmission routes have been traced by genetical characterization.

3) In 2004, KTL was nominated the National Reference Laboratory in the WHO Measles/Rubella laboratory network and accredited by WHO in 2006. An ongoing national accreditation process is projected to be finished by the end of 2007.

4) The follow-up of the immunity in our unique vaccinated cohort has given important information about the success of the current MMR vaccination programme. Although the antibody levels have been shown to decline, the rate of decline has been very slow during the last ten years suggesting a long persistence of low level antibodies. The cellular immunity studies have revealed the existence of cell-mediated immunity to mumps virus even when antibody levels have fallen below the measurable level.

5) Seroepidemiological studies showed that vaccine-induced antibodies remain at a significantly lower level than naturally acquired, although the seropositivity in all, also vaccinated, age groups is high. These results emphasize the need for continuous monitoring of population antibody levels and seropositivity.

Key publications

Davidkin I, Peltola H, Leinikki P and Valle M. Duration of rubella immunity induced by two-dose measles, mumps and rubella (MMR) vaccination. A fifteen-year follow-up in Finland Vaccine, 2000;18:3106-12.

Peltola H, Davidkin I, Paunio M, Valle M, Leinikki P and Heinonen O-P. Mumps and rubella eliminated from Finland. JAMA 2000;284:2643-47.

Paunio M, Hedman K, Davidkin I, Peltola H. IgG avidity to distinguish secondary from primary measles vaccination failures: prospects for a more effective global measles elimination strategy. Expert Opin Pharmacother. 2003;4:1215-25.

Davidkin I, Jokinen S, Paananen A, Leinikki P, Peltola H. Etiology of mumps-like illnesses in MMR-vaccinated children. J Infect Dis 2005;191:719-23.

Jokinen S, Österlund P, Julkunen I, Davidkin I. Cellular immunity to mumps virus in young adults 21 years after MMR vaccination. J Infect Dis, 2007;196:861-7.

2.3.12. Mycobacterial infections

Project leaders: Merja Marjamäki MSc and Petri Ruutu MD, PhD

Description

KTL implements the surveillance for mycobacteria in National Infectious Disease Register, carries out the national mycobacterial reference laboratory functions, coordinates the national advisory expert group on tuberculosis (TB) control, and carries out research in support of the TB control programme. The mycobacterial reference laboratory is responsible for the national tuberculosis drug

resistance surveillance and species identification or confirmation all clinical mycobacterial isolates, including atypical mycobacteria and M. bovis BCG. A KTL staff member is the formal Programme Manager of the National TB Programme named by MSAH.

TB incidence has been falling steadily in Finland. The proportion of tuberculosis in foreign born patients is increasing, being now about 15%, and some multidrug resistance in this subpopulation has been seen, in the presence of a major MDR problem in neighbouring countries Estonia and Russia. Active contribution has been implemented to EuroTB by provision of high-quality annual data set, an enhanced Drug Resistance Surveillance (DRS) surveillance data set, and serving in the Steering Committee throughout the evaluation period.

Major achievements

1) The NIDR has been proven to have a very high coverage of all microbiologically proven cases in a large cohort study. It has provided a high quality tool for demonstrating the decline of TB to one of the lowest incidences globally, and for monitoring the effects of the change in the national policy on BCG vaccination in 2006.

2) The mandatory notification of all mycobacterial laboratory findings and the confirmation of all mycobacterial isolates in the reference laboratory have contributed to cleaning atypical mycobacterial infections from cases notified as clinical tuberculosis. This also provided a sensitive tool for detecting the increase in adverse effects from BCG vaccination after the change of the vaccine strain in 2003 and contributed to the subsequent switching of BCG vaccination from universal to risk groups only.

3) In the national cohort study great diversity was observed in the anti-TB treatments given, stressing the need for a revised national TB control programme. KTL contributed significantly to publications on national guidelines on specific areas of TB control, and the new comprehensive National TB Control Programme 2006.

4) During 2000-2006 a total of 2477 new Finnish clinical *M. tuberculosis* isolates and 2920 new atypical mycobacterial isolates have been received and processed for antibiotic susceptibility testing and species identification to fulfil the reference laboratory functions. Further, large numbers of both clinical and environmental isolates have been submitted for further studies by collaborators. KTL is monitoring the epidemiology of *M. tuberculosis* as well as non-tuberculous mycobacteria by systematically fingerprinting all new MTB isolates in order to complement standard epidemiology for detecting and analyzing ongoing transmission routes.

5) Characterization of the most common mutations that are linked to drug resistance in Finland and implementing new rapid molecular methods for the detection of drug-resistant TB.

Key Publications

Puustinen K, Marjamaki M, Rastogi N, Sola C, Filliol I, Ruutu P, Holmstrom P, Viljanen MK, Soini H. Characterization of Finnish *Mycobacterium tuberculosis* isolates by spoligotyping. J Clin Microbiol 2003; 41:1525-8.

Marttila HJ, Marjamaki M, Viljanen MK, Soini H. Performance of BACTEC 960 Mycobacteria growth indicator tube in the susceptibility testing of genetically characterized *Mycobacterium tuberculosis* isolates. Eur J Clin Microbiol Infect Dis 2003;22:757-9.

Kokki M, Holmström P, Ruutu P. High sensitivity for culture confirmed tuberculosis in a laboratory-based national integrated infectious disease surveillance system in Finland. Eurosurveillance 2005;10:90-3.

Mäkinen J, Marttila HJ, Marjamäki M, Viljanen MK, Soini H. Comparison of two commercially available DNA line probe assays for detection of multi-drug resistant *Mycobacterium tuberculosis.* J Clin Microbiol 2006;44:350-2.

Vasankari T, Kokki M, Holmström P, Liippo K, Sarna S, Ruutu P. Great diversity of tuberculosis treatment in Finland. Eurosurveillance, 2007;12(1); epublication.

2.3.13. Pertussis

Project Leader: Qiushui He, MD, PhD

Description

Resurgence of pertussis has been observed in many countries including Finland. In Finland, the whole-cell pertussis vaccine has been replaced by acellular vaccine since 2005. Antigenic variations in components included in acellular vaccine have been found between *B. pertussis* vaccine strains and circulating isolates. Study areas include (1) evolution and molecular epidemiology of *B. pertussis*, (2) impact of changing from whole cell to acellular vaccine on incidence of disease and bacterial population, (3) role of antigens and specific epitopes in relation to immunity, and (4) persistence of cell-mediated and humoral immunity after infection and vaccination.

KTL develops molecular tools for rapid diagnosis of pertussis and for identification of antigenic variants and helps validating the diagnostic methods used at clinical microbiology laboratories. The reference functions of this laboratory include collection of *Bordetella* isolates, analyzing of the isolates by standardized typing methods and reporting result to the clinical microbiology laboratories. Methods are also developed for studying genetic susceptibility to bacterial diseases in pediatric populations.

The laboratory has long-term collaborations with the University of Turku and the Turku Immunology Centre, a research and graduate programme established in 1993. KTL has previously participated in a EUpertstrain project (QLK2-2001-01819) and KTL currently co-ordinates a network entitled "European Network for Comparative and Functional Genomics of *Bordetella pertussis*" in which 13 leading pertussis reference and research laboratories in nine European countries are involved. The laboratory also collaborates with other countries such as China and Serbia.

Major achievements

1) KTL has developed PCR method for rapid detection of *B. pertussis* from nasopharyngesl swabs which has been used routinely nationwide for the diagnosis of pertussis. The laboratory has developed real-time PCR methods for rapid identification of antigenic variants of *B. pertussis.* A total of appx. 700 *B. pertussis* isolates have been collected and tested.

2) The antigenic divergence with respect to Ptx and Prn has been found between the vaccine strains and circulating isolates in Finland. A shift of predominant serotype from Fimbriae (Fim) 2 to Fim3 was observed since 2000, and about 85% of strains isolated in 2003 were Fim3, which coincided with a nationwide epidemic of pertussis. Furthermore, clonal expansion of *B. pertussis* has occurred and caused the recent epidemics in the country.

3) Increasing number of pertussis cases in adolescents and adults has been observed in highly vaccinated populations. They transmit bacteria to vulnerable newborns and infants who are too young to have received all doses of vaccination and thus suffer a severe and life-threatening illness. Regular booster immunization of adolescents and adults with acellular pertussis vaccines could be successful for reducing the spread of *B. pertussis* infections among the human populations. The persistence of pertussis specific antibodies and cell-mediated immunity was evaluated in adolescents 5 years after a booster dose of acellular pertussis vaccine. The results suggest that the interval between routine acellular pertussis booster immunizations might be extended beyond 5 years.

4) Immunization against pertussis was introduced in China in the 1960s. Since the 1970s, no culture-confirmed pertussis cases have been reported in the country. Furthermore, the current laboratory methods (e.g. culture, EIA and PCR) are not being used to diagnose pertussis in China. In collaboration with the Beijing Children's Hospital, the current laboratory methods are introduced and used for diagnosis of pertussis in the hospital. We rediscovered infants with culture-confirmed pertussis, who were initially diagnosed as having other respiratory diseases. The result indicates that pertussis is not uncommon in the Chinese population and still causes substantial illness in infants and young children.

Key publications

Mäkinen J, Viljanen MK, Mertsola J, Arvilommi H, He Q. Rapid identification of *Bordetella pertussis* pertactin gene variants using LightCycler real-time polymerase chain reaction combined with melting curve analysis and gel electorphoresis. *Emerg Infect Dis* 2001;7:952-8.

Wang J, Yang J, Li J, Mertsola J, Arvilommi H, Yuan L, Shen X, He Q. Infantile pertussis rediscovered in China. Emerg Infect Dis 2002;8;859-61.

He Q, Mäkinen J, Berbers G, Mooi FR, Viljanen MK, Arvilommi H, Mertsola J. Bordetella pertussis protein pertactin induces type-specific antibodies: one possible explanation for the emergence of antigenic variants? J Infect Dis 2003;187:1200-5.

Elomaa A, Advani A, Donnelly D, Antila M, Mertsola J, Hallander H, He Q. Strain variation among *Bordetella pertussis* isolates in Finland where the whole-cell pertussis vaccine has been used for 50 years. J Clin Microbiol 2005;43:3681-7.

Edelman K, He Q, Mäkinen J, Sahlberg A, Haanperä M, Schuerman JW, Wolter J, Mertsola J. Immunity to pertussis five years after booster immunization in adolescence. Clin Infect Dis *2*007;44:1271-7.

2.4. National immunization programme

2.4.1. Expert advice for development of National Immunization Programme (NIP)

Project leader: Terhi Kilpi, MD, PhD

Decision-making process

The provisions on the national immunization programme, ie. vaccines to be included, schedules and target groups, are laid down by decree of the Ministry of Social Affairs and Health. According to the Communicable Diseases Act, the National Public Health Institute (KTL) is the expert institution and the National Advisory Board on Communicable Diseases in connection with the Ministry of Social Affairs is the expert body in the combat of communicable diseases. It is thus the responsibility of KTL to advise the Ministry in the immunization programme issues. The role of the National Advisory Board of Communicable Diseases is to decide whether or not it is willing to support the detailed evaluations and recommendations produced by KTL.

KTL expert work is done in and coordinated by the following expert groups:

National Advisory Committee on Vaccination (KRAR)

The National Advisory Committee on Vaccination is composed of experts from KTL (currently 4 members), Ministry of Social Affairs and Health (1 member), National Agency for Medicines (1 member) and other interested bodies in the field, such as health care professional associations, medical societies or universities (altogether 6 members). KRAR is appointed by and gives its recommendations to the Director General of KTL. KRAR typically deals with major immunization policy issues, including introduction of new vaccines or other significant changes in NIP.

National Advisory Committee on Vaccination has defined the following criteria for evaluation of the need to introduce a new vaccine into the age-based schedule of all individuals:

1. Expected public health benefit
2. Safety of vaccine invidually
3. Safety effects on population level
4. Cost-effectiveness

KTL Advisory Committee on Immunization Practices

The KTL Committee on Immunization Practices is a practical tool for implementation and development of NIP. It consists of KTL experts from the fields of general vaccinology, virology, bacteriology, infectious disease epidemiology, immunology, vaccine safety and programme implementation. The only non-KTL member of this committee represents the Finnish Defence Forces.

Vaccine/disease specific expert groups

Before National Advisory Committee on Vaccination forms its opinion on introduction of a new vaccine, a vaccine specific working group, similarly composed of experts from KTL and other bodies and organizations, is usually established to provide an evidence-based report and conclusions on the four criteria listed above.

In 2001 a varicella specific expert group recommended introduction of universal varicella vaccination with a two-dose policy but National Advisory Committee on Vaccination turned down this proposal. In 2002, an expert group established to consider introduction of pneumococcal

conjugate vaccine concluded that the cost-effectiveness of the vaccine does not justify universal vaccination of all infants. The expert group evaluations that have resulted in programme changes during the 2000's are listed in the following Table 2.

Table 2. ***Recent changes in NIP***

Year	Vaccine	Type of change	Target group
2002	Influenza, annual	Introduction	All individuals aged ≥65 years
2003	Diphtheria, tetanus, acellular pertussis (DTaP/dtap)	Introduction	All children at 6 years of age
2005	Pentavalent combination vaccine against diphtheria, tetanus, pertussis, polio, Haemophilus influenzae type b (DTaP-IPV-Hib)	Introduction	All infants at 3, 5 and 12 months of age
2005	Tick-born encephalitis (TBE)	5-year campaign	All individuals over 7 years of age living permanently on Åland, the island group between Finland and Sweden
2006	BCG	Restriction	High-risk groups only (instead of previous universal newborn vaccination programme)
2007	Influenza, annual	Introduction	All children aged 6 to 35 months

2.4.2. Procurement and distribution of vaccines for the National Immunization Programme

Project leader: Rose-Marie Ölander, MSc

Description

By the Communicable Diseases Act and Decree, KTL has overall responsibility to provide the municipalities with all the vaccines needed for the implementation of the National Immunization Programme. The vaccines (1.5 million doses per year) are distributed to the hospital pharmacies and pharmaceutical centres and provided free of charge in the health care centres to the inhabitants in the municipalities. The vaccine procurement and distribution are financed by the state budget. The annual budget is approximately 10 million euros. In addition, some rare vaccines, rabies

immunoglobulin and immune sera for the treatment of diphtheria and botulism are supplied to hospitals, health centres and pharmacies. The responsibility for procurement, stockpiling and distribution of vaccines needed for the preparedness of influenza pandemic and other biological threats caused e.g. by terrorist activity lies also in KTL. These vaccines are only distributed with the permission of the Ministry of Social Affairs and Health.

All vaccines that are used in Finland are imported. The vaccines used in the National Immunization programme or for stockpiling are purchased after an open EU-tender procedure. A procurement working group within KTL gives the procurement recommendation to the Director General who makes the final decision. The storage and distribution of the vaccines have been gradually outsourced to three wholesale distributors of pharmaceutical products since 2005. All products are distributed through the wholesalers from the beginning of 2007.

The customers (hospital pharmacies and pharmaceutical centres) send the vaccine orders to KTL. KTL checks, accepts and forwards the orders to the wholesale distributors electronically. To manage the logistics of vaccine supply, KTL has established an electronic data system that is used by KTL and the wholesale companies for documentation and follow-up of vaccine orders and deliveries. The data system also retrieves aggregate data from the Finnish population register. The system helps KTL to ensure that the vaccine stocks are sufficient and that the vaccines are distributed in accordance with the expected population size in each municipality.

In case of an influenza pandemic, a rapid distribution of pre-pandemic and pandemic vaccines for the whole population of five million within two to three weeks will be needed. The existing data system and the population data will be utilized in managing pandemic vaccine logistics. A pre-distribution plan is under construction. When a decision to start mass vaccination has been made, the plan will be fine-tuned and the delivery orders sent electronically to the wholesale distributors without delay.

Vaccine customers in the hospital pharmacies and pharmaceutical centres are provided through the KTL web site with continuously updated information about vaccine logistics and use, e.g. delivery schedules for the seasonal influenza vaccine to the individual municipalities, possible shortage of vaccines due to delay in delivery or product changes.

The responsibilities assigned to the Vaccine Supply Unit, the Vaccine Quality Control Unit and the Register for Vaccine Adverse Events enable KTL to have an uninterrupted updated picture about all vaccines that are distributed, sold and used in Finland.

2.4.3. Implementation of National Immunization Programme

Project leader: Satu Rapola, MD, PhD

Description

KTL continuously evaluates the immunization policy, i.e necessity of the vaccines currently included in the NIP, optimal timing of the vaccinations (vaccination schedules), use of combination of vaccines and feasibility of introduction of newly licenced vaccines. KTL also prepares recommendations and instructions for the use of vaccines and provides health professionals, citizens and the media with appropriate information.

The municipalities (public health centres) are responsible for vaccinating the population in their area. KTL guides and promotes the implementation of the vaccination programme (see below), and thus shares the responsibility of the implementation of changes in the vaccination programme.

To be able to reach the personnel in the municipalities, who are responsible for administration of vaccines, KTL has established a network of contact persons by asking each municipality to identify one or two. Through this network the health care personnel in the health centres are provided with detailed instructions. All materials on KTL web-site are printable and can be used in local training.

All information regarding the practical implementation is synchronized with the purchasing and distribution of the vaccines included in the National Immunization Programme.

Major achievements

1) A major change in the NIP took place in 2005 when Finland stopped producing whole cell pertussis vaccine and introduced a 5-valent combination vaccine. Preparatory activities took several years including an extensive education process which was carried out with KTL leadership in 2004.

2) In the beginning of 2006, a five year vaccination campaign against tick-born encephalitis was introduced in Åland. In September 2006, Finland switched from universal BCG vaccination of all newborns to vaccinating targeted risk groups only. Detailed instructions on these changes and their implementation were communicated by KTL to the local health centres through several channels, including Internet and the network of dedicated local experts.

3) In 2007, state funded influenza vaccinations will be extended to cover all children aged 6-35 months. KTL is currently running a specific campaign to support the implementation of influenza vaccinations.

Key publications

Hovi T, Kuronen T, Rapola S, Kilpi T. Kansanterveyslaitoksen rokotussuositustyöryhmä: Influenssarokotus kaikille 65 vuotta täyttäneille. Kansanterveyslaitoksen influenssarokotussuositus syksyllä 2002 (KTL Advisory Committee on Immunization Practices: Influenza vaccination for all aged at least 65 years in autumn 2002). Suom Lääkäril (Finn Med J) 2002;57:2411-2413.

Rapola S, Hovi T, Ölander R, Kuronen T, Hulkko T, Mertsola J, Kilpi T. Uudistuksia kansalliseen rokotusohjelmaan vuoden 2003 alusta (Reforms to the National Immunizatio Programme from the beginning of 2003). Suom Lääkäril (Finn Med J) 2003; 58:182-185.

Rapola S. Uusi lasten ja nuorten rokotusohjelma käyttöön 1.1.2005 (New vaccination programme for children and adolescents introduced on 1 January 2005). Kansanterveys (Journal of National Public Health Institute) 2005;(1):3-5.

Rapola S. Rokotukset puutiaisaivotulehdusten torjumiseksi alkavat Ahvenanmaalla (Vaccinations against tick-born encephalitis start in Åland). Kansanterveys (Journal of National Public Health Institute) 2006;(1):23.

Rapola S. Finland switched from universal tuberculosis vaccination of all newborns to targeted risk group vaccination. V&I News 2006(7):5-6.

2.4.4. Training, advice and communication to vaccinators

Project leaders: Satu Rapola, MD, PhD and Saila Pitkänen PHN, MA

Description

KTL concentrates on communication with health care professionals mainly through web-based communication. Through internet all information is rapidly accessible to all professionals.

Major achievements

1) Vaccinator's Manual: The core guidance for vaccinators is published in the Vaccinator's Manual. It is a joint venture of KTL and Duodecim Medical Publications Ltd (owned by The Finnish Medical Society Duodecim). The handbook was made electronically available from the KTL website in 2003 (www.ktl.fi/portal/suomi/julkaisut/oppaat_ja_kirjat/ rokottajan_kasikirja/). The electronic version is continuously updated. A printed version of the manual is published according to need; a total of 6 updated versions have been published since 1993. The 5th edition included 335 frequently asked questions and answers to them, but these were omitted from the 6th edition, and are available only from the web. The first Swedish language translation of the manual was published on the internet in 2005 and has since been updated in parallel with the Finnish language version. Guidance given in the manual builds on scientific evidence whenever possible, and is approved by the KTL Advisory Committee on Immunization Practices. The book contains detailed descriptions of all vaccines available in Finland and practical instructions on their use. Brief epidemiological updates on the vaccine preventable diseases, administration of vaccines, immunization of special target groups and adverse events following immunization are covered in the 7 main chapters dedicated to these issues.

2) Other information materials: The main emphasis is on web-based communication, which allows easy access to information for vaccinators all over Finland. KTL maintains comprehensive web pages which seek to provide all essential information on vaccines and immunizations. The web pages also contain a range of materials, e.g. vaccine recommendations, booklets, leaflets, slides, and videos on immunization techniques. All the materials are produced by KTL employees. For the annual influenza vaccination campaign, special campaign pages have been set up which contain a variety of promotional materials and ideas for campaign activities. Most of the web content is in both official languages, Finnish and Swedish. The web pages are updated regularly. Notification of all new pages and materials is sent via e-mail to contact persons across the country (contact network described in 2.5.3). Contact persons distribute the information further in their areas. In addition to the web pages, information to vaccinators in also communicated through professional journals.

3) Telephone counselling service: A telephone service is available to health care professionals three hours every working day. Specially trained public health nurses backed up by a physician assist the health care professionals to solve any vaccine or vaccination related issues that come up in their work. "Frequently Asked Questions" -directory on KTL web-site receives most of its questions through this counselling service and is updated regularly.

4) Training courses and lectures: when appropriate, the experts of KTL give lectures and organize vaccination related education in collaboration with other health care professionals. For the time being a 2 day lecture course to be held in February 2008 is being prepared. This course is aimed for 500-600 health professionals who work in the field of vaccines and vaccination in Finland. KTL experts also participate in international vaccinology related training such as the Advanced Course in Vaccinology which is annually organized by the Fondation Mérieux, and the EPIET Vaccinology Module.

Key publications

Nohynek H, Rapola S. Rokotukset (Vaccinations). In: Lääkärin käsikirja (Physician's Manual). Jyväskylä, Duodecim 2006:71-75.

Nohynek H, Hulkko T, Rapola S, Strömberg N, Kilpi T. Rokottajan käsikirja 2005 (Vaccinator's Manual). Helsinki, Duodecim, 2005. 240p.

Hulkko T, Kilpi T, Pitkänen S, Rapola S, Strömberg N. Neuvolan rokotusopas (Information for parents on vaccinations). Helsinki, Mannerheimin Lastensuojeluliitto (The Mannerheim League for Child Welfare), 2007

2.4.5. Monitoring the effectiveness of National Immunization Programme

Project leader: Tuija Leino, MD, PhD

Description

The effectiveness of vaccination programme is most directly evaluated by stringent infectious diseases surveillance. For evaluating a specific vaccination, immunization records of disease cases, as well as information on travelling, and risk behaviour, are of importance. Specific disease surveillance, helping to monitor the vaccination programme, is being carried out as a part of the National Infectious Disease Register.

Serological surveys as well as various other immunological studies performed in specific KTL laboratories e.g. for measles, mumps and rubella and pertussis provide valuable information on vaccination programme. Additional studies are important when vaccines or schedules are changed. It would be tempting, for example, to change the routine programme of tetanus and diphtheria, now running with iterated decennial boosters during the entire adulthood. The estimated proportions of protected at each adult age cohort has therefore been studied. With the introduction of pentavalent combination vaccine in 2005, serological studies have been started to monitor the effectiveness of its components. In addition, KTL has taken part in several international studies, such as ESEN network, which have provided data on our serological status on the population level, when several vaccine preventable diseases are concerned (e.g. measles, mumps, rubella, varicella, diphtheria).

Mathematical modelling is also used for analysing and predicting the effectiveness of the running immunization programme.

Major achievements

In addition to those for polio, BCG, pertussis, MMR and Hib listed in sections mentioned above

1) Immunization data are collected and added to National Infectious Disease Register for all measles, mumps, and rubella cases diagnosed in individuals born after 1976, Hib cases in those born after 1985, pertussis cases in children under 2 years of age, as well as all diphtheria, polio and TBE cases.

2) The survey on tetanus and diphtheria indicated that the vast majority of adults and elderly are well protected against both tetanus and diphtheria and it would therefore be reasonable to postpone the booster for 20 years especially for those with previous local post-vaccination reactions.

3) An evaluation of targeted risk group vaccinations against hepatitis B was published in 2006, with a verdict that it was advisable to continue with the targeted programme, only with minor adjustments to widen the risk groups. This decision is based on good vaccination coverage among risk groups (e.g. i.v. drug users), well functioning needle exchange programme and a dramatic decrease in acute hepatitis B -cases during the last decade.

4) The "administrative compliance" of vaccination programme, i.e. how well the programme is accepted and vaccines taken as provided is evaluated by regular vaccination coverage surveys. These consist of 1 000 children born in a certain year sampled from a population register. According the latest survey among the children born in 2001, surveying their vaccination doses for the first 3 years, 95% of children get all their vaccinations timely, and for each vaccine taken separately, the point estimates for coverage are around 97%.

Key publications

Leino T. Hepatiitti B –rokotusohjelman arviointi. (Evaluation of Hepatitis B –vaccination programme). Kansanterveyslaitoksen julkaisusarja (Publications of the National Public Health Institute) B, 9/2006.

Leino T, Koskenniemi E, Saranpää P-R, Stromberg N, Kilpi T. Rokotuskattavuus edelleen huippuluokkaa (Very high vaccination coverage – international false alarms had no effect in Finland) Suom Lääkäril (Finn Med J) 2007;62:739-43.

2.4.6. Register of and response strategies for adverse effects

Project leader: Tea Nieminen, MD, PhD

Description

KTL maintains a register of adverse reactions to vaccines on behalf of the National Agency for Medicines (NAM). NAM uses the accumulated data for regulatory control of vaccines. KTL, in turn, utilizes the register data in the evaluation of the effectiveness of NIP and the risks and benefits of vaccinations overall. According to national regulations the health care workers should report all serious adverse events, and are encouraged to report any adverse events of special interest. The on-line register enables constant evaluation of the incidence and severity of possible adverse effects linked to each vaccine and, thus, comparison of the benefits achieved by NIP with the reported disadvantages. Thus the benefits and harms of each vaccine are always thoroughly estimated and balanced. KTL also communicates vaccine safety issues to the public, media and health care personnel.

KTL is also monitors the quality of all the vaccines distributed in Finland; the vaccines included in NIP as well as those commercially available or used in any vaccine trial carried out in Finland. The unit reports the results of this work directly to NAM.

Major achievements

1) Rapid detection of adverse events following immunization with BCG after change of the product in August 2002**.** After the product manufactured by SSI (Statens Serum Institute, Denmark) was introduced, there was a rapid increase in adverse events following BCG vaccination from less than 20/y to 110-161 reports/y and an approximately tenfold increase in serious adverse events. The majority of them were cases of osteomyelitis: 6 cases in 2003 and 8 cases in 2004. In addition to the reporting system described above, KTL actively monitored all microbiologically confirmed BCG-cases in co-operation with the National Infectious Disease Register and traced the cases that had not yet been reported to the register.

2) Comprehensive communication of adverse events following immunization (AEFIs) on KTL webpages; including online listing of all reported AEFIs.

Key publications

Kilpi T. Rokotuksista on hyötyä - mutta mitkä ovat haitat (Vaccinations have their benefits--but what are the adverse effects). Duodecim 2002;118: 63-9.

Postila V, Kilpi T. Use of vaccine surveillance data in the evaluation of safety of vaccines. Vaccine 2004; 22: 2076-9.

Kilpi T, Ölander RM. Kan effektiva och säkra vacciner vara skadliga för barn? (Can effective and safe vaccines be harmful for children?). Finska Läkaresällskapets Handlingar 2006:166;67-74.

Nieminen T, Elonsalo U, Tikkanen H. Vuoden 2005 rokotusten epäillyt haittavaikutukset Suomessa. (Reported adverse events following immunization in Finland in 2007) Kansanterveys-lehti (Journal of the National Public Health Institute) 2007:5-6:22-4.

2.5. Other expert advice

2.5.1. Advice for non-NIP immunizations

In addition to the expert advice given to the Ministry of Social Affairs and Health on NIP, KTL also gives recommendations on the use of vaccines not included in NIP. These recommendations are formulated by the KTL Committee on Immunization Practices and published in the Vaccinator's Manual, which is updated regularly on the Internet both in Finnish and in Swedish. The recommendations are also communicated to the health care personnel through the daily telephone counselling service provided by KTL.

2.5.2. Traveller's health

Since 1993, KTL has published a Finnish language edition of the International Traveller´s Health Advisory in collaboration with national experts and Duodecim Medical Publications Ltd. By 2007, a total of 12 updated editions have come out. The manual, which is intended for health professionals, is also available from web as pdf version and html version allowing search. Presently a more elaborate web based version intended for travel industry and travellers is under construction. KTL provides travel health related advice to health professionals by phone on daily basis (dedicated phone line open for 2 hours/day). In 2006, a total 3600 calls were answered, the majority of which came from public health nurses working in municipal health clinics.

KTL experts have participated in numerous travel health related teaching activities nationally (both supervising medical, nursing and elective study students, planning courses, and lecturing) and are presently among the key organizers of the 2nd Northern European Conference on Travel Medicine, to take place in Helsinki in May 2008.

Key publication

Siikamäki H, Vapalahti O, Nohynek H. Denguekuume - kasvava maailmanlaajuinen ongelma ja suomalaisten kaukomatkailijoiden tauti (Dengue fever - a growing global problem and a disease of Finns traveling far). Duodecim 2003;119:2051-61.

2.6. International collaboration in surveillance and vaccinology

2.6.1. EU and WHO collaboration

KTL has been nominated by MSAH as the national expert organisation that participates in the EU infectious disease surveillance, outbreak investigation and control, and related activities. KTL is the national technical contact point to WHO in surveillance, outbreak investigation and vaccine policies.

European Union

Since the late 1990s, KTL has participated in approximately 15 Disease Specific Surveillance Networks (DSN) of EU, coordinated by a hub in one national centre. The activity by KTL includes provision of data to each DSN from the National Infectious Disease Registry at various intervals, participation of the epidemiology and microbiology national delegates in the annual network meetings, membership in the Advisory Groups of many of the DSNs, as well as in the working groups to develop these activities. KTL has had a key role in developing the conceptual basis, the methodology and protocols by which all the DSNs are being evaluated externally currently.

Since late 1990s, KTL is represented in the EuroSurveillance editorial board. KTL representatives have actively contributed to the development of the journal by providing and reviewing articles for the weekly, monthly and quarterly issues of EuroSurveillance.

KTL experts have supported MSAH through participating as experts in numerous expert meetings of various EU structures for developing the statutory basis and its practical implementation regarding surveillance, early warning and response system, as well as preparedness to biothreats.

Since the establishment of the European Centre for Disease Control (ECDC) in 2005, KTL representatives have intensely participated in its Advisory Forum and multiple working groups to support its strategic planning and the implementation of changes in the existing EU communicable disease structures, including the participation in the practical implementation of external evaluation of the DSNs.

KTL is the national training site for the European Programme of Intervention Epidemiology Training (EPIET), and has trained several EPIET fellows during the period under evaluation. KTL has also considerably contributed instructors for EPIET training modules elsewhere.

Several KTL experts serve as reviewers for EU research funding applications (both for DG SanCo and DG Research).

World Health Organisation (WHO)

KTL is the national agency providing data and information to WHO on infectious disease statistics and vaccine policies. KTL staff has represented Finland in a range of expert meetings organised by WHO for building preparedness to major biothreats, particularly an influenza pandemic, and the revised International Health Regulations (IHR 2005). KTL was recently nominated by law as the national contact organisation for the implementation of IHR, and introduced consequently a continuous national on-call service required by IHR.

On nomination by MSAH, KTL experts have extensively participated in the technical and policy-forming meetings of UNAIDS on HIV and AIDS.

KTL vaccinology experts have actively participated in several WHO led initiatives in the field of pneumococcal conjugate vaccine development (immunological criteria for licensure; standardization of nasopharyngeal sampling to detect pneumococcal carriage; standardization of

chest roentgenograms to detect childhood pneumonia; pneumococcal disease burden measurement; global serotype distribution; target product profile for new pneumococcal vaccines) as well vaccine safety (Global Committee on Vaccine Safety).

Key publications

World Health Organization. Pneumococcal conjugate vaccines. Recommendation for the production and control of pneumococcal conjugate vaccines. WHO Technical Report Series No 927. 2005.

World Health Organization Pneumonia Vaccine Trial Investigators´ Group. Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children. WHO/V&B/01.35, Geneva 2001.

O'Brien KL, Nohynek H, the WHO Pneumococcal Vaccine Trials Carriage Working Group. Report from a WHO Working Group: Standard method for detecting upper respiratory carriage of *Streptococcus pneumoniae*. Pediatr Infect Dis J 2003;22:133-40.

Cherian T, Mulholland KE, Carlin J, Ostensen H, Amin R, de Campo M, Greenberg D, Lagos R, Lucero M, Madhi S, O´Brien K, Obaro S, Steinhoff M, and the WHO Radiology Working Group. Standardised interpretation of paediatric chest radiographs for the diagnosis of pneumonia. WHO Bulletin 2005;83:353-9.

2.6.2. Baltic-Nordic collaboration

Project leader: Markku Kuusi, MD, PhD

From 1998 to 2001 KTL participated in the project "Infectious Disease Control in the Barents and Baltic Sea Regions" financed by the Nordic Council of Ministers. The objectives of this project were to strengthen infectious disease control in the areas adjacent to the Nordic countries through transfer of knowledge, building a network and developing an action plan. Three 2-week courses in infectious disease epidemiology and eight two-day courses were organized in the Baltic States and Northwestern Russia. Epidemiologists from KTL participated in these courses as lecturers and facilitators.

From 2004 KTL has participated in EpiNorth project financed by the European Commission and the Nordic Council of Ministers. This project has six components: EpiNorth journal, EpiData, EpiVax, EpiTrain, EpiNews, and EpiLinks. The main activities have been publishing the journal in English and Russian, and organizing courses for epidemiologists from Nordic, Baltic and Russian public health institutes. More information can be found at www.epinorth.org. Epidemiologists from KTL have provided surveillance data for the project, given lectures on the courses, and reviewed articles for the journal.

Although the absolute numbers of MRSA cases still are relatively low in the Nordic countries a significant increase has been observed in the 5 years in all the Nordic countries. Realising the threat to the health care systems in the region The Scandinavian Society of Antimicrobial Chemotherapy (SSAC) in 2003 formed a "SSAC Working Party on MRSA" with representatives from all Nordic countries (Denmark, Finland, Iceland, Norway and Sweden). A report on the epidemiology, similarities and dissimilarities among the individual countries as well as suggestions for future initiatives were published by the group in 2004. In addition, a joint pilot project to characterize and compare MRSA strains frequently found in Denmark, Finland and Sweden during years 2003-2004 was initiated in 2004. Majority of the MRSA strains analysed were found in at least one other

Nordic country, confirming the need for a close and intensive collaboration between the Nordic countries. KTL has been actively involved in both initiatives.

Key publications

Robert Skov, Hans Jørn Kolmos, Reijo Peltonen, Jaana Vuopio-Varkila, Hjordis Hardardottir, Olafur Gudlaugsson, Stig Harthug, Yngvar Tveten, Barbro Olsson-Liljequist, Christina Åhrén. The First Report of the SSAC Nordic Working Party on MRSA, Year 2004. Scandinavian Society for Antimicrobial Chemotherapy (SSAC); June 2005 (http://www.srga.org/SSAC/doc/2005/SSAC_MRSAreport_2004.pdf)

Haeggman S, Rhod Larsen A, Vainio A, Olsson-Liljequist B, Skov R, Vuopio-Varkila J. Comparison of epidemic MRSA isolated in the three Nordic countries Denmark, Finland and Sweden during 2003-2004 -How similar are they? Clin Microb Infect 2006;Suppl 4:P459.

2.6.3. Collaboration with Russia

Prevention of blood-borne infections among injecting drug users

Project leaders: Mika Salminen, PhD and Irja Davidkin, PhD

The incidence of HIV and other blood-borne infections associated with injecting drug use (IDU) and sex work have since the late 1990s increased in the Russian Federation areas close to the Finnish border. A similar evolution has taken place in the EU-member countries Estonia, Latvia and to possibly a lesser extent in Lithuania.

KTL has collaborated with the St. Petersburg Pasteur Institute (responsible for HIV/AIDS surveillance in the Russian Federation North-Western region) since the early 1990s and with the Tallin Merimetsa central hospital, the University of Tartu and the Estonian National Institute for Health Development since the late 1990s. Through the collaboration, the molecular epidemiology of the HIV-epidemics in the area have been rapidly characterised and the inter-relations of the different outbreaks worked out.

The demand for well trained clinical and laboratory personnel familiar with effective HIV-treatment has also grown rapidly. Using neighbouring area collaboration grant funding, KTL in cooperation with the Helsinki university hospital has executed training seminars for infectious disease specialists and laboratory personnel. The training seminars were held in 2004 in Tallinn, Estonia and 2005 in Zelenogorsk, the Russian Federation.

The collaboration with Estonia has been extended to cover technology transfer to the Merimetsa central hospital in Tallinn and Tartu University, where through researcher training in Helsinki assays for antiretroviral drug resistance have been set up for treatment optimisation.

Hepatitis A surveillance in North-West Russia

The main objective of the viral hepatitis project was to study the epidemiology and surveillance of hepatitis A diseases in the region, and in particular to investigate the molecular epidemiology of hepatitis A. The ultimate goal was to prevent hepatitis A through improved surveillance. The participating institutes in this collaboration were the Saint-Petersburg Pasteur Institute, the Surveillance Centres in St.Petersburg, in Leningrad Oblast and in the Republic of Karelia.

Major achievements

1) Networking and transfer of best practices for HIV & hepatitis prevention among IDU in the neighbouring Russian Federation and Baltic states. Building on the experiences of the Finnish low threshold health promotion and service centre (LTHSC) model, cooperation with a goal of enhancing the local responses in the area have been coordinated by the KTL in partnership with other actors such as STAKES. KTL executed a series of training and networking seminars in 1999-2005, targeted to workers and administration of LTHSC:s in the region, contributing to development of local models of risk reduction, especially in Latvia and Estonia.

2) In Murmansk, which has one of the most serious IDU-associated HIV-epidemics of the region (excluding St. Petersburg), the Finnish government has been directly sponsored the setting ups of an LTHSC in the same locales as the AIDS-centre. Coordination of the Baltic networks have since 2006 been transferred to the Latvian AIDS-centre.

3) Cooperation in epidemiological and molecular studies have established the links and non-links of the different HIV-epidemics in the region, showing that the Russian, Estonian and Estonian IDU-epidemics are related in time and mode of transmission, but not through direct contacts between the drug users. Technology transfer of molecular epidemiological tools and HIV drug resistance assay technology has been carried out.

4) Facilitation of the use of oral fluid testing technology for lowering the threshold of participation for hard-to-reach populations. In 2006, KTL participated in a behavioural and HIV & hepatitis C prevalence study among hard-to-reach sex workers in Tallinn which was run by the Estonian National Institute for Health Development.

5) Novel laboratory methods for the epidemiological surveillance and prevention of hepatitis A were set up. Technology transfer for molecular epidemiological studies of HAV to the St. Petersburg Pasteur Institute was introduced.

Key publications

Davidkin I, Zheleznova N, Jokinen S, Gorchakova O. Broman M, Mukomolov S. Molecular epidemiology of hepatitis A in St. Petersburg, Russia, 1997-2003. J Med Virol, 2007,79:657-62.

Smolskaya T, Liitsola K, Zetterberg V, Golovanova E, Kevlova N, Konovalova N, Sevastianova K, Brummer-Korvenkontio H, and Salminen MO. HIV Epidemiology in the Northwestern Federal District of Russia: Dominance of HIV Type 1 Subtype A. AIDS Res Hum Retroviruses 2006;22:1074-80.

Zetterberg V, Ustina V, Liitsola K, Zilmer K, Kalikova N, Sevastianova K, Brummer-Korvenkontio H, Leinikki P, and Salminen MO, Two viral strains and a possible novel recombinant are responsible for the explosive injecting drug use-associated HIV type 1 epidemic in Estonia. AIDS Res Hum Retroviruses 2004;20:1148-56.

Drug resistance surveillance of tuberculosis in Murmansk

Project Leaders: Hanna Soini, PhD and Merja Marjamäki, MSc

Description

Tuberculosis (TB) and multi-drug resistant-TB (MDR-TB) remain a serious problem in the Russian Federation and Russia has been classified as a high burden country by WHO. KTL has an ongoing

project, the Murmansk-Finland Tuberculosis Project with the Finnish Lung Health Organization (a WHO collaborating centre). The project was started in 1998. The purpose of this project is to give assistance to the TB control programme of Murmansk Region to successfully address the problems of treatment adherence and late care seeking as well as problems caused by MDR and HIV epidemics in TB control.

Major Achievements

1) Construction of BSL-3 laboratories for the civilians as well as for the penitentiary care. Introduction and validation of new laboratory methods according to the WHO recommendations for the civilians and the penitentiary care, under KTL supervision. Transfer of quality assurance programme for laboratory services. Effective networking of laboratories performing microscopy examinations on TB in Murmansk Region.

2) Improved cooperation between Central TB-laboratory and penitentiary care as a result of regular supervisory visits. Continuous training of laboratory staff in seminars in Russia and Finland, and yearly study visits to Finland.

3) Characterization of the tuberculosis drug resistance situation in the Murmansk Region by a population based surveillance. Genotyping of the isolates has been started in order to obtain epidemiological information.

Invasive childhood infections in St. Petersburg

Project leader: Hanna Nohynek, MD, PhD

From 2000 to 2004, KTL collaborated with STAKES, Finland, and the Children´s Infectious Diseases Hospital in St. Petersburg to establish the etiology of invasive childhood infections. This was in preparation of possible introduction of Hib, pneumococcal and/or meningococcal vaccines into the national vaccination programme. The study protocol was written according GCP guidelines, and Standard Operation Procedures developed to cover the clinical, microbiology and data management processes. Several on-site visits by the KTL consultants were made during which study specific and general vaccinology related lectures were given.

Major achievements

1. Finalizing and carrying out the study plan without major delays.

2. Establishing well functioning microbiological systems and quality assurance for identification and serotyping of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis*

Key publications

Kaijalainen T, Kharit SM, Kvetnaya AS, Sirkiä K, Herva E, Parkov OV, Nohynek H. Invasive infections caused by *Haemophilus influenzae, Streptococcus pneumoniae* and *Neisseria meningitidis* among children in St. Petersburg, Russia. Eur Clin Microb Infect Dis (in press).

2.7. Preparedness for major biothreats

2.7.1. Development of KTL functions and role in preparedness

Since late 1990s KTL has developed its capacity to act in national coordinating and advising capacity to meet major biothreats. The national preparedness is based on surveillance and control functions that are repeatedly implemented in normal times. Facing a major biothreat, KTL dynamically mobilizes staff prioritising its tasks according to the intensity of the threat. The normally functioning processes include well developed national laboratory based infectious disease surveillance, which is implemented electronically and involves continuous interaction with the health care services, particularly the hospital districts. The early notification of food- or water-borne outbreaks, numbering 50 – 100 per year, triggers regularly investigation, control and coordination interaction between KTL, the National Food Safety Authority (includes the veterinary authorities and laboratories on the national level), hospital district infection control teams, State Provincial Office veterinary and environmental authorities, as well as health and environmental/veterinary authorities in the municipal level. KTL also collaborates regularly with the hospital district infection control teams on standards and technical guidelines of protective and isolation measures in hospitals, which are particularly important when a large scale biothreat is faced.

As an outcome of the collaboration with the parties mentioned above, KTL has created and published on its website a large number of recommendations for measures to be taken, when either rare cases of imported dangerous diseases (eg diphtheria, haemorrhagic fevers) or an outbreak caused by a wide range of microbes are suspected or verified. KTL has also developed the technical procedures and collaborative processes that are needed with various authorities, when serious imported disease is suspected on an incoming long-haul flight.

KTL has had a major role nationally in the international threats caused by the dissemination of Anthrax spores in USA (2001) and the global SARS epidemic (2003), which served as good preparedness exercises.

During the Anthrax threat KTL was able to mobilize surge capacity that intensely monitored the threat, made daily situation assessments, advised the ministry and the health care services as well as several other sectors on measures to be taken. This included technical advice to the public transport, post office, and police organisations regarding risk assessment and handling these letters in the mail and after receipt, as well as instructions for the health for handling persons possibly exposed to the suspected material. An advisory hotline to the public was also organized.

Triggered by the WHO global alert on SARS in March, 2003, KTL rapidly reorganised its relevant infectious disease units to solely work on the SARS situation, rapidly set up recommendations on surveillance and control for the health care services, and intensely supported the clinical services by phone consultation in risk assessment of suspect cases and measures needed. Press conferences were organized by KTL, for a period almost daily, advisory telephone hotline service was organized for the public, and the web pages were actively used for information distribution. At the peak level of the outbreak 40,000 daily visits were registered at the KTL SARS web pages. Advise was given to a wide range of organisations including travel industry, educational facilities etc.

KTL has a wide spectrum of reference laboratory functions covering almost the whole range of microbes of concern as potential biothreats. It also has a BSL3 laboratory for handling dangerous pathogens, with provisions in place to use the BSL4 laboratory in Stockholm, should the need arise. In 2005, KTL established with the Finnish Defence Forces a Biological Threats Unit, with shared

staff in KTL, and an objective of developing and testing for use laboratory methods for field diagnosis of agents that may be used deliberately. In various outbreak investigation situations KTL regularly collaborates with and advises collaborating parties, including national food safety, animal and environmental microbiology laboratories, clinical and environmental laboratories and investigators in the regional and municipal level.

In the Anthrax threat situation in 2001, KTL advised in the appropriate use of diagnostic and environmental PCR testing, and established collaboration with the national veterinary laboratory (now in Food Safety Authority), which implemented the culture-based diagnostics needed. In the SARS threat, KTL quickly established a collaborative process whereby university associated diagnostic laboratories in Helsinki and Turku served as the primary diagnostic sites and the test methods were established at KTL for a backup. Close to 30 suspected cases were observed and investigated in both laboratories, none were confirmed as SARS.

2.7.2. KTL role in national preparedness for an influenza pandemic

As regards national preparedness for pandemic influenza, KTL followed the recommendations of WHO in the mid-1990es and established a permanent working group for pandemic preparedness. The group created and later annually reviewed and, when pertinent, updated a modest “KTL Preparedness Plan for Influenza Pandemic”. The Ministry of Social Affairs and Health approved the preparedness plan but until recently, the plan was not extended beyond activities considered direct responsibilities of KTL (global monitoring, surveillance and diagnostics in Finland, plans for vaccine and antivirals purchases). On the recommendation of this group, KTL introduced a condition into the tenders of influenza vaccine purchases: if a pandemic would emerge during the 2-year contract period the manufacturer in question would provide Finland with a potential pandemic vaccine in quantities proportional to the purchased seasonal vaccine.

The potential of emerging influenza pandemic rose to a higher level in 2003 with the emergence of the H5N1 avian flu epidemic in South-East Asia and its later spread to Middle-Asia, Europe and more recently further to Africa. The associated relatively rare but often lethal human cases globally facilitated preparing of national plan to minimize the hazards of a potential pandemic. An ad hoc national multisectorial working group for pandemic preparedness was established in Finland in 2005 including members, several permanent advisers and both expert secretaries from KTL. Approximately 70 per cent of the 200 page text of the National Plan, published in early 2006, was drafted by KTL experts. KTL experts also participated in the revision of the draft text according to comments sent by a broad spectrum of relevant parties. The final text (also in English) is available on the web pages of the Ministry of Social Affairs and Health
http://www.stm.fi/Resource.phx/publishing/documents/11181/index.htx

The plan concentrates in planning and implementation in the health care sector but also includes summaries of required/planned preparations in other sectors of the society. Meanwhile, much on the initiatives of KTL experts, Finland has also proceeded in material preparedness by purchasing a stockpile of oseltamivir, equal to one treatment course for one fourth of the population, and made agreements on both prepandemic and pandemic vaccine procurement in quantities sufficient to one dose of each vaccine to all inhabitants of Finland. Recognising the difficulties in the production of an efficient H5N1 vaccine, the Preparedness Plan also includes a chapter on ethical considerations for a situation in which the quantities of the vaccines (and/or antivirals) are not sufficient to everybody in need. Maintaining a fully functional health care system was considered the most important factor for minimizing nationally the damages caused by a pandemic. Hence, health care

personnel in a danger of contracting the pandemic virus was designated as the prioritised target group for vaccine and antivirals administration.

The National Plan gives the basic epidemic scenario to be used in planning as well as the processes in health care that need to be organised in a way different from a normal situation. The national plan must be translated into sectoral, regional, municipal and institutional plans. The implementation has continued and KTL experts have had a significant role e.g. in giving lectures in provincial training courses, by consultation and by participating in various ad hoc working groups. The permanent KTL Working group for Pandemic Preparedness, supplemented with representatives from the Ministry, The Finnish Defence Forces and The National Occupational Health Institute as well as communications experts, has been an advisory group for the Ministry in coordinating these activities, and will also in future take care of regular reviewing and updating of the National Plan. KTL experts have also led specific ad hoc working groups to further prepare solutions for issues that were not fully met in the national plan.

Laboratory diagnosis of suspected human cases of avian influenza is concentrated in major virus laboratories carrying out daily case-based diagnostic services. KTL virus laboratories serve as a backup and are prepared for necessary epidemiological surveys. Cell culture of clinical specimens is restricted to BSL3 laboratories one in the Helsinki based clinical laboratory (HUSLAB) and two backup units at KTL. Travellers have been advised on KTL web service on how to avoid risks during travel, and travellers returning from H5N1-infected areas with respiratory symptoms have a few times started a designated diagnostic algorithm, defined in the guidelines on KTL web service. The A5N1-test results have been negative in all cases so far, but detailed analysis of potential exposure to the virus has also suggested very low probability of infection in the studied cases.

KTL is preparing to improve the capacity to detect emerging outbreaks in two complementing approaches under development one based on on-line analysis of electronic symptoms records in the primary health care units and the other a more classical sentinel system including patient sampling and viral analysis.

2.7.3. Crisis situation communication

KTL has intensely developed its capacity to implement outbreak and crisis situation communication. Dedicated personnel in KTL infectious disease departments and partly outsourced technical transmission of epidemic alerts ensure rapid and standardised dissemination of alerts to a wide range of national and regional level organisations, which is regularly implemented in various outbreak and other situations requiring rapid communication to the health care services and the public.

Collaboration between the infectious disease-related departments and the newly established communications unit in KTL ensures appropriate content of the messages and effective interaction with media. The technological capacity of KTL IT systems has been strengthened to meet high intensity needs in web service. KTL has the capability of setting up telephone hotline service with high capacity. However, in most anticipated situations the Ministry would be responsible for the technical organisation, and KTL staff would train and supervise the activity, as was the case in the recent H5N1 situation.

3. RESEARCH

3.1. Microbes, microbiota and human health

3.1.1. Oral bacterial microbiota

Project leader: Eija Könönen, DDM, PhD

Description

During the first days of life, the colonization of the mucosal surfaces of the oral cavity and upper respiratory tract by various bacteria starts and, gradually, part of them form the indigenous microbiota. Distinct habitats harbor different microbial compositions, which are influenced by both innate and environmental factors. For example, in the mouth the age-related pattern of bacterial colonization is partly connected with the eruption of teeth. Although oral commensals are regarded beneficial to their host, some species or clones contain characteristics potentially detrimental for the health status of an individual and in specific circumstances can cause infections inside or outside the oral cavity.

Major achievements

1) As a continuation for our previous studies on the development of the oral microbiota in childhood, we demonstrated the subsequent colonization pattern in detail within some bacterial groups representing common genera of the oral cavity (*Streptococcus*, *Actinomyces*, *Prevotella*, and *Fusobacterium)*. In this context, we have evaluated commercial diagnostic methods and developed alternatives to improve the identification of difficult-to-identify organisms.

2) When investigating the population structure and kinetics among early-colonizing commensal populations, a key organism in oral biofilms, *Fusobacterium nucleatum*, was used as a representative. The strain collection originated from a subcohort of FinOM (Finnish Otitis Media cohort study) infants, followed from 2 months to 2 years of age. Arbitrarily primed PCR typing demonstrated wide genetic diversity within these populations, where up to 7 simultaneous AP-PCR types in one infant could be present at a time, but also a frequent turnover of strains especially during the first year of life. This kind of clonal heterogeneity and frequent turnover rates offer antigenic variation which could explain the persistent colonization of commensal species in the oral ecosystem. Furthermore, we demonstrated that during episodes of acute otitis media anaerobic organisms present in saliva can be aspirated to infants' nasopharynges, where anaerobes hardly exist during health, and this is especially frequent in infants with recurrent infections.

Key publications:

Sarkonen N, Könönen E, Summanen P, Kanervo A, Takala A, Jousimies-Somer H. Oral colonization of infants with *Actinomyces* species by two years of age. J Dent Res 2000;79:864-7.

Sarkonen N, Könönen E, Summanen P, Könönen M, Jousimies-Somer H. Phenotypic identification of *Actinomyces* and related species from human sources. J Clin Microbiol 2001;39:3955-3961.

Könönen E, Jousimies-Somer H, Bryk A, Kilpi T, Kilian M. Establishment of streptococci in the upper respiratory tract: longitudinal changes in the mouth and nasopharynx up to two years of age. J Med Microbiol 2002;51:723-30.

Haraldsson G, Holbrook WP, Könönen E. Clonal similarity of salivary and nasopharyngeal *Fusobacterium nucleatum* in infants with acute otitis media experience. J Med Microbiol 2004;53:161-5.

Haraldsson G, Holbrook WP, Könönen E. Clonal persistence of oral *Fusobacterium nucleatum* in infancy. J Dent Res 2004;83:500-4.

3.1.2. Bacteria-host cell interactions

Project leaders: Ilkka Julkunen, MD, PhD and Minja Miettinen, PhD

Description

Humans are living in close contact with pathogenic and commensal microbes. The gut microbiota plays an essential role in the well being of humans. By using human primary model cell systems, macrophages and dendritic cells we have studied bacteria-host interactions using several different probiotic nonpathogenic bacteria and pathogenic *Streptococcus pyogenes* and *Salmonella enterica*. The rationale is to study how different bacteria activate human macrophages and DCs and characterize bacteria-induced cytokine gene expression profile. By this approach it may also be possible to determine the mechanism of action of probiotic bacteria in humans.

Work dealing with probiotic and pathogenic bacteria aims at identifying mechanisms regulating cellular responses to the bacteria and understanding how human leukocytes discriminate between pathogenic and commensal bacteria. We will also take part in clinical trials in order to seek for novel probiotic bacteria and we head for understanding their mechanism of action.

Major achievements

1) We have demonstrated that a widely used probiotic bacteria *Lactobacillus rhamnosus* GG (LGG) is capable of inducing a strong proinflammatory and Th1 type response in human macrophages. This may in part explain the beneficial effects of LGG in the prevention of allergies. However, LGG fails to induce proinflammatory responses in human DCs, while pathogenic bacteria are very potent inducers of cytokine response in these cells.

2) Stimulation of human macrophages and dendritic cells by pathogenic bacteria (such as *S. pyogenes* and *S. enterica*) leads to the activation of several different host cell signaling systems and multiple transcription factor systems. Some of these pathways are similarly activated by bacteria and viruses. Detailed understanding of the inflammatory response induced by pathogenic bacteria may provide novel strategies to limit too strong inflammatory response that may potentially lead to tissue pathology.

3) Stimulation of human leukocytes with several different probiotic bacterial species such as lactobacilli, bifidobacteria or lactic acid bacteria used in food industry have shown that the bacteria may induce pro- or anti-inflammatory cytokine production profiles. This information is essential for the planning of clinical trials with potentially new probiotic bacteria.

Key publications

Miettinen M, Lehtonen A, Julkunen I .and Matikainen S. Lactobacilli and Streptococci activate NF-kB and STATs in human macrophages. J Immunol 2000;164:3733-40.

Veckman V, Miettinen M, Pirhonen J, Sirén J, Matikainen S, Julkunen I. Streptococci and lactobacilli differentially induce maturation and production of cytokines and chemokines in human monocyte-derived dendritic cells. J Leukoc Biol 2004;75:764-71.

Pietilä TE, Veckman V, Kyllönen P, Lähteenmäki K, Korhonen TK, Julkunen I. Activation, cytokine production and intracellular survival of bacteria in *Salmonella-infected human monocyte-derived macrophages and dendritic cells.* J Leukoc Biol 2005;78:909-20.

Strengell M, Lehtonen A, Matikainen S, Julkunen I. IL-21 enhances SOCS gene expression and inhibits LPS-induced cytokine production in human monocyte-derived dendritic cells. J Leukoc Biol 2006;79:1279-85.

Pietilä T, Veckman V, Lehtonen A, Lin R, Hiscott, Julkunen I. Multiple NF-kB and IFN regulatory factor (IRF) family transcription factors regulate CCL19 gene expression in human monocyte-derived dendritic cells. J Immunol 2007;178:253-61.

3.1.3. Microbiota and health

Aerobic bacteria

Project leaders: Jari Jalava, PhD and Anja Siitonen, PhD

Description

Human normal microbiota is a diverse community of microbes. The most diverse and complex part of human microbiota is the bacteriota of human gastrointestinal (GI) tract which can contain as much as 800 different bacterial species and approximately 10^{10} to 10^{11}bacterial cells / g of GI content. Human microbiota has a crucial role for human health. Our normal microbiota protects us from the invasion of many pathogenic bacteria. It has an important role in digestion and utilization of nutrients, especially breaking down ingested polysaccharides that are otherwise indigestible. Normal microbiota also stimulates the development of host's immune system. However, GI tract microbiota has also been proposed to have influence in the etiology of several diseases like inflammatory bowel diseases, type I diabetes, allergy and GI tract cancers. Recent studies have shown that it also has a role in the development of obesity.

Our research aims at improving our understanding about the role of the microbiota for human health. At the moment we are focusing our research on two main topics: 1) the role of GI microbiota in the aetiology of type I diabetes, 2) characterization of bacterial populations of nasopharyngeal microbiota during acute and convalescent phases of otitis media.

Major achievements

1) Development of methods for studying normal microbiota bacteria. These include novel methods for identification of bacteria using pyrosequencing technique.

2) Studies on dissemination and persistence of antibiotic-resistant bacteria in the human microbiota after experimental or therapeutic use of antibiotics. These studies have shown that antibiotic treatments have long-term effects on the composition of microbiota.

Key publications

Haanperä M, Jalava J, Huovinen P, Meurman O and Rantakokko-Jalava K. Identification of Alpha-Hemolytic Streptococci by Pyrosequencing the 16S rRNA Gene and by Use of VITEK 2. J Clin Microbiol 2007;45:762-70.

Nyberg S, Österblad M, Hakanen A, Löfmark S, Edlund C, Huovinen P and Jalava J. Long-term antimicrobial resistance in *Escherichia coli* from human intestinal microbiota after administration of clindamycin. Scan J Infect Dis 2007;39:417-24.

Seppälä H, Haanperä M, Al-Juhaish M, Järvinen H, Jalava J and Huovinen P. Antimicrobial susceptibility patterns and macrolide resistance genes of viridans group streptococci from normal flora. J Antimicrob Chemother 2003;52:636-44.

Rautio M, Saxen H, Siitonen A, Nikku R, Jousimies-Somer H. Bacteriology of histopathology defined appendicitis in children. Pediatric Inf Dis J 2000;19:1078-83

Anaerobic bacteria

Project leader: Eija Könönen, DDM, PhD

Description

Anaerobic bacteria are integral components of the commensal microbiota associated with the mucocutaneous surfaces of the human digestive tract, being found in the mouth, small and large intestines, as well as being part of the microbiota of the urogenital tract and skin. Their presence is essential for the development of the mucosal immune system, maintenance of a normal physiological environment, and providing essential nutrients for the host. Although anaerobic commensals play significant roles in human and animal health, in specific conditions when the environment changes due to trauma, immunosuppression or antimicrobial therapy, they can cause damage in a susceptible host and result even in life-threatening infections. Knowledge about the composition of the predominant commensal microbiota at different body sites is warranted to anticipate and recognize potential organisms in clinical specimens adjacent to their natural anatomical site. Due to the increasing number of immunocompromized patients the number of cases caused by members of the commensal microbiota is increasing.

Identification of anaerobic bacteria to the species level is a considerable task for clinical microbiological laboratories, in particular, when molecular means of characterization, particularly the use of 16S ribosomal RNA gene sequence analysis, has revolutionized bacterial taxonomy. The use of 16S rRNA sequencing for identification is showing that a substantial proportion of isolates from clinical material do not belong to validly published species, and novel species and genera are being proposed each year, many of which represent novel lineages. However, even closely related species can differ in virulence and antimicrobial susceptibilities, which makes their proper characterization clinically relevant.

Major achievements

1) KTL has been actively involved in research on occurrence and identification of anaerobic bacteria in human clinical specimens. We have been active in building international collaborative networks. In this context, atypical bacterial isolates have been further characterized leading to the description of several new species, especially within gram-negative genera *Porphyromonas* and *Alistipes*, isolated from various human sources

2) Our expertise on anaerobic bacteria is in great demand among professionals in the field of clinical microbiology, and has been used in international top-ranked microbiology manuals, such as Wadsworth-KTl Anaerobic Bacteriology Manual, Manual of Clinical Microbiology, and Bergey's Systematic Bacteriology.

Key publications

Downes J, Munson MA, Spratt DA, Kononen E, Tarkka E, Jousimies-Somer H, Wade WG. Characterisation of *Eubacterium*-like strains isolated from oral infections. J Med Microbiol 2001;50:947-51.

Rautio M, Eerola E, Väisänen-Tunkelrott ML, Molitoris D, Lawson P, Collins MD, Jousimies-Somer H. Reclassification of *Bacteroides putredinis* (Weinberg et al., 1937) in a new genus *Alistipes* gen. nov., as *Alistipes putredinis* comb. nov., and description of *Alistipes finegoldii* sp. nov., from human sources. Syst Appl Microbiol 2003;26:182-8.

Finegold SM, Song Y, Liu C, Hecht DW, Summanen P, Könönen E, Allen SD. *Clostridium clostridioforme*: a mixture of three clinically important species. Eur J Clin Microbiol Infect Dis 2005;24:319-24.

Song Y, Könönen E, Rautio M, Liu C, Bryk A, Eerola E, Finegold SM. Alistipes onderdonkii sp. nov. and *Alistipes shahii* sp. nov., of human origin. Int J Syst Evol Microbiol 2006;56:1985-90.

Könönen E, Wade WG. Propionibacterium, *Lactobacillus*, *Actinomyces*, and other non-spore-forming anaerobic gram-positive rods. In: Manual of Clinical Microbiology, 9th edition, American Society for Microbiology, Washington DC, 2007.

3.1.4. Antimicrobial consumption and resistance

Project leaders: Pentti Huovinen, MD, PhD and Eija Könönen, DDM, PhD

Description

Selective pressure caused by antimicrobial consumption and the fitness of antimicrobial resistant bacteria are the key factors affecting the emergence, spread and persistence of antimicrobial resistant bacteria. For the last fifteen years we have studied the selective pressure caused by antimicrobial consumption. Main focus has been on streptococci and the use of macrolides, however also other antibiotic groups and other important bacteria are now covered.

KTL has studied association between regional macrolide resistance in *Streptococcus pyogenes* and macrolide use, regional rates of antimicrobial resistance in *Streptococcus pneumoniae* and regional antimicrobial use, and regional antimicrobial resistance rates in *Escherichia coli* and regional outpatient antimicrobial use in Finland.

Major achievements

1) A statistically significant association existed between regional erythromycin resistance in *S. pyogenes* and consumption of macrolides; association with azithromycin use alone was not found.

2) Total macrolide use and azithromycin use were associated with increased macrolide resistance, and beta-lactam use and cephalosporin use were connected to increased low-level penicillin resistance in *S. pneumoniae*.

3) Level of nitrofurantoin consumption was connected with the level of nitrofurantoin resistance. The following links were found between the change in use and change in resistance: amoxicillin vs. ampicillin, ampicillin vs. amoxicillin-clavulanic acid, and trimethoprim vs. trimethoprim. No other positive associations were found. In particular, there was no association between fluoroquinolone use and resistance.

4) Emergence of the resistance due to beta-lactamase production among oral anaerobic populations and salivary beta-lactamase activities increased during the first year of life with age and usage of antimicrobial agents. KTL also demonstrated that translocation of oral anaerobes, including beta-lactamase-producing strains, via saliva to the nasopharynx occurs during acute otitis media episodes, indicating the possibility of their involvement in respiratory tract biofilms during infection.

Key publications

Pihlajamäki M, Kotilainen P, Kaurila T, Klaukka T, Palva E, Huovinen P. Macrolide-resistant Streptococcus pneumoniae and use of antimicrobial agents. Clin Infect Dis 2001;33: 483-8.

Nyfors S, Könönen E, Syrjänen R, Komulainen E, Jousimies-Somer H. Emergence of penicillin resistance among *Fusobacterium nucleatum* populations of commensal oral flora during early childhood. J Antimicrob Chemother 2003;51:107-12.

Nyfors S, Syrjänen R, Könönen E. Impact of antimicrobial exposure and beta-lactamase-producing bacteria on salivary beta-lactamase activity in infancy. Int J Antimicrob Agents 2004;24:463-7.

Bergman M, Huikko S, Pihlajamäki M, Laippala P, Palva E, Huovinen P, Seppälä H. Effect of macrolide consumption on erythromycin resistance in Streptococcus pyogenes in Finland in 1997-2001. Clin Infect Dis 2004; 38:1251-6.

Bergman M, Huikko S, Huovinen P, Paakkari P, Seppälä H. Macrolide and azithromycin use are linked to increased macrolide resistance in Streptococcus pneumoniae. Antimicrob Agents Chemother 2006; 50:3646-50.

3.1.5. Mechanisms of antimicrobial resistance

Project leaders: Jari Jalava, PhD and Antti Hakanen, MD, PhD

Description

In Finland, antibiotic resistance among *Streptococcus pneumoniae* is increasing. This is especially true with penicillin and macrolide resistance. Antibiotic resistance determinants are transferred from normal microbiota alfahemolytic streptococci to pathogenic *S. pneumoniae* strains. We have been studying macrolide resistance among streptococci for several years. The main focus has been on macrolide resistance and macrolide resistance mechanisms.

Fluoroquinolone resistance is increasing worldwide. Especially members of *Enterobacteriaceae* and also food borne pathogens like *Campylobacter* sp are often resistant to these antimicrobials. We have studied quinolone resistance mechanisms and detection for several years.

Major achievements

1) New macrolide resistance mechanisms have been described. The latest finding is novel telithromycin resistance mechanism found in clinical *S. pneumoniae* isolates. The exact resistance mechanisms in not yet known, but data from *Streptococcus pyogenes* indicate that it may have something to do with methylation of ribosomal RNA or mutation in some other ribosomal component.

2) Erythromycin and telithromycin resistance in streptococci, mediated by erm-methylases have been studied at molecular level.

3) A new quinolone resistance phenomenon in *Salmonella enterica* isolates has been described and a collaboration study is ongoing to solve the mechanisms behind it. We assume that new transferable quinolone resistance genes, *qnr* genes, are potential contributors of this new resistance phenotype.

Key publications

Hakanen A, Jalava J, Kotilainen P, Jousimies-Somer H, Siitonen A, Huovinen P. gyrA polymorphism in *Campylobacter jejuni*: Detection of *gyrA* mutations in 162 *C. jejuni* isolates by single-strand conformation polymorphism and DNA sequencing. Antimicrob Agents Chemother 2002;46:2644-7.

Hakanen AJ, Lindgren M, Huovinen P, Jalava J, Siitonen A, Kotilainen P. New quinolone resistance phenomenon in *Salmonella enterica*: nalidixic acid-susceptible isolates with reduced fluoroquinolone susceptibility. J Clin Microbiol 2005;43:5775-8.

Rantala M, Huikko S, Huovinen P. and Jalava J. Prevalence and molecular genetics of macrolide resistance among Streptococcus pneumoniae isolates collected in Finland in 2002. Antimicrob Agents Chemother 2005;49:4180-4.

Douthwaite S, Jalava J and Jakobsen L. Ketolide resistance in *Streptococcus pyogenes* correlates with the degree of rRNA dimethylation by Erm. Mol Microbiol 2005;58:613-22.

Rantala M, Nyberg S, Lindgren M, Huovinen P, Jalava J, Skyttä R, Teirilä L, Vainio A, Virolainen-Julkunen A and Kaijalainen T. Molecular epidemiology of telithromycin resistant pneumococci in Finland. Antimicrob Agents Chemother 2007;51:1885-7.

3.2. Pathogenesis and epidemiology of infections

3.2.1. Bacterial respiratory tract pathogens

Project leader: Maija Leinonen, PhD

Description

Respiratory tract infections including pneumonia are major causes of morbidity and mortality especially in children and in the elderly. The most common causative agents of both upper and lower respiratory tract infections, *Streptococcus pneumoniae* and *Haemophilus influenzae*, are also a part of normal microbiota of the airways and this causes problems in the etiological diagnosis. At the present, no totally reliable method for the etiological diagnosis of e.g. pneumococcal pneumonia exists. The main focus, recently, has been the development of PCR methods both for the etiological diagnosis and identification of these bacteria. The developed methods have been applied to study pneumococcal etiology in otitis media, other upper respiratory infections and pneumonia in collaboration with several research groups abroad (e.g. Israel, Italy, UK, USA) and Finland (University hospitals of Oulu, Turku, Helsinki and Kuopio)

In the national reference laboratory for pneumococcus and *H. influenzae*, new molecular methods for pneumococcal identification and microarray chip for the capsular typing of pneumococcal isolates and for demonstration of type-specific pneumococcal carriage have been developed. We have also participated in Finnish pneumococcal vaccination studies being responsible for the microbiological laboratory analysis in these studies.

Recent studies showing that formation of biofilms, in which bacteria are in nonculturable form, pose new challenges for the development of diagnostic methods and for the pathogenetic studies. At present, the methods to study the biofilm formation of pneumococcal and *H. influenzae* isolates have been developed in our laboratory

Major achievements

1) We have developed real time PCR methods for the demonstration of pneumococcal virulence genes and and studied their usefulness in pneumococcal identification. Unencapsulated pneumococci commonly lack virulence genes, but they can also occasionally be present in -hemolytic streptococci.

2) In biofilm studies, pneumococcal and *H.influenzae* biofilms are grown in microtiter plates and the formation of biofilms is monitored by color reaction, confocal and electron microscopy, and by expression of biofilm-specific genes. In collaboration with M. Uhari´s group (Children´s Hospital, Oulu) we have shown that different pneumococcal isolates (e.g. invasive and otitis isolates) differ in their ability to form biofilms and xylitol can prevent biofilm formation.

3) A unique sample collection from 900 military recruits (300 asthmatics and 600 nonasthmatic) to study the carriage of respiratory tract bacteria in the beginning and at the end of the service and during infectious episodes requiring consultation by physician. *MBL2* and *GPRA* genotypes seem to increase the risk of respiratory infection and to affect carriage of potentially pathogenic bacteria.

Key publications

Lim WS, Macfarlane JT, Boswell TC, Harrison TG, Rose D, Leinonen M, Saikku P. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 2001;56:296-301.

Michelow IC, Lozano J, Olsen K, Goto C, Rollins NK, Ghaffar F, Rodriguez-Cerrato V, Leinonen M, McCracken GH, Jr. Diagnosis of Streptococcus pneumoniae lower respiratory infection in hospitalized children by culture, polymerase chain reaction, serological testing, and urinary antigen detection. Clin Infect Dis 2002;34:E1-11.

Palmu AAI, Saukkoriipi A, Lahdenkari MI, Kuisma LK, Mäkelä PH, Kilpi TM, Leinonen M. Does the presence of pneumococcal DNA in middle-ear fluid indicate pneumococcal etiology in acute otitis media? J Infect Dis 2004;189:775-84.

Kristo A, Uhari M, Kontiokari T, Glumoff V, Kaijalainen T, Leinonen M, Luotonen J, Koivunen P, Kujala T, Pokka T, Alho OP. Nasal middle meatal specimen bacteriology as a predictor of the course of acute respiratory infection in children. Pediatr Infect Dis J. 2006;25:108-12.

Hanage WP, Kaijalainen T, Saukkoriipi A, Rickcord JL, Spratt BG. A successful, diverse disease-associated lineage of nontypeable pneumococci that has lost the capsular biosynthesis locus. J Clin Microbiol. 2006;44:743-9.

3.2.2. Otitis media

Project leader: Terhi Kilpi, MD, PhD

Description

Acute otitis media (AOM) is closely associated with upper respiratory tract infections. More than 90% of children with AOM have symptoms of upper respiratory tract infection at the time of diagnosis and the occurrence of AOM episodes peaks 3-4 days after onset of symptoms of respiratory infection. The current concept is that the respiratory viral infection can contribute to development of AOM through several mechanisms, e.g. by causing dysfunction of the Eustachian tube, leukocyte dysfunction or changes in the nasopharyngeal bacterial microbiota. Nasopharyngeal carriage of potential otitis pathogens is another significant contributor to bacterial AOM. The prevalence of pneumococcal carriage is higher during respiratory infection and AOM than during health. Furthermore, during pneumococcal AOM, pneumococci are practically always found in the middle ear and in the nasopharynx and the serotypes are usually the same in both sites.

Development of a vaccine is a series of systematic scientific research starting from understanding of the pathogenesis of the disease and the defence mechanisms of the host, and ending up in demonstration of efficacy of the new vaccine in prevention of disease. The Finnish Otitis Media (FinOM) Cohort Study, was conducted immediately before the FinOM efficacy trial of two pneumococcal conjugate vaccines for the prevention of pneumococcal (Pnc) AOM. The purpose of the study was to give detailed background data on AOM among Finnish children, to describe the natural course of nasopharyngeal carriage of *Streptococcus pneumoniae* (Pnc) and its relationship to AOM, to investigate the interplay between viral infection, pneumococcal acquisition and carriage in the development of Pnc AOM, and to evaluate the natural development of antibodies to pneumococcal polysaccharide and protein antigens in relation to age, pneumococcal carriage and AOM, and whether or not such antibodies affect the risk of subsequent pneumococcal carriage and AOM.

In the FinOM Cohort Study, 329 healthy children were followed at scheduled age-based and sick-visits from 2 to 24 months of age at a study clinic established for the purpose. Whenever AOM was diagnosed during the follow-up, myringotomy with aspiration was performed for bacterial and viral etiologic diagnosis. Nasopharyngeal samples for detection of respiratory viruses, *Streptococcus pneumoniae* and *Haemophilus influenzae* were also obtained at both scheduled and sick visits.

Major achievements

1) Characterization of bacteriology of AOM in a cohort of Finnish children followed for the first two years of life.

2) Characterization of epidemiology of pneumococcal carriage in Finnish children during the first two years of life: gradual increase with age (from 9 to 43%) but generally lower than in many other countries, higher carriage during respiratory infection than during health, and almost invariably present during pneumococcal AOM.

3) We demonstrated that the majority of Pnc AOM events develop in association with newly acquired carriage of pneumococcus rather than after prolonged carriage.

4) We found that antibody concentrations to three pneumococcal proteins (PsaA, PspA and pneumolysin) increased with age and were strongly associated with pneumococcal exposure, whether by carriage or infection (acute otitis media). Protection provided by these antibodies remains unclear.

Key publications

Rapola S, Jäntti V, Haikala R, Syrjänen R, Carlone GM, Sampson JS, Briles DE, Paton JC, Takala AK, Kilpi TM, Käyhty H. Natural development of antibodies to pneumococcal surface protein A, pneumococcal surface adhesin A, and pneumolysin in relation to pneumococcal carriage and acute otitis media. J Infect Dis. 2000;182:1146-52.

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3.2.3. Specific virus infections associated with acute otitis media

Project leader: Tapani Hovi MD, PhD

Description

This project was established as a part of the Finnish otitis media (FinOM) studies. The FinOM Cohort Study enabled prospective follow up of acute respiratory infections as risk factors of acute otitis media (AOM) in young children, examination of presence of specific virus groups in the nasopharynx (NPA) and middle ear fluid (MEF) during acute otitis, and of accumulation of serological evidence for viral infections until the age of two years. In the FinOM Vaccine Trial (virological analysis covered only a proportion of study children, and systematically collected NPA and MEF specimens from about 1800 children are still untouched in the freezers. The range of viruses identified in acute respiratory infections has increased since the days of the FinOM studies and the methodology has significantly improved. We have a plan to reanalyze the etiology of viral infections in AOM using the current methodology and a sample of the frozen specimens. The project currently also includes collaboration with clinicians working at the Helsinki University Central Hospital.

Major achievements

1) Demonstration that the epidemiology of AOM in young children tightly follows the epidemiology of upper respiratory infections (URI). Study on the etiology of URI revealed that for most virus groups, about 40% of episodes lead to AOM. For the respiratory syncytial virus this figure was somewhat higher.

2) The studies demonstrated picornaviruses as the major causative agent in URI associated with AOM and an early onset and high frequency of rhinovirus infections in young children. This was one of the first studies reporting enteroviruses as an important agent in URI. Critical evaluation of sensitivity and specificity of the in-house RT-PCR method for rhinovirus detection revealed, among other things, that children may harbor picornavirus RNA in the nasopharynx in the absence of local symptoms.

3) Evaluation of potential association of a specific virus group with frequently recurring respiratory infections (Result: any viral infection available will be caught) and with specific bacterial species in MEF (no distinct preferences found). Picornaviruses are frequently detected in association with AOM because they are so intensely circulating in child populations.

Key publications

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Nokso-Koivisto J, Räty R, Blomqvist S, Kleemola M, Syrjänen R, Pitkäranta A, Kilpi T, Hovi T. Presence of specific viruses in middle ear fluids and respiratory secretions of young children with acute otitis media. J Med Virol 2004;72:241-8.

Kleemola M, Nokso-Koivisto J, Herva E, Syrjänen R, Lahdenkari M, Kilpi T, Hovi T. Is there any specific association between respiratory viruses and bacteria in acute otitis media of young children. J Infect 2006;52:181-7.

3.2.4. Community acquired pneumonia

Project leaders: Terhi Kilpi, MD, PhD and Arto Palmu, MD, PhD

Description

Pneumonia is a common and severe enough disease among those over 65 years of age to predict that an efficacious vaccine would become an important public health tool for general use. *Streptococcus pneumoniae* is the most important pathogen in community-acquired pneumonia (CAP) and better vaccines than the currently available 23-valent polysaccharide vaccine should be sought to prevent also non-bacteremic pneumonia in the elderly. However, pneumococcal pneumonia has proven a difficult endpoint both in vaccine trials and in epidemiological studies. These difficulties are reflected in the widely different estimates of the incidence of pneumococcal pneumonia published.

The KTL Department of Vaccines has started a large research project on this topic in collaboration with a major vaccine manufacturer (GlaxoSmithKline). The Finnish Community-Acquired Pneumonia Epidemiological (FinCAP Epi) study was initiated in May 2005 to prepare, test and document methods and a local basis for a phase III vaccine trial designed to evaluate the efficacy of a novel pneumococcal vaccine for prevention of pneumococcal pneumonia among the >65 population.

The specific study objectives of the FinCAP Epi study are divided into three research questions. Feasibility part explores the feasibility of the trial in terms of whether we are able to capture enough community-acquired pneumonia (CAP) cases and collect the samples and data needed. Case definition part evaluates whether additional diagnostics to culture of blood and high quality sputum

sample, like urinary antigen test or application of quantitative PCR methodology could increase the sensitivity of pneumococcal pneumonia diagnosis without losing too much of the specificity. Finally, epidemiology part explores the incidence of pneumococcal pneumonia in the source population as a basis for estimation of sample size for the vaccine trial.

The difficulties and uncertainties in determination of the etiology of community-acquired pneumonia (CAP) are especially relevant for a vaccine trial. Poor specificity in the identification of the true endpoint disease will result in vaccine efficacy estimates biased towards no effect. Furthermore, a poorly specific endpoint also implies a larger sample size to obtain statistically significant findings, although the biased estimate cannot be corrected by increasing the sample size. However, a highly specific but insensitive endpoint definition will also increase the sample size needed and decrease the final attractiveness of the vaccine because it results in low estimates of the disease burden. It may have the additional problem of focusing only on a (possibly not typical) fraction of the disease, so that in the end the vaccine effectiveness for the real target would remain obscure. For these reasons endpoint definition is crucial for a vaccine trial looking for prevention of pneumococcal pneumonia.

Major achievements

1) The feasibility of our methodology was proven by our successful start and conduct of a large epidemiological study on CAP. Nearly 500 elderly CAP cases (89% of that predicted in the protocol), 102 acute respiratory tract infection controls and 127 COPD controls have been recruited by the end of the two-year study (May 2005 to May 2007). The study samples including blood culture, venous blood sample (whole blood, serum and buffy coat sample), urine, nasopharyngeal and oropharyngeal swabs, sputum and clinical laboratory samples have been obtained from the majority of subjects as expected in the study protocol. Additionally, extensive data for demographics and baseline risk factors, chest X-ray evaluation, clinical findings, treatment and follow-up have been collected.

2) Extensive microbiological analyses (including semi-quantitative culture, real-time quantitative PCR, antigen tests, serology) have been performed on these samples using validated methods. No studies are available in which all these microbiological assays have been compared side-by-side. Development of the case definition is underway based on the study data using the large database of collected data. Novel approaches like Latent Class Analysis (LCA) methodology and Composite reference standard (CRS) are being explored and used in addition to using the diverse comparison group data.

3) First preliminary estimates for the incidence of pneumococcal pneumonia have been calculated and the first sample size estimations have been conducted to help in planning of the Phase III vaccine trial.

This study has started in May 2005 and it is currently ongoing. First results have been presented as posters in scientific meetings.

Finnish Community Acquired Pneumonia (FinCAP) vaccine trial

The ultimate objective of the project is conduct a large clinical phase III vaccine trial in the elderly. The aim is to document the efficacy of the vaccine against pneumococcal pneumonia as the primary outcome. This trial will be performed in cooperation with a vaccine manufacturer entering into phase III with a novel pneumococcal vaccine. Results being supportive world-wide licensure will be applied for based on the trial data. Initial preparations for an enormous Phase III trial have been started. Experience from and initial results of the FinCAP Epi study have been used to assess the

feasibility of conducting such a large trial and to calculate the sample size which probably is in the range of tens of thousands.

Immunological and safety profiles for new experimental vaccines will need to be assessed in Phase I and II studies before entering into large Phase III trials.
In addition to conducting the FinCAP Epi study also clinical vaccine studies are underway at the Department of Vaccines. Altogether 600 elderly subjects have been vaccinated with the 23-valent polysaccharide vaccine and followed for three years after vaccination and sampled for serum. The main objective of this study is to assess the immunogenicity of the polysaccharide vaccine in the elderly and define non-responders to the polysaccharide vaccine. The aim is to re-vaccinate the subjects vaccinated with the polysaccharide vaccine with a new experimental vaccine in the near future and assess whether the new experimental vaccines can overcome poor responsiveness.

Another vaccine study, phase I study, is underway to assess the immunogenicity, tolerability and safety of novel adjuvanted pneumococcal conjugate vaccines in elderly.

Major achievements

1) 600 elderly subjects have been enrolled in the polysaccharide vaccine study and nearly 90% of them have been followed for the full three years. A novel ranking method based on immunology data has been applied to define the non-responders. This method makes the non-responder definition independent of rigid thresholds for antibody levels.

2) 109 healthy elderly subjects have been enrolled and vaccinated in the Phase I study. This study is still ongoing.

3) Phase III Trial preparations have been started.

3.2.5. Enteric bacterial infections

Project leader: Anja Siitonen, PhD

Description

The tasks of laboratory-based surveillance of the zoonotic and enteric bacteria that cause gastrointestinal infections and food poisonings via contaminated food or water are defined by the national and EC legislation. The Enteric Bacteria Laboratory works in close collaboration with the Departments of the Infectious Diseases Epidemiology and Environmental Health, Ministry of Social Affairs and Health, Ministry of Agriculture and Forestry, the Finnish Food Safety Authority Evira, and the newly-established Finnish Zoonoses Centre. Internationally, close contacts are kept with the Enter-net, the international surveillance network for human gastrointestinal infections, and the PulseNet, the molecular international surveillance network for food-borne infections.

The reference functions cover investigations of *Salmonella*, *Escherichia coli* (including VTEC, EPEC, EIEC, ETEC), *Shigella* spp., *Yersinia* spp., *Campylobacter* spp., *Vibrio* spp., *Listeria monocytogenes*, and *Clostridium perfringens*. The isolates received from all Finnish clinical microbiology laboratories are verified and characterized in real time by different phenotypic methods (biotyping, serotyping, phage typing,), and the results are reported to the sending laboratories. Susceptibility of all *Salmonella*, *Shigella* and VTEC isolates to 12 antimicrobial agents has been monitored since the year 2000. KTL also provides Finnish Food Safety Authority Evira with the phage typing of *Salmonella* isolates of animal and other non-human origins. In addition, of the Nordic Countries, phage typing of the VTEC O157 strains is done in KTL only. Further

characterization of the strains is carried out by genotypic techniques, such as PCR-based methods, plasmid analysis, pulsed-field gel electrophoresis (PFGE), multi-locus variable number tandem repeat analysis (MLVA) and sequencing. The genotypic methods have been harmonized nationally with Finnish Food Safety Authority Evira, and the PFGE method also internationally in connection with the Salm-gene project of EU and with the PulseNet network. The DNA profiles of the strains are saved in electronic libraries established for the most important food-borne pathogens. The laboratory-based data, together with the analytic epidemiological data, set the basis for the trace-back investigations in food-borne outbreaks.

The high quality of the results is controlled by participating in external quality assurance schemes arranged by WHO Global Salm-Surv, HPA, RIVM, UK-NEQAS and PulseNet Europe and covering both phenotypic and genotypic methods. Although KTL laboratory has not been accredited yet, external quality assurance schemes have been performed with excellent results.

Major achievements

1) During 2000-2006, almost 22 000 enteric or food-borne bacterial isolates were characterized, and the reports sent to the clinical microbiology laboratories. The pheno- and genotyping of the strains allowed successful detection of several outbreaks. The conditions to prevent DNA degradation due to bacterial DNAse were discovered enabling PFGE genotyping of all strains. Annually, the database has been utilized for control of about 50 international or national food-borne outbreaks.

2) About 80% of the salmonella infections in Finland are associated with travelling abroad. About 50 different *Salmonella* serotypes cause annually 300-500 domestic *Salmonella* infections. Of these serotypes, *Salmonella* Typhimurium definite phage type DT1, which differs genetically from the foreign isolates, is the most important with reservoirs in domestic production animals. About 100 different *Salmonella* serotypes are found annually in 2000-2500 *Salmonella infections* of foreign origin. Of these serotypes,, *Salmonella* Enteritidis phage types PT4 and PT1 are the most common ones. Occasionally, they have caused also domestic infections but have no constant reservoir in Finnish animals.

3) About 80% of infections caused by verotoxin-producing *E.coli* (VTEC) strains are of domestic origin, and a high proportion (49%) of all VTEC infections is family-related. A validated multiplex PCR method, detecting 5 virulence-associated genes (*stx*$_1$, *stx*$_2$, *eae*, *hly*, *saa*), has facilitated the diagnostics. Sorbitol non-fermenting O157 and sorbitol fermenting non-O157 are equally common causes of VTEC infections, 53% and 47%, respectively. Our surveillance has also revealed an increasing number of infections caused by rare sorbitol fermenting O157 phage type PT 88 strains that have similarity with German strains. Infections in 20 patients caused by strains of serogroups O103, O145, O157 or O174 have been traced to domestic cattle.

4) Standard operation procedure, including multiplex PCR for virulence genes of *Shigella*/EIEC was recently developed at Enteric Bacteria Laboratory to improve the traditional diagnostics by biochemical and serological methods.

5) All *L. monocytogenes* strains isolated from health-threatening infections in Finns belong to two serotypes only, to either 1/2 or 4. In order to detect potential infection clusters, a PFGE genotyping method has been set up and a DNA fingerprint database created. *V. cholerae* non-O1, non-O139 strains that are present in territorial waters of the Baltic Sea, have been found to cause serious life-threatening infections in Finns with compromising health factors.

6) During 2000-2006, the national electronic database libraries for *Salmonella*, VTEC, *L. monocytogenes, Yersinia* spp., *V. cholerae*, *Campylobacter* and *Shigella* spp. containing over 7000 PFGE profiles were created. All typing methods have been harmonized and the molecular typing

data is comparable also at the national level between EBL and the Finnish Food Safety Authority Evira. The data have been valuable when human food-borne infections have been traced to certain non-human origins.

Key publications

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Koort JMK, Lukinmaa S, Rantala M, Unkila E, Siitonen A. Techical improvement to prevent DNA degradation of enteric pathogens in pulsed-field gel electrophoresis. J Clin Microbiol 2002; 40:3497-8.

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Lukinmaa S, Miettinen M, Nakari U-M, Korkeala H, Siitonen A. Listeria monocytogenes isolates from invasive infections: Variation of sero- and genotypes during an 11-year period in Finland. J Clin Microbiol 2003;41:1694-700.

Eklund M, Bielaszewska M, Nakari U-M, Karch H, Siitonen A. Molecular and phenotype profiling of sorbitol-fermenting *Escherichia coli* O157:H^- isolates from Finland. Clin Microbiol Infect 2006;12:634-41.

3.3. Efficacy, safety and effectiveness of vaccines

3.3.1. Finnish Otitis Media (FinOM) vaccine trial

Project leader: Terhi Kilpi, MD, PhD

Description

Streptococcus pneumoniae is the most commonly reported bacterial cause of acute otitis media, accounting for 28 to 55 percent of cases. Of the 90 pneumococcal serotypes that have been identified so far, the most common ones that cause acute otitis media are 3, 6B, 9V, 14, 19F, and 23F. In the first attempts to prevent pneumococcal otitis in young children, a polysaccharide vaccine was used, but its immunogenicity and efficacy were low. Multivalent conjugate vaccines have proved immunogenic in infants,inducing immunologic memory and the formation of antibodies detectable in mucosal secretions and reducing nasopharyngeal carriage of pneumococci.

In the FinOM Vaccine Trial, we studied the protective efficacy of two heptavalent pneumococcal conjugate vaccines (PncCRM and PncOMPC) against culture-confirmed, serotypespecific pneumococcal acute otitis media in children. Altogether 2 497 infants were randomly assigned to receive either one of the two pneumococcal conjugate vaccines or control vaccine (hepatitis B vaccine) at 2, 4, 6, and 12 months of age and followed at a study clinic from 2 to 24 months of age. When AOM was diagnosed, middle ear fluid was aspirated for bacterial culture. To assess the immunogenicity of the vaccines and determine serological correlates of protection, serum samples were obtained at 7 and 13 months of age (see 3.5.2).

The follow-up was later continued by inviting all study children who were still living in the study area to a single follow-up visit in spring 2001 when they were 4 to 5 years old. At this time, we also

collected information on any tube placement performed after the child had completed the follow-up in the FinOM Vaccine Trial.

Major achievements

1) Completion of the clinical phase of the trial with excellent compliance despite the challenging trial design including myringotomies.

2) Reliable efficacy estimates for both vaccines were determined and they turned out to be surprisingly similar.

3) Demonstration of long-term efficacy of PncCRM against tympanostomy tube placements.

Key publications

Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, Takala A, Kayhty H, Karma P, Kohberger R, Siber G, Makela PH. Efficacy of pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001;344:403-9.

Kilpi T, Åhman H, Jokinen J, Lankinen KS, Palmu A, Savolainen H, Grönholm G, Leinonen M, Hovi T, Eskola J, Käyhty H, Bohidar N, Sadoff JC, and Mäkelä PH for the Finnish Otitis Media (FinOM) Study Group. Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children. Randomised controlled trial of a sevenvalent pneumococcal polysaccharide-meningococcal outer membrane conjugate vaccine in 1666 children. Clin Infect Dis 2003; 37:1155-64.

Palmu A, J Verho, J Jokinen, P Karma, T Kilpi. The seven-valent pneumococcal conjugate vaccine reduces tympanostomy tube placement in children. Pediatr Inf Dis J 2004;23:732-8.

3.3.2. Acute Respiratory Tract Infection (ARIVAC) vaccine trial

Project leader: Hanna Nohynek, MD, PhD

Description

The ARIVAC project is a KTL coordinated international venture to carry out a phase III efficacy study of an investigational 11-valent pneumococcal conjugate vaccine (11PCV) against radiologically defined childhood pneumonia in the Philippines. The trial was started as a collaborative initiative after several years of bilateral preparatory activities ranging from hospital based childhood pneumonia etiology and laboratory based diagnostics tests development studies, to field based immunogenicity, safety and ARI case management prevention studies (between the Research Institute for Tropical Medicine and KTL, and RITM and University of Queensland). The ARIVAC consortium was formed in 1997 to carry out the phase III trial with a sanofi pasteur (then Pasteur Merieux) candidate vaccine. University of Colorado joined the consortium to provide developing country pediatrics and virology expertise.

The main aim of the trial driving the sample size was to prevent radiological pneumonia defined using the standard WHO protocol. The secondary and tertiary aims were vaccine efficacy (VE) against clinical pneumonia and degrees of severity; immunogenicity and serological correlates of protection, safety, and reactogenicity of the vaccine, VE on pneumococcal carriage and viral-bacterial co-infections, and viral epidemiology in the trial context.

In preparation for the study, the consortium participated in the development of the WHO standard radiology protocol, WHO standard pneumococcal carriage studies methodology guidelines along

with the other pneumococcal trialists groups and establishment of serological thresholds for licensure.

The trial was carried out on the island of Bohol, the Philippines. Enrollment lasted for 3,5 years, and followup of the study infants for 4,5 years, i.e. until their 24thmonth of age or the end of the trial. The trial related scientific and administrative coordination was with KTL. Day-to-day management was divided into 5 components with KTL responsibility as consultants in 1. clinical and 2. safety surveillance, 3. laboratory (bacteriology, clinical chemistry), and 4. field operations. Data management consultation was UQ responsibility and virology UCo responsibility.

Major achievements

1) Field component of the study started on 5th July 2000, and completed by 31st December 2004 with 94% enrollment rate and less than 5% drop-out rate, a total 12 190 infants making the final sample size of the study.

2) Main laboratory analyses and their quality assurance completed by January 2006 (blood and CSF culture, serotyping of *Streptococcus pneumoniae*, clinical chemistry) and data base locked for analyses.

3) Primary plan of analysis completed and code opened for the primary outcome (radiologically defined pneumonia) and most secondary outcomes (immunogenicity of 11PCV, safety and reactogenicity, impact on carriage and different degrees of severity of infection) on February 2006.

4) Main results of the study were reported in ICID in June 2006. Vaccine efficacy [VE] was 23% [95% CI -1,1 - 41,2] against radiologically defined pneumonia in the per protocol analysis; VE in children 3-11 mo old was more pronounced, i.e. 34%, [95% CI 4,8 - 54,3] than in those 12-23 mo old; no impact on clinical pneumonia was observed; 11PCV was immunogenic; among the 11PCV recipients, a small excess of serious adverse respiratory events was observed in the first 28 days after the 1st and 2nd dose of vaccine, and of non-respiratory events after the 1st dose.

5) Sustaining the continuation of the trial despite major obstacles: the vaccine manufacturer decided to stop the commercialization of the vaccine in 2001; the main funder European Union DG Research pulled out its support to the trial in 2004, and a false claim of the vaccine causing the death of a child and request from a local lawyer to the Provincial Health Office of Bohol to stop the trial prematurely in 2003

Key publications

Lupisan S, Herva E, Sombrero LT, Quiambao BP, Capeding MRZ, Abucejo PE, Esparar G, Arcay J, Ruutu P. Invasive bacterial infections of children in a rural province in central Philippines. Am J Trop Med Hyg 2000;62:341-6.

Puumalainen T, Dagan R, Wuorimaa T, Zeta-Capeding R, Lucero M, Ollgren J, Käyhty H, Nohynek H. Greater antibody responses to an eleven valent mixed carrier diphtheria- or tetanus-conjugated pneumococcal vaccine in Filipino than in Finnish or Israeli infants. Pediatr Infect Dis J. 2003;22:141-50.

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pneumococcal diphtheria/tetanus conjugated vaccine: A randomised controlled trial in Filipino infants. J Infect Dis 2004;189:2077-84

3.3.3. PneumoCarr (The Pneumococcal Carriage Group)

Project leader: Helena Käyhty, PhD

Description

PneumoCarr is one of the projects in the Grand Challenges in Global Health Initiative, funded by the Bill and Melinda Gates Foundation. The goal of the PneumoCarr project is to advance the use pneumococcal colonization as an alternative or additional measure of the vaccine efficacy in vaccine trials. KTL is coordinating the 5 year-project which started in the beginning of 2006. Pneumococcal research centres from Finland (KTL), the Philippines (RITM), Australia (University of Melbourne), the Gambia (Medical Research Council Laboratories), Great Britain (Institute of Child Health), Israel (the Ben Gurion University), Kenya (Kenyan Medical Research Institute), South Africa (University of Witwaterstrand) and the USA (Johns Hopkins School of Public Health) participate in the project as partners and a group from Denmark (Statens Serum Institute) as a collaborator. A Modelling Group, consisting of four researchers in the fields of mathematics and statistics and a data manager, has been set up at KTL. The Modelling Group uses both existing data sets from partners and the collaborator and from add-on studies currently run by partners. The Vaccine Immunology Laboratory at KTL will conduct laboratory analyses from a set of samples collected in studies included in PneumoCarr.

The Finnish Academy awarded a 3-year research grant to advance studies on pneumococcal epidemiology. This funding started in January 2007 and will be used to support PneumoCarr research by sustaining expertise in the fields of medicine and infectious disease epidemiology at KTL. The grant will also make it possible to perform genetic typing of pneumococcal clones in one of the data sets.

Major achievements

1) The Modeling Group has devoted the first year of the project to developing statistical methods for the analysis of observational data on pneumococcal colonization and for the analysis of longitudinal data sets on the natural dynamics of pneumococcal colonization.

Key publications

Käyhty H, Auranen K, Nohynek H, Dagan R, Mäkelä H, the Pneumococcal Carriage Group (PneumoCarr). Nasopharyngeal colonization: a target for pneumococcal vaccination. Expert Rev. Vaccines 2006;5;651-68.

3.3.4. Assessment of natural and vaccine-induced immunity

Project leader: Helena Käyhty, PhD

Description

Evaluation of immune response to capsular polysaccharide (PS) based vaccines relies on measurement of anti-PS antibody concentrations by enzyme immunoassay (EIA). Vaccine Immunology Laboratory has actively participated in interlaboratory evaluation and validation of the EIAs for meningococcal (Men), *H. influenzae* type b (Hib) and pneumococcal anti-PS antibodies. The demonstration of the functional activity of antibodies evoked by different Men, Hib and pneumococcal vaccines has been regarded essential in vaccine trials. ROIM has participated actively in interlaboratory evaluation and standardization of the opsonophagocytic assay (OPA) for pneumococcal antibodies coordinated by WHO, CDC, FDA and PAHO. Pneumococcal protein antigens have been recognized as potential vaccine candidates. The functional mechanisms of antibodies to pneumococcal protein antigens have not been totally elucidated. We are setting up alternative functional assays to OPA for anti pneumolysin and anti-Pht antibodies based on the hemolytic activity of pneumolysin and factor H binding activity of Pht.

We have evaluated different laboratory methods for showing protective immunity evoked by meningococcal group B protein vaccines. To this end we have developed and validated an animal model for showing the protective activity of antibodies evoked by meningococcal group B outer membrane protein vaccines. A novel pneumococcal conjugate vaccine (PCV11-PD) that uses a *H. influenzae* (NTHi) protein D as a carrier provides protection against acute otitis media (AOM) caused by NTHi. Protein D belongs to a glycerophosphodiester phosphodiesterase family. We are currently investigating whether antibodies evoked by PCV11-PD can inhibit the enzymatic activity of this protein and if this inhibition could be used as a correlate of protection.

Serological assays for measurement of tetanus, diphtheria and pertussis antibodies are maintained in the Department of Vaccines and used for serosurveys in order to assess the vaccination programme and the immunity in the Finnish population. Serological assays for detection of measles, mumps, rubella, varicella, polio, hepatitis A and B antibodies are running in the Department of Viral Diseases and Immunology.

Seroepidemiology: Serological surveillance of immunity to diphtheria, tetanus, pertussis, polio, measles, mumps, rubella, varicella, hepatitis A and B in the Finnish population have been, and will when necessary, be performed to determine the antibody prevalence and immunity to these vaccine preventable diseases. We have participated in ESEN (European Sero-Epidemiology Network) projects. The aim of the European Sero-Epidemiology Network was to establish comparability of the serological surveillance of vaccine preventable diseases in Europe.

Correlates of protection: A major goal of the work is to be able to predict vaccine efficacy by laboratory measurements. We have extended this further by studying whether antibodies to pneumococcal proteins developed naturally, without vaccination but e.g. via contacts with bacteria, can be associated with the risk of subsequent pneumococcal disease or colonization. The main studies providing data for these calculations come from the FinOM Cohort Study (3.3.1), FinOM Vaccine Trial (3.4.1) and ARIVAC study (3.4.3). In all these trials extensive serological determinations have been done by using EIA for antibody concentration and avidity and OPA for measurement of the functional activity of antibodies. Both serum and mucosal antibodies have been investigated. At present we are also investigating whether the assay for inhibition of GLpQ correlates with the protection evoked by PCV11-PD.

Major achievements

1) Interlaboratory assay standardization and validation process of several methods for measuring immune response to PS based vaccines has been adopted. EIAs for Hib and Pnc anti-PS antibodies have been accredited in 2005 (ISO/IEC17025). Pht protein is involved in the binding of complement component factor H and we are now studying if antibodies to Pht proteins can affect on this and if we can develop a robust functional assay for anti-Pht antibodies evoked by future protein vaccines or by pneumococcal contacts. Antibodies to protein D of NTHI can inhibit the GLpQ enzyme activity. A robust assay for detection of this activity has been developed and validated to be used for sera from vaccine trials. The laboratories performing diphtheria, pertussis, measles, mumps, rubella, varicella, hepatitis A and B have been involved in the European Seroepidemiological Network (ESEN 1 and ESEN 2). One of the objectives of the project was to establish comparable methodologies for serological surveillance by standardising laboratory methods.

2) In the FinOM Vaccine Trial an association between antibody concentration and risk of AOM was found, but with large differences between serotypes. The same methodology will be further used for determination of association of antibody concentrations and pneumococcal carriage in PneumoCarr studies (3.4.4). OPA and antibody avidity assay can give important complementary data when evaluating immune response to PS based vaccines. In general, antibodies to protein antigens could not be associated with subsequent pneumococcal disease. However, lack of salivary antibodies to PspA proteins was associated with increased risk of pneumococcal AOM. The Pnc conjugate vaccine used in the ARIVAC study was highly immunogenic. The correlates of protection against pneumococcal carriage are being determined.

Key publications

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Jokinen JT, Åhman H, Kilpi TM, Mäkelä PH, Käyhty MH. Concentration of anti-pneumococcal antibodies as a serological correlate of protection: an application to acute otitis media. J Infect Dis. 2004;190:545-50.

Ekström N, Åhman H, Verho J, Jokinen J, Väkeväinen M, Kilpi T, Käyhty H. Kinetics and avidity of antibodies evoked by two pneumococcal conjugate vaccines, PncCRM and PncOMPC, in the Finnish Otitis Media Vaccine Trial. Infect Immun 2005;73:369-77.

Ekström N, Verho J, Väkeväinen M, Kilpi T, Käyhty H for the FinOM Study Group. Functional activity of antibodies elicited by heptavlent pneumococal conjugate vaccines PncCRM and PncOMPC in the Finnish Otitis Media Vaccine Trial. Infect Immun 2007:75:1794-800.

3.3.5. Immune response in specific target groups

Project leader: Helena Käyhty, PhD

Description

Effective prevention of infections caused by *Streptococcus pneumoniae* (Pnc) has become a public health priority as the population of elderly adults susceptible to pneumococcal infections is growing and the antibiotic resistant pneumococcal strains are emerging. The efficacy of the current pneumococcal polysaccharide vaccine (PPV) against pneumonia is unsatisfactory in the elderly population. Improved vaccines are urgently needed. The research group (FinCAP immu) was established in 2005 in ROIM and is specialized in research on immunity to pneumococcal infections among the elderly. The project was part of the KTL programme for healthy aging.

The research aims at providing important knowledge about the immunology behind the increased susceptibility to pneumococcal diseases and poor efficacy of the PPV in the elderly population. We characterize the development of natural antibody-mediated immunity to Pnc by age by determining the concentration and functionality of antibodies to selected pneumococcal polysaccharides and proteins. The effect of aging on complement activity, cytokine secretion, and on the activity and receptor expression of phagocytes is evaluated to increase the basic immunological understanding. To understand the reasons for the unsatisfactory efficacy of PPV, we characterize the functional immune response to PPV in the elderly. Especially, we will focus on an important group of elderly adults who fail to respond to PPV (poor responders). We will examine if the antibody status of poor responders prior to vaccination resembles that of elderly adults with pneumococcal CAP by comparing IgG and IgM concentration and function from the pre-vaccination sera of poor and high responders and from the sera of patients in the FinCAP epi study with pneumococcal pneumonia or as a control with acute respiratory infection. To find out whether poor responders can be immunized successfully with new vaccines, we will participate in studies characterizing their functional immune response to a novel adjuvanted pneumococcal conjugate vaccine (PCV). Since a lot of information on age-associated immunological changes affecting immunity to infections comes from animal studies, we will test the comparability of the data on immunity to Pnc obtained from mice and men.

In addition to elderly several immunocompromised patient groups are at increased risk for pneumococcal infections. These same groups respond poorly to pneumococcal polysaccharide vaccines, while several studies suggest that response to conjugate vaccines is satisfactory. In collaboration with Finnish, Ugandan, Malawian and South African groups we have evaluated immune responses to Hib, Men and pneumococcal vaccines among bone marrow transplant and cancer patients, among infant and adult HIV infected patients and children with recurrent respiratory infections.

Major achievements

1) Laboratory studies on development of natural antibody-mediated immunity by age from the sera of elderly and younger adults obtained from the Health 2000 study have been completed and manuscripts (3) are under preparation. Parts of the results were reported in the 5th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD5) in 2006.

2) To study effect of aging on cytokine secretion as well as on phagocytic activity and receptor expression, we have established and validated the laboratory methods. Recruitment of elderly (n=63) and young adults (n=30) has been completed. Laboratory analyses are currently underway. Results of preliminary analysis to set up optimal conditions for studying cytokine secretion were presented in ISPPD5.

3) Adult HIV infected individuals respond to pneumococcal conjugate vaccine equally to uninfected individuals. However, the response is lower among those with low CD4 counts (<200). After vaccination with pneumococcal or Hib conjugate vaccine HIV infected children have antibody concentrations comparable to those of uninfected children, but the functional activity can be lower among the HIV infected children.

4) Immunization of bone marrow transplant donors before transplant with a conjugate vaccine, but not with PS vaccine, can augment the response of the recipient to vaccination after transplant. Adult patients with chronic chronic lymphocytic leukaemia respond to pneumococcal conjugate vaccine better than to polysaccharide vaccine. However, the mean antibody concentrations remain lower than in samples of healthy controls.

Key publications

Miiro G, Käyhty H, Watera C, Tolmie H, Whitworth JAG, Gilks CF, French N. Conjugate pneumococcal vaccine in HIV-infected Ugandans and the effect of past polysaccharide vaccine vaccine receipt. J Infect Dis 2005:192:1801-6.

Madhi SA, Kuwanda L, Cutland C, Saarinen L, Käyhty H, Klugman KP. Immunogenicity and effectiveness of *Haemophilus influenzae* type b conjugate vaccine in HIV infected and uninfected African children. Vaccine 2005;23:5517-25.

Madhi SA, Kuwanda L, Cutland C, Holm A, Käyhty H, Klugman KP. Quantitative and qualitative antibody responses to a 9-valent pneumococcal conjugate vaccine among African HIV infected and HIV uninfected children. Pediatr Infect Dis J 2005;24:410-6

Parkkali T, Käyhty H, Hovi T, Ölander RM, Roivainen M, Volin L, Ruutu T, Lahdenkari M, Ruutu P. A randomized study on donor immunization with tetanus-diphtheria, *Haemophilus influenzae* type b and inactivated poliovirus vaccines to improve the recipient responses to the same vaccines after allogenic bone marrow transplantation. Bone Marrow Transplant 2007:39:179-88.

3.4. Evaluation of immunization programmes

3.4.1. Prediction of immunization programme effectiveness using mathematical models

Project leader: Kari Auranen, PhD

Description

Mathematical and statistical modes can provide a valuable aid in summarising knowledge about the epidemiology of an infection. Models can be used to advance our understanding about the natural history of the infection and disease as well as quantify anticipated effects of large-scale vaccinations. Mathematical models can also be used to point gaps in relevant knowledge regarding the natural history of the infection. At KTL, the activity in the field of infectious disease modelling was started a decade ago with the analysis and modelling of the epidemiology of *Haemophilus influenzae* type b (Hib) carriage and disease (the INFEMAT project).

The latter part of that project was completed during the years 2000-2003, and resulted in the characterization of the impact of vaccination on Hib carriage and disease in the population. In particular, the analysis showed the importance of a sustainable effect of vaccination on carriage for the overall effectiveness of Hib vaccination. The project involved development of novel statistical methods to analyse incompletely observed data about asymptomatic carriage as well as the

development of an individual-based micro-simulation model to study the post-vaccination epidemiology of Hib.

Another line of research applying statistical modelling of infectious disease data has concentrated on the transmission of *Streptococcus pneumoniae* (pneumococcus). We have assessed the importance of within-family transmission, with estimates of the duration of carriage as well as acquisition rates. Another topic has been the analysis of the relationship of pneumococcal carriage and (pneumococcal) acute ear infection (AOM). We have for example shown that disease (AOM) mostly follows soon after the instance of acquisition of nasopharyngeal carriage. Research on the epidemiology of pneumococcal carriage has recently expanded to another project (PneumoCarr). As part of the PneumoCarr project, the overall effectiveness of pneumococcal vaccination will be assessed in different epidemiological conditions, using the micro-simulation platform initially developed for Hib.

Mathematical models are currently applied to assess the population effects of vaccination against varicella, including the possible non-beneficial effects on the zoster incidence. This reserach relies partly to collaboration with other European groups, in particular in the POLYMOD project where novel data have been gathered about the distribution of daily social contacts relevant for transmission. Other vaccine-preventable diseases under evaluation, including analysis through mathematical modelling, include measles.

Major achievements

1) Development of a micro-simulation platform to analyse the epidemiology of asymptomatic infection (Hib and Pnc)

2) Analysis of the pre- and post-vaccination epidemiology of *Haemophilus influenzae* type b, showing the importance of a sustainable vaccine effect on colonisation

3) Development of statistical models to analyse longitudinal data from bacterial asymptomatic carriage, including the relationship between acquisition of carriage and the onset of disease (ear infection)

Key publications

Syrjänen R, Auranen K, Leino T, Kilpi T, Mäkelä PH. Pneumococcal acute otitis media in relation to pneumococcal nasopharyngeal carriage. Pediatr Infect Dis J 2005;24: 801-6.

Leino T, Takala T, Auranen K, Mäkelä PH, Takala AK. Indirect protection obtained by *Haemophilus influenzae* type b vaccinations; analysis in a structured population model. Epidemiol Infect 2004;132:959-66.

Auranen K, Eichner M, Leino T, Takala T, Mäkelä PH, Takala AK. Modelling transmission, immunity and disease of *Haemophilus influenzae* type b in a structured population. Epidemiol Infect 2004;132:947-57.

Leino T, Auranen K, Jokinen J, Leinonen M, Tervonen P, Takala AK. Pneumococcal carriage in children during their first two years; important role of family exposure. Pediatr Infect Dis 2001;20:1024-9.

Auranen K, Arjas E, Leino T, Takala AK. Transmission of pneumococcal carriage in families: a latent Markov process model for longitudinal binary data. Journal of the American Statistical Association 2000;125:583-91.

3.4.2. Cost-effectiveness analyses

Project leader: Heini Salo, MSc

Description

In KTL, the first projects of the economic evaluations of the immunization programmes started at the beginning of 2001. The cost-effectiveness of pneumococcal conjugate (published in 2005) and varicella vaccinations were evaluated. These analyses did not take into account any potential indirect effects of the vaccines. The cost-effectiveness analysis of influenza vaccination of healthy children was published in 2006.

The National Advisory Committee for Vaccination has been asked to give in 2008 its expert opinion on the introduction of three vaccines (rotavirus, varicella and pneumococcal conjugate vaccine) into NIP. Varicella vaccine and pneumococcal conjugate vaccine (PCV7) are going to be re-evaluated taking into account the potential indirect effects of the vaccines. The cost-effectiveness analysis of varicella vaccination will be based on a dynamic mathematical model of varicella zoster virus (VZV) transmission. The modeling is done in KTL. The cost-effectiveness analysis of rotavirus vaccines started in 2006 by first estimating the burden of disease of rotavirus infection, and is an ongoing project.

KTL is a partner in a European Commission project POLYMOD which started at October 2004. The project is developing and applying mathematical, economic and risk assessment models of infectious diseases. KTL has collaborated closely with the POLYMOD project in the cost-effectiveness studies of both rotavirus and varicella vaccinations.

Major achievements

1) The economic evaluation has been established as one of the evaluation instruments when a new vaccine is considered into national immunization programme.

2) Developments of economic modelling to be based on mathematical models to better take in to the account the population effects of vaccinations when needed (e.g. the economic re-evaluation of varicella vaccine).

Key publications

Salo H, Sintonen H, Nuorti P, Linna M, Nohynek H, Verho J, Kilpi T. Economic evaluation of pneumococcal conjugate vaccination in Finland. Scand J Infect Dis 2005;37:821-32.

Salo H, Kilpi T, Sintonen H, Linna M, Peltola V, Heikkinen T. Cost-effectiveness of influenza vaccination of healthy children. Vaccine 2006;24:4934-41.

3.5. Regulation of host defence functions

Microbial infections and other alien invasion into the human body triggers both innate and adaptive immune responses, each involving a range of different cell types and complex intracellular and intercellular signalling networks. Expression of the genes whose products are responsible for these phenomena is delicately regulated to guarantee the desired end result, elimination of the alien agent from the body, and generation of immunity protecting the body from future attempts of invasion. Symptoms of infectious diseases often include expression of the innate responses such as inflammation, while dysregulation of both humoral and cell-mediated efferent pathways of the

adaptive responses may result in auto-immune diseases. Understanding the mechanisms and the regulation of host defences in further detail is necessary in order to develop new interventions for infectious and inflammatory diseases. This chapter describes KTL projects on selected topics in this vast research field.

3.5.1. Leukocyte trafficking

Project leaders: Sirpa Jalkanen, MD, PhD and Marko Salmi, MD, PhD

Description

Continuous lymphocyte recirculation between blood and lymphatic organs is the key element of our immune system as it allows the evoking of rapid and appropriate immune response against invading microbes, whenever needed. Leukocyte extravasation to sites of inflammation is prerequisite for effective elimination of infectious agents, but the trafficking can continue in an uncontrolled manner resulting in severe diseases such as diabetes, arthritis, psoriasis.

The main goals of the project have been to identify and characterize molecular mechanisms mediating harmful cell trafficking to sites of inflammation and to elucidate the unknown mechanisms guiding the lymphocytes into the lymphatics. In this work we have used modern approaches and methodology in cell and molecular biology, protein chemistry, imaging and preclinical animal models. Most importantly our discoveries have been exploited in translational research settings involving our clinical networks.

In the future, the study groups will concentrate to promote health and prevent diseases by elucidating the pathogenesis of emerging inflammatory and bacterial diseases and developing tools for controlling such diseases. The major aims of the Centre are to elucidate the so far unknown mechanisms that the microbes and cancer cells use to manipulate the cell trafficking mechanisms. The overall goal is to discover unique targets to be utilized in developing new diagnostic and therapeutic tools to fight against infections and cancer spread.

The Cell Trafficking unit was a National Centre of Excellence 2000-2005. The KTL groups studying leukocyte trafficking are also intimately connected to University of Turku and form the central groups in National Centre of Excellence in Host Defence in 2008-2013.

Major Achievements

1) Elucidation of the mechanisms of action of two ectoenzymes, CD73 and Vascular Adhesion Protein-1 (VAP-1) in leukocyte trafficking and providing proof-of-concept of their potential to be used as targets for drug development.

2) Identification of the role of VAP-1 in development of diabetic complications (vasculopathies)

3) Discovery of the role of macrophage mannose receptor and common lymphatic endothelial and vascular endothelial receptor-1 (CLEVER-1) in lymphatic vasculature.

Key publications

Salmi M, Yegutkin G, Lehvonen R, Koskinen K, Salminen T, Jalkanen S. A cell surface amine oxidase directly controls lymphocyte migration. Immunity 2001;14:265-76.

Irjala H, Johansson E-L, Grénman R, Alanen K, Salmi M, Jalkanen S. Mannose receptor is a novel ligand for L-selectin and mediates lymphocyte binding to lymphatic endothelium. J Exp Med 2001;194:1033-42.

Stolen C, Ichihara-Marttila F, Yegutkin GG, Bono P, Skurnik M, Hänninen A, Jalkanen S, Salmi M. An endothelial enzyme VAP-1 is needed in vivo for leukocyte traffic. Immunity 2005;22:105-15.

Salmi M, Jalkanen S. Cell-surface enzymes in control of leukocyte trafficking. Nature Rev Immunol 2005;5:760-71.

Nieminen M, Henttinen T, Merinen M, Marttila-Ichihara F, Eriksson JE, Jalkanen S. Vimentin function in lymphocyte adhesion and transcellular migration. Nature Cell Biol 2006;8:156-62.

3.5.2. Intestinal immunology, allergies and autoimmune diseases

Project leader: Outi Vaarala, MD, PhD

Description

Incidence of type 1 diabetes in children has increased in most industrialized countries. In Finland the incidence rate has increased fourfold over the last 50 years. There are also strong indications that the prevalence of atopic diseases has increased substantially in Western countries over the same time period.

The development of autoimmune diseases and allergies is a result of the failure in the immune tolerance that allows the expansion of pathogenic immune responses to self in autoimmune diseases or environmental antigens in allergies. Surveillance without autoimmune disease or allergies is thus dependent on the regulatory mechanisms that control the immune responses. Intestinal immune system is a key organ for the development of oral tolerance, which is impaired e.g. in food allergies and celiac disease. Several studies indicate that intestinal immune system controls also autoreactivity in autoimmune disease, such as in type 1 diabetes and rheumatoid arthritis.

Thus, KTL is focusing the studies on mechanisms of immune tolerance and especially in the role of gut immune system in the development of allergies and autoimmune diseases. The activities include studies of the function of the immune cells, T-cells and dendritic cells isolated from the patients with allergies or autoimmune diseases. The mechanistic studies of the immune system are incorporated into the clinical intervention studies for the prevention of allergies and type 1 diabetes aimed to understand the mechanisms of the intervention, but also the pathogenic and protective pathways in the disease process.

KTL is participating in the European T-cell laboratory in the international TRIGR study supported by NIH. In the TRIGR study 2013 children at genetic risk of type 1 diabetes are randomized to receive either ordinary cow milk formula or hydrolysed cow milk formula during the first 6-8 months of life to test whether the use of hydrolysed formula reduces the development of beta-cell autoimmunity and type 1 diabetes. The recruitment of the TRIGR study was finished in December 2006 and the follow-up continues until 2012.

Project leader is also the principal investigator of the national FINDIA-study in which the insulin-free cow milk formula is tested in the prevention of insulin-specific immunity and beta-cell autoimmunity in the children at genetic risk of type 1 diabetes. The recruitment of the children was finished in the autumn 2005 and the study protocol includes follow-up until the age of 2 years.

The collaboration with the Hospital for Children and Adolescents at Helsinki University and with the international and national clinical centres participating in the prevention trials is important for our activities.

Major achievements

1) Sub-clinical intestinal immune activation is present in the children with type 1 diabetes. The role of the gut immune system in the development of type 1 diabetes has been a pioneer finding.

2) Dietary bovine insulin is the primary inducer of insulin-specific immune response in infants. Based on these findings, "the gut hypothesis" about the development of type 1 diabetes in children has been created. This hypothesis suggests that the underlying sub-clinical intestinal inflammation allows the development of destructive beta-cell autoimmunity in genetically susceptible individuals who are not able to control the immune response to dietary insulin due to interference of environmental factors which break oral tolerance. Enterovirus infections or other infections enhance the immune response to dietary insulin and could be factors breaking tolerance.

3) Treatment with human insulin activates insulin-specific regulatory T-cells in children with newly-diagnosed type 1 diabetes. This effect of the exogenous autoantigen explains the difficulties to detect *in vitro* T-cell proliferation responses to insulin in patients. Furthermore, autoantigen treatment-induced activation of regulatory T-cells may contribute to the clinical remission of the disease and further studies of the insulin analogs able to induce regulatory mechanisms and support tolerance are initiated.

4) Probiotics when given to the infants with a family risk of allergy induce low-grade inflammation that protects against eczema.

5) Hyporesponsiveness of T-cells, seen as impaired cytokine response, is seen in rheumatoid arthritis and is reversed by TNF-alpha blocking. IL-6 expression is increased in the small intestinal biopsy samples taken from patients with rheumatoid arthritis, which confirms the observations of subclinical intestinal inflammation in rheumatoid arthritis.

Key publications

Paronen J, Knip M, Savilahti E, Virtanen SM, Ilonen J, Åkerblom HK, Vaarala O and the Finnish TRIGR Study Group. The effect of cow milk exposure and maternal type 1 diabetes on cellular and humoral immunization to dietary insulin in infants at genetic risk for type 1 diabetes. Diabetes 2000;49:1657-65.

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Westerholm-Ormio M, Vaarala O, Pihkala P, Ilonen J, Savilahti E. Immunologic activity in the small intestinal mucosa of pediatric patients with type 1 diabetes. Diabetes 2003;52:2287-95.

Viljanen M, Pohjavuori E, Haahtela T, Korpela R, Kuitunen M, Sarnesto A, Vaarala O, Savilahti E. Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome. Journal Allergy Clin Immunol 2005;115: 1254-9.

Mäkela M, Vaarala O, Hermann R, Salminen K, Vahlberg T, Veijola R, Hyöty H, Knip M, Simell O, Ilonen J. Enteral virus infections in early childhood and an enhanced type 1 diabetes-associated antibody response to dietary insulin. J Autoimmun 2006;27:54-61.

Tiittanen M, Huupponen JT, Knip M, Vaarala O. Insulin treatment in patients with type 1 diabetes induces up-regulation of regulatory T-cell markers in peripheral blood mononuclear cells stimulated with insulin in vitro. Diabetes 2006;55:3446-54.

3.5.3. Pathogenesis of influenza virus infection and regulation of immune responses

Project leader: Ilkka Julkunen MD, PhD,

Description

Influenza virus with its pandemic potential is one of the major viral pathogens worldwide. The primary cellular target of influenza virus is the respiratory epithelium of the lungs. Other cell types such as tissue macrophages and dendritic cells (DCs) are also infected by the virus. Innate immune responses, which includes the production of antiviral and other cytokines greatly affect the outcome of the infection. In addition, cytokines and antigen presentation by DCs regulate the development adaptive immune responses. We have analyzed the activation of innate immune responses in influenza A and other respiratory virus (SARS and Sendai) infections using human lung epithelial cell, macrophage and DC model systems. We have characterized the molecular mechanisms and signaling pathways involved in virus-induced activation of innate immune responses. In addition, we have studied cytokine signaling and their role in NK and T cell activation. Thus our work has characterized the cellular interplay and the role of cytokines in the activation host antiviral responses in human cells.

Future research topics are tightly linked to the presently ongoing projects. However, our molecular biology, virology and immunology experience will be targeted to human and avian influenza viruses. We will initiate BSL-3 level work to enhance our preparedness for pandemic influenza. Avian influenza viruses as well as recombinant human influenza A viruses carrying mutations in certain viral virulence factors (NS1 protein) will be used to study human macrophage and DC rsponses to these viruses. A working hypothesis is that highly pathogenic avian influenza A viruses induce hyperproduction of host inflammatory cytokine response. We will also investigate whether antiviral cytokines and host cell signaling inhibitors can inhibit avian influenza A virus replication in human cells and whether the overproduction of cytokine responses can be inhibited. Our immunological expertise and recombinant influenza virus proteins will be used to characterize the nature of humoral and cell-mediated immune responses in early childhood influenza A virus infection (primary infection). In addition we will take part in clinical influenza vaccination (including avian influenza) trials to characterize the nature and persistence of vaccine-induce humoral and cell-mediated anti-influenza immune responses.

Major achievements

1) Influenza A viruses can induce a relatively poor antiviral innate immune (cytokine) response in human lung epithelial cells and in primary human macrophages and DCs. Pretreatment of cells with IFN-a or TNF-a enhance the expression of host cell signaling molecules involved in viral RNA recognition, which leads to dramatically enhanced antiviral gene expression in response to influenza A virus infection. The observation indicates that IFNs may be beneficial to treat severe influenza A virus infection cases. IFNs also significantly enhance NK and T cell activation.

2) In human primary macrophages and DCs certain Th1 type cytokines (IFN-a, IFN-g, IL-12) cytokines and cellular receptors recognizing microbial structures (Toll-like receptors, TLR) work synergistically to enhance innate immune responses. Influenza A virus-induced IFN-a/b and IL-18

work synergistically to enhance T cell activation and Th1 type immune responses, events that are required for efficient eradication of virus infections.

3) We have produced and purified influenza A and B virus (as well as SARS nucleoprotein) recombinant proteins that are immunogenic and can be used for detailed analysis of humoral and cell-mediated immune responses in influenza virus infection or in vaccine-induced responses.

Key publications

Pirhonen J, Matikainen S and Julkunen I. Regulation of IL-12 and IL-23 gene expression in viral infections. J Immunol 2002;169:5673-8.

Strengell M, Matikainen S, Sirén J, Foster D, Julkunen I and Sareneva T. IL-21 in synergy with IL-15 or IL-18 enhances IFN-g production in human NK and T cells. J Immunol 2003;170:5464-9.

Österlund P, Veckman V, Sirén J, Klucher KM, Matikainen S and Julkunen I. Gene expression and antiviral activity of type I IFNs and IL-29 in virus-infected human monocyte-derived dendritic cells. J Virol 2005;79:9608-17.

Matikainen S, Sirén J, Tissari J, Veckman V, Pirhonen J, Severa M, Sun Q, Lin R, Meri S, Hiscott J, Uzé G and Julkunen I. TNF-a enhances influenza A virus-induced expression of antiviral cytokines by activating RIG-I gene expression. J Virol 2006;80:3515-2.

Melén K, Kinnunen L, Fagerlund R, Ikonen N, Twu KY, Krug RM and Julkunen I. Nuclear and nucleolar targeting of influenza A virus NS1 protein: striking differences between different virus subtypes. J Virol 2007:81, 5995-06.

3.5.4 Pathogenesis of reactive arthritis

Project leader: Kaisa Granfors, PhD

Description

Development and severity of reactive arthritis (ReA) is associated with the tissue antigen HLA-B27, but the exact role of HLA-B27 in the pathogenesis of the disease is not known. It is obvious that HLA-B27 positive persons developing ReA have a defect in elimination of ReA-triggering bacteria and that the causative bacteria persist for long times in their bodies.

Impaired elimination of these bacteria (*Salmonella enteritidis, Yersinia enterocolitica*) has been shown in HLA-B27 positive cells *in vitro*, in transfected U937 monocytic cells. As only one type of monocytic cells are present in our experimental system, the observed effect of HLA-B27 cannot be due to the classical antigen presentation, but rather must be related to another function such as recently characterized misfolding of HLA-B27. It is clear, that in most cases the triggering bacteria do not persist in the inflamed joints, but obviously in mucosal areas where these infections take place. In joints bacterial antigens, especially lipopolysaccharide (LPS) are present.

The main objectives of research are the characterization of the mechanisms, which participate in the enhanced replication and incomplete elimination of *Salmonella* in HLA-B27 positive cells, and exact characterization of the mechanisms involved in strong activation of HLA-B27 positive cells upon LPS stimulation. The role of HLA-B27 is clarified especially by comparing syngeneic cell lines, which differ only in the expression of this important tissue antigen. This approach bypasses

the individual variation between the persons, which has often made it difficult to draw definite conclusions about the role of HLA-B27 in various studies. Importance of misfolding efficiency of HLA-B27 and characteristics of intracellular signalling pathways leading to abnormal reactions in HLA-B27 positive cells, as well as impact of bacterial characteristics (gene expression) during intracellular survival are the main study topics.

Major achievements

1) In patients with *Salmonella* infection, HLA-B27 does not strongly confer susceptibility to *Salmonella* infection. *Salmonella* excretion from the patients does not correlate with HLA-B27 positivity or with the occurrence of joint symptoms. HLA-B27-positive patients had a significantly increased risk of developing joint and tendon symptoms. Moreover, HLA-B27 positivity correlated with the development of more severe and prolonged joint symptoms. *In vitro, Salmonella* replicates intracellularly in HLA-B27 positive human monocytic U937 cells, but replication is not seen in HLA-B27 negative control cells.

2) Mutagenesis studies revealed that the folding efficiency of HLA-B27 heavy chain determines the severity of the effects caused by HLA-B27, as intracellular replication of *Salmonella* is only seen in the cells expressing strongly misfolding form of HLA-B27.

3) The p38 MAP kinase activity seems to play a crucial role in controlling intracellular replication of *Salmonella* in U937 cells. The p38 kinase pathway does not function properly in HLA-B27-expressing cells. Enhanced replication of *Salmonella* in HLA-B27-expressing cells requires that the heavy chain contains glutamic acid at position 45 and cysteine at position 67.

4) *In vitro* studies show also that when stimulated with LPS HLA-B27 positive monocytic U937 cells show strong and long lasting NF-κB activation, and enhanced production of TNFα. Enhanced production of this cytokine may explain induction of inflammation especially in HLA-B27 positive persons. Interestingly, anti-TNFα treatments have been shown to be especially effective in spondyloarthropathies in general, also in reactive arthritis.

5) The expression of 124 out of 5080 *Salmonella* genes studied differed significantly after 8 hours intracellular infection of HLA-B27-positive and negative U937 monocytic cells on the basis of microarray. Quantitative real-time RT-PCR was used to confirm the microarray data for genes from different functional categories.

Key publications

Ekman P, Kirveskari J, Granfors K. The modification of disease outcome in Salmonella patients by HLA-B27. Arthritis Rheum 2000;43:1527-34.

Ekman P, Saarinen M, He Q, Gripenberg-Lerche C, Grönberg A, Arvilommi H, Granfors K. HLA-B27-transfected (Salmonella-permissive) and HLA-A2-transfected (Salmonella nonpermissive) human monocytic U937 cells differ in their production of cytokines. Infect Immun 2002;70:1609-14.

Penttinen MA, Holmberg CI, Sistonen L, Granfors K. HLA-B27 modulates nuclear factor κB activation in human monocytic cells exposed to lipopolysaccharide. Arthritis Rheum 2002;46:2172-80.

Penttinen MA, Heiskanen KM, Mohapatra R, DeLay ML, Colbert RA, Sistonen L, Granfors K. Enhanced intracellular replication of Salmonella enteritidis in HLA-B27-expressing human

monocytic cells: dependency on glutamic acid at position 45 in the B pocket of HLA-B27. Arthritis Rheum 2004;50:2255-63.

Sahlberg AS, Penttinen MA, Heiskanen KM, Colbert RA, Sistonen L, Granfors K. Evidence that the p38 MAP kinase pathway is dysregulated in HLA-B27-expressing human monocytic cells: Correlation with HLA-B27 misfolding. Arthritis Rheum 2007: August issue 2007,

3.6 Molecular microbiology and pathogenesis

3.6.1. Staphylococcus aureus and Bacillus subtilis

Project leaders: Vesa Kontinen, MD, PhD

Description

The molecular bacteriology research group studies molecular mechanisms of gram-positive bacteria with the emphasis on such mechanisms that are important for bacterial virulence and pathogenesis or development of bacterial cells for production of heterologous proteins (bacterial cell factory). Until 2004 the main focus areas were protein secretion and signal transduction mechanisms of the gram-positive model bacterium *Bacillus subtilis*.

During the last two years some aspects of virulence mechanisms of *Staphylococcus aureus* has been another major research topic. Currently, about 50% of the research in the group is focused on *S. aureus*. The aim is to characterize function and structure of selected components involved in late stages of protein secretion, cell wall biosynthesis, proteolysis and bacterial response to cationic antimicrobial peptides. We also characterize in a collaborative project septic *S. aureus* infections by analyzing proteomes of strains isolated from infections. Furthermore, we perform immunoproteome analyzes to characterize immunoresponses in septic staphylococcal infections. The obtained results may enable developing new antimicrobial therapies against pathogenic bacteria, improving infection diagnosis or improving protein production technologies.

Major achievements

1) The PrsA lipoprotein is involved in lateral cell wall biosynthesis and determination of rod cell shape in gram-positive bacteria of the firmicutes group (unpublished result). It is a potential new anti-microbial drug target. PrsA was shown to be a Parvulin-type peptidyl-prolyl *cis-trans* isomerase which is required for efficient secretion of some heterologous extracellular proteins.

2) The genes which are differentially expressed in *B. subtilis* and *S. aureus* cells as a response to treatment with cationic antimicrobial peptides (CAMP stimulons/regulons) were identified. A two-component system which senses the human cathelicidin LL-37 in a highly specific manner was identified in *B. subtilis*.

3) The D-alanylation of teichoic acids modulates the activity of two-component systems involved in the sensing of membrane-active cationic antimicrobial peptides, cell wall antibiotics and/or misfolded proteins at the membrane-cell wall interface. Inactivation of the *dlt* operon encoding the D-alanylation system improves the secretion of some heterologous proteins in *B. subtilis* (patent).

Key publications

Hyyryläinen H-L, Vitikainen M, Thwaite J, Wu H, Harwood,C, Sarvas M, Kontinen VP and Stephenson K. D-Alanine substitution of teichoic acids as a modulator of protein folding and stability at the cytoplasmic membrane-cell wall interface of *Bacillus subtilis*. J Biol Chem 2000;275 :26696-703.

Pummi T, Leskelä S, Wahlström E, Gerth U, Tjalsma H, Hecker M, Sarvas M and Kontinen VP. ClpXP protease regulates the signal peptide cleavage of secretory preproteins in *Bacillus subtilis* with a mechansim distinct from that of the Ecs ABC transporter. J Bacteriol 2002;184:1010-8.

Vitikainen M, Lappalainen I, Seppälä R, Antelmann H, Boer H, Taira S, Savilahti H, Hecker M, Sarvas M and Kontinen VP. Structure-function analysis of PrsA reveals roles for the parvulin-like and flanking N- and C-terminal domains in protein folding and secretion in *Bacillus subtilis*. J Biol Chem2004;279:19302-14.

Pietiäinen M, Gardemeister M, Mecklin M, Leskelä S, Sarvas M and Kontinen VP. Cationic antimicrobial peptides elicit a complex stress response in *Bacillus subtilis* that involves ECF-type sigma factors and two-component systems. Microbiology 2005;151:1577-92.

Hyyryläinen H-L, Pietiäinen M, Lunden T, Ekman A, Antelmann H, Hecker M, Valmu L, Sarvas M and Kontinen VP. The density of negative charge in the cell wall influences two-component signal transduction in *Bacillus subtilis*. Microbiology 2007; 153:2126-36.

3.6.2. Evolution and molecular epidemiology of Bordetella pertussis

Project Leader: Qiushui He, MD, PhD

Description

Pertussis is the only vaccine preventable disease that is re-emerging in immunized populations. One of the causes for the resurgence seems to be the adaptation of *Bordetella pertussis* to vaccine-induced immunity. Indeed, the antigenic variations have been found between *B. pertussis* vaccine strains and circulating isolates in many countries. The main objectives of this project are to monitor changes in bacterial populations, to identify and characterise emergence of new strains that may have the potential to cause nation-wide epidemics of disease, and to study the impact of the changes of *B. pertussis* on the prevention and incidence of disease.

Major achievements

1) The current circulating isolates differ from strains used for vaccine production and from "old" isolates in respect to components included in acellular pertussis vaccines in Finland.

2) Clonal expansion of *B. pertussis* has occurred and caused the recent nationwide epidemics. The recent epidemic-causing strains have had highest number of lost genes compared to the vaccine strains and "old" isolates. The genome reduction was found to be mediated by insertion sequence elements

3) Changes of *B. pertussis* in Finland were compared to that in France with similar vaccination history. Isolates from Finland and France were similar genetically but varied temporally.

4) Pertactin (Prn), an outer membrane protein of *B. pertussis* is included in most of acellular vaccines. So far 11 Prn variants have been identified. The variation was essentially limited to a region that is composed of repeating units of 5 (GGXXP) amino acids and is located adjacent to an

RGD motif implicated in adherence. Vaccine strains and "old" isolates produced Prn1, whereas almost all of current circulating strains have Prn2. *B. pertussis* Prn was found to induce type-specific antibodies and to affect the production of serum anti-Prn antibodies.

Data obtained from the project suggest the continuous evolution of *B. pertussis* and stress the importance of the long-term monitoring of emerging strains, and have significantly contributed to the understanding of evolution and molecular epidemiology of *B. pertussis* in immunized populations.

Key publications

Mäkinen J, Viljanen MK, Mertsola J, Arvilommi H, He Q. Rapid identification of *Bordetella pertussis* pertactin gene variants using LightCycler real-time polymerase chain reaction combined with melting curve analysis and gel electorphoresis. Emerg Infect Dis 2001;7:952-8.

He Q, Mäkinen J, Berbers G, Mooi FR, Viljanen MK, Arvilommi H, Mertsola J. Bordetella pertussis protein pertactin induces type-specific antibodies: one possible explanation for the emergence of antigenic variants? J Infect Dis 2003;187:1200-5.

Elomaa A, Advani A, Donnelly D, Antila M, Mertsola J, Hallander H, He Q. Strain variation among *Bordetella pertussis* isolates in Finland where the whole-cell pertussis vaccine has been used for 50 years. J Clin Microbiol 2005;43:3681-7.

Caro V, Elomaa A, Brun D, Mertsola J, He Q, Guiso N. Bordetella pertussis, Finland and France. Emerg Infect Dis 2006;12:987-9.

Elomaa A, Advani A, Donnelly D, Antila M, Mertsola J, He Q, Hallander H. Population dynamics of *Bordetella pertussis* circulating in Finland and Sweden: neighbouring countries with different vaccination histories. Vaccine 2007;25:918-26.

3.6.3. *Chlamydia pneumoniae*

Project leader: Mirja Puolakkainen, MD, PhD

Description

The goals of this project are to analyze the pathogenesis of acute and chronic *C. pneumoniae* infection at cellular and molecular level, host cell responses upon infection and microbe-host cell interactions.

CD8+ T cells play an important role in protective immunity against experimental *C. pneumoniae* infection. KTL has designed different vaccine constructs and regimens to induce T cell immunity in this model. Immunization of mice with plasmid DNA and recombinant viral vector (SFV) expressing chlamydial proteins MOMP, Omp2 and Hsp60 was able to induce humoral and/or cellular immune response but only partial, if any protection against intranasal *C. pneumoniae* challenge. However, a *C. pneumoniae* protein obviously secreted by its type three secretion systems, chlamydial outer protein N (CopN, aka LcrE) can be used a vaccine. Bacillus-produced, heat-inactivated LcrE protein administered together with a potent adjuvant (LT) induced strong humoral and cellular immune response and significant level of protection in the experimental infection model.

Major achievements

1) CD8 epitopes were identified in several *C. pneumoniae* proteins using the genomic chlamydial sequence data and a computer-base epitope prediction method, and the corresponding peptides were used to immunize mice. Nineteen *C. pneumoniae*-derived peptides were identified as CD8 epitopes by their ability to induce cytotoxic response after peptide immunization. Seven of the identified epitopes were able to induce long-term peptide-specific CTL lines and three were natural epitopes presented by infected cells.

2) To identidy human CD8 epitopes, we have established an infection model in transgenic HHD mice expressing only human class I molecule (HLA-A2.1). It was observed that immunization with a whole chlamydial protein induced an HLA-A2.1-restricted peptide-specific cell line, indicating that the classical human class I molecule can support the development of murine CD8+ T cell response against a chlamydial protein.

3) The kinetics and protein specificity of the systemic and mucosal antibody response induced by intranasal *C. pneumoniae* infection in mice was assessed using recombinant *C. pneumoniae* proteins. After primary infection, the circulating antibodies recognized mainly Omp2 protein, whereas mucosal secretory IgA antibodies recognized Omp4 protein. After reinfection, also production of Hsp60- and MOMP-reacting circulating as well as Omp2- and Hsp60-reacting IgA antibodies was induced.

4) To elucidate critical mechanisms by which *C. pneumoniae* induces development of persistent infection in a human epithelial cell line, we have analyzed host cell transcriptional responses during acute and interferon-gamma induced persistent infection. The mRNA expression of nine host cell genes was shown to be differentially altered during persistent infection and some of these changes are also reflected in the corresponding proteins levels.

Key publications

Penttilä T, Vuola JM, Puurula V, Anttila M, Sarvas M, Rautonen N, Mäkelä PH, Puolakkainen M. Characterization of the immunity to *Chlamydia pneumoniae* induced by vaccination of mice with DNA vectors expressing a cytoplasmic protein (Hsp60) or outer membrane proteins (MOMP and Omp2). Vaccine 2001;19:1256-65.

Sarén A, Pascolo S, Stevanovic S, Dumrese T, Puolakkainen M, Sarvas M, Rammensee HG, Vuola JM. Identification of *Chlamydia pneumoniae* derived mouse CD8 epitopes. Infect Immun 2002;70:3336-43.

Tammiruusu A, Haveri A, Pascolo S, Lahesmaa R, Stevanovic S, Rammensee H-G, Sarvas M, Puolakkainen M, Vuola JM. Clearance of *Chlamydia pneumoniae* infection in H-2 class I-/- Human Leukocyte Antigen-A2.1 Monochain transgenic mice. Scand J Immunol 2005;62:131-9.

Tammiruusu A, Penttilä T, Sarvas M, Puolakkainen M, Vuola JM. Intranasal administration of Chlamydial outer protein N (CopN) induces partial protection against pulmonary *Chlamydia pneumoniae* infection in a mouse model. Vaccine 2007;25:283-90.

Mannonen L, Nikula T, Haveri A, Reinikainen A, Vuola JM, Lahesmaa R, Puolakkainen M. Upregulation of host cell genes during interferon-gamma induced persistent *Chlamydia pneumoniae* infection in HL cells. J Infect Dis 2007;195:212-19.

3.6.4. Hepatitis C virus - host cell interactions and cytokine signalling

Project leader: Ilkka Julkunen, MD, PhD and Krister Melen, PhD

Description

Hepatitis C virus (HCV) infection is an important viral pathogen with approximately 200 million cases world wide. In Finland, 1200-1800 new HCV cases have been detected annually during the last 15 years. The disease cures spontaneously only in rare cases (ca 15%). Presently the drug of choice for treating HCV infections is a combination therapy with ribavirin and IFN-a. However, HCV is relatively resistant to the antiviral therapy. To better treat and prevent HCV infections more information on the transmission, molecular epidemiology, pathogenesis and mechanisms of antiviral resistance of HCV is required. Also understanding the mechanisms of action of IFNs and other antiviral cytokines (such as TNF-a) is also important in further development of these substances as antiviral drugs.

Major achievements

1) One reason for HCV to remain chronic in humans is that the virus can downregulate the expression of host antiviral genes. We and others have shown that HCV-encoded proteases, NS2 and NS3 can directly inhibit host cell cytokine gene expression by interfering with the activation of multiple host signaling pathways involved in the production of antiviral and proinflammatory cytokines. These observations indicate HCV proteases (like in HIV) to be important targets for antiviral intervention.

2) HCV, especially the genotype 1 is relatively resistant to the antiviral actions of IFN-a. KTL has characterized the nuclear import mechanisms of IFN-a and TNF-a activated STAT and NF-kB transcription factors, respectively, which appear to be targets of intervention by HCV proteins. KTL has shown that the structural region of HCV, especially the core protein can interfere with the activation and nuclear import of STAT signalling molecules in IFN-a treated cells, which leads to reduced antiviral activity of IFNs in HCV protein expressing cells.

3) KTL has expressed and purified all HCV structural and nonstructural proteins (10 proteins), which enables to analyze their functions, biochemical and immunogenic properties. These reagents can be used for detailed analysis of humoral and cell-mediated immunity in HCV infected individuals and correlate immunological parameters with the efficacy of antiviral therapy as well as in individuals that cure spontaneously. Special emphasis has also been devoted to analyze the incidence and severity of HCV infection during pregnancy.

4) HCV project includes more detailed characterization of mechanisms involved in inhibition of host cell signalling pathways and innate immune responses by different HCV proteins. Recent development in establishing HCV strains that grow in cell culture will also enable more detailed studies on HCV-host interactions. Further analysis of mechanisms of resistance of different HCV genotypes or gene clones to antiviral therapy will also be carried out. This includes analysis of the effects of different HCV core gene clones on the IFN system. We will also continue to be involved in the epidemiology of HCV infection during pregnancy.

Key publications

Melén K, Kinnunen L and Julkunen I. Arginine/lysine-rich structural element is involved in IFN-induced nuclear import of STATs. J Biol Chem 2001;276:16447-55.

Keskinen P, Melén K and Julkunen I. Expression of structural proteins of HCV impairs IFN-a-mediated antiviral response. Virology 2002;299:164-71.

Melén K, Nyqvist M, Fagerlund R, Keskinen P, and Julkunen I. Expression of hepatitis C virus core protein inhibits interferon-induced nuclear import of STATs. J Med Virol 2004;73:536-47.

Fagerlund R, Kinnunen L, Julkunen I and Melén K. NF-kB is transported into the nucleus by importin a3 and a4. J Biol Chem 2005;280:15942-51.

Kaukinen P, Sillanpää M, Kotenko S, Lin R, Hiscott J, Melén K and Julkunen I. Hepatitis C virus NS2 and NS3/4A proteins are potent inhibitors of host cell cytokine/ chemokine gene expression. Virology J 2006;3:66.

3.6.5. Molecular biology, epidemiology and taxonomy of human picornaviruses

Project leaders: Tapani Hovi, MD, PhD and Merja Roivainen, PhD

Description

This is initially a spin-off project from the poliovirus (family: *Picornaviridae*) surveillance programme and later expanded to support the characterization of picornaviruses associated with respiratory infections. The main goal is to increase our understanding of the molecular biology, evolutionary patterns and strain variability of picornaviruses and of consequences of these phenomena to epidemiology, pathogenesis and molecular diagnosis of infections. Currently we are systematically studying enterovirus epidemiology exploiting different approaches to assess the relative prevalence of different types. A parallel topic is a proof-of-principle study on possibilities to enhance enterovirus immunogenicity by adsorption to polymeric microparticles.

Major achievements

1) Strong contribution to the scientific background and design of the current taxonomy of human enteroviruses and rhinoviruses (T.H. is a member of the Picornavirus Study Group of the International Committee on Taxonomy of Viruses). Final documentation for the close genetic relationship between enteroviruses and rhinoviruses, resulting in the recent joining of the two genera.

2) Identification and partial characterization of 3 new enterovirus types. Accumulation of an own gene bank comprising partial sequences of about 1000 independent enterovirus strains enabling efficient enterovirus identification service to laboratories in Finland, and to 12 other European countries in the context of poliovirus surveillance.

3) Systematic characterization, in several genomic regions, of prototype strains of all 100 human rhinovirus (HRV) serotypes revealing the division of HRV strains into 2 species plus an outlier serotype (HRV87) belonging to human enterovirus species D. Demonstration that, in spite of now being classified in the genus *Enterovirus*, HRV differ from the classical enteroviruses by less distinct segregation into genetically defined serotypes.

4) Identification of a capsid protein VP1 domain with a conserved amino acid sequence regulating the stability of capsid structure and relevant to early interactions of virus particle with host cell. Demonstration, in a collaborative project, that in the HRV - host cell interaction, the overall physicochemical surface pattern of the virus particle, rather than the exact amino acid sequence of capsid proteins, is critical for binding to receptor protein.

5) Demonstration of distinctly different patterns of evolution for enteroviruses ranging from coxsackievirus B4 with poliovirus-like co-circulation of several different genetic lineages to echovirus 30 showing a single major lineage evolving stepwise similar to influenzaviruses. Demonstration that in the evolution of human enterovirus B strains, capsid protein sequences

maintain the serotype identity, while genes encoding the non-structural proteins are subject to frequent exchange of genetic information between different serotypes through recombinations.

Key publications

Airaksinen A, Roivainen M, Hovi T. Coxsackievirus A9 mutants with enhanced or hindered A particle formation and decreased infectivity. J Virol 2001;75:952-60.

Savolainen C, Blomqvist S, Mulders M, Hovi T. Genetic clustering of all 102 human rhinovirus prototype strains - serotype 87 is close to human enterovirus 70. J Gen Virol 2002;83:333-40.

Vlasak M, Roivainen M, Reithmayer M, Goesler I, Laine P, Snyers L, Hovi T, Blaas D. The minor receptor group of human rhinovirus (HRV) includes HRV23 and HRV25, but the presence of lysine in VP1 HI loop is not sufficient for receptor binding. J Virol 2005;79:7389-95.

Laine P, Savolainen C, Blomqvist S, Andries K, Hovi T. Alignment of capsid protein VP1 sequences of all human rhinovirus prototype strains: conserved motifs and functional domains. J Gen Virol 2006;87:129-38.

Smura TP, Junttila N, Blomqvist S, Norder H, Kaijalainen S, Paananen A, Magnius LO Hovi T, Roivainen M. Enterovirus 94, a proposed new serotype in human enterovirus species D. J Gen Virol 2007;88:849-58.

3.6.6 HIV variability and molecular epidemiology

Project leader: Mika Salminen, PhD

Description

This line of research is divided into several subprojects which all utilise some aspects of viral variability and use virus genetic information. The research has resulted in spin-offs to produce useful tools for surveillance and diagnostics of hiv that have been incorporated into the national routine surveillance programme, but also achievements which are closer to basic science. The tools are based on original research findings and innovations done at KTL or by KTL researchers. Major subprojects are 1) development of PCR and sequencing based tools for studies of viral variation 2) development of standardised phylogenetic analysis-based classification schemes used for molecular epidemiological studies 3) development of novel non-culture based tools to clone and analyse complete hiv-genomes and their variation 4) development of totally novel *in silico* methods for the detection and mapping of genetic recombination among viruses 5) development of in house tools for antiretroviral (ARV) drug resistance mutation detection and clinical interpretation.

Major achievements

1) Development of routinely employed subtyping schemes that are used to type all hiv-strain samples sent to the national infectious disease registry strain collection. The information collected can be used to identify cases related to IDU and is also used as an independent predictor of importation of hiv. Using the methodology an outbreak of hiv among IDU in Finland could be shown to be clonal and recent. The typing scheme can be specifically used to identify and distinguish cases related to neighbouring area epidemics of both Russian and Estonian origin. In addition, strains originating from South-East Asia are easily distinguishable. Additionally, strain typing can be used for detailed analysis of overlaps between traditional transmission categories.

2) In 1995, development of a new *in silico* method that is today widely used to map recombination in viral sequences. The method (Bootscanning) has been extensively used in the field and has

strongly contributed to the scientific communitys understanding of hiv evolution and taxonomic classification, especially the strong role that co-infection, superinfection and recombination plays in hiv evolution. The method has been applied into both on-line and standalone computer software and is taught at several international advanced courses as a generalisable method. It has also been applied to evolutionary analysis of other viruses such as entero- and hantaviruses.

3) Cloning, sequencing and genetic characterisation of several reference strains of novel hiv subtypes and recombinant forms

4) Use of molecular epidemiological methods to characterise hiv epidemics in the neighbouring areas of North-Western Russia and the Baltic countries, particularly Estonia. This has made it possible to follow the impact of these major epidemics to the Finnish situation.

5) Together with the infectious disease policlinic at the University Hospital in Helsinki, the unit has developed in-house methods for the interpretation of ARV drug resistance mutations. These interpretations are used in day-to-day clinical management of drug treatment optimisation in Finland.

Key publications

Liitsola K, Ristola M, Holmstrom P, Salminen M, Brummer-Korvenkontio H, Simola S, Suni J and Leinikki P. An outbreak of the circulating recombinant form AECM240 HIV-1 in the Finnish injection drug user population. AIDS 2000;14:2613-5.

Salminen M. HIV inter-subtype recombination - consequences for the epidemic. AIDS Reviews 2000;2:178-89.

Wilbe, K., M. Salminen, T. Laukkanen, F. McCutchan, S.C. Ray, J. Albert, and T. Leitner, Characterization of novel recombinant HIV-1 genomes using the branching index. Virology 2003;316:116-25.

Zetterberg V, Ustina V, Liitsola K, Zilmer K, Kalikova N, Sevastianova K, Brummer-Korvenkontio H, Leinikki P and Salminen MO. Two viral strains and a possible novel recombinant are responsible for the explosive injecting drug use-associated HIV type 1 epidemic in Estonia. AIDS Res Hum Retroviruses 2004;20:1148-56.

Smolskaya T, Liitsola K, Zetterberg V, Golovanova E, Kevlova N, Konovalova N, Sevastianova K, Brummer-Korvenkontio H and Salminen MO. HIV epidemiology in the Northwestern Federal District of Russia: Dominance of HIV type 1 subtype A. AIDS Res Hum Retroviruses, 2006;22:1074-80.

3.6.7. Streptococcus pyogenes

Project leader: Jaana Vuopio-Varkila, MD, PhD

Description:

Diseases caused by the Lancefield group A *Streptococcus*, *S.pyogenes*, are among the most varied in terms of clinical spectra and severity, ranging from superficial infections such as pharyngitis to skin infections (impetigo, erysipelas, and cellulitis) and rarer life-treatening presentations such as toxic shock syndrome and necrotizing fasciitis. The organism is also responsible for nonsuppurative sequelae such as acute rheumatic fever and acute glomerulonephritis. A resurgence in interest in these diseases followed reports from the US and several countries within Europe of increasing numbers of cases of invasive disease during the late 1980s and beyond. Other ß-haemolytic streptococci, including Lancefield groups B, C and G, are also common infectious agents in humans.

The disease spectrum of group C and G streptococci resembles significantly that of group A. The research conducted at KTL focus on host and microbial factors, molecular epidemiology and clinical risk factors linked to severe and recurrent beta-haemolytic streptococcal infections. Research collaboration in Finland and abroad: Tampere University, Helsinki University, Karolinska Institute, Sweden, Health Protection Agency, UK, the Strep-EURO group (see below) and The Methodist Hospital Research Institute, Texas, USA.

Major achievements

1) The Strep-EURO "Severe Streptococcus pyogenes infections in Europe" (funded by EU RTD V framework) project conducted in 2003-2005 provided uniform epidemiological, microbiological and clinical data on severe GAS infections in 11 European countries. Although nation-wide coverage was not reached in all of the participating countries, this was the largest study ever conducted on severe GAS infections. A total of 5,586 cases were registered, among which there were 493 cases of streptococcal toxic shock and 306 of necrotising fasciitis. The overall mortality was 19%. These data highlight the importance of the disease. The main database of the project was managed and maintained at KTL. Several publications are currently in preparation.

2) Microbe related factors, such as M proteins, may be linked to severity of disease and as well as to risk of mortality and resurgence of disease. Genomic variation of the microbe may play a role in emergence and disappearance of certain circulating streptococcal clones over time. KTL has been able to show that that happens at least for both serotype M1 (*emm*1) and serotype T28 (*emm*28) strains.

3) In many countries, type M1 strains have associated with waves of severe infections, but only few individuals among those who contract the pathogen develop a serious infection. KTL has shown that anti-M protein antibodies are not often encountered in the healthy population, but anti-Sic protein (streptococcal inhibitor of complement) antibodies can arise very rapidly by positive selection in human populations during certain group A streptococcal epidemics.

4) KTL has participated in a Finnish Academy funded MICMAN-research programme during years 2003-2005. The focus was on the human and bacterial genome aspects linked to infection susceptibility and clinical disease spectrum. KTL studied both acute and recurrent streptococcal infections, and erysipelas served as the disease phenotype. KTL was able to identify more than 50 pedigrees with a history of erysipelas. The fine mapping of whole genome analysis is underway. Several publications are in preparation or submitted to international journals.

Key publications

Hoe NP, Cole R, Liu M, Kordari P, Dou S-J, Adams GJ, Palzkill T, Huang W, McLellan D, Hu M, Vuopio-Varkila J, Cate TR, Pichichero ME, Edwards KM, Eskola J, Low DE, Musser JM. Human immune response to streptococcal inhibitor of complement (Sic), a serotype M1 group A *Streptococcus* extracellular protein involved in epidemic waves. J Infect Dis 2000;182:1425-36.

Hoe NP, Vuopio-Varkila J, Vaara M, Grigsby D, Lorenzo D, Fu Y-X, Pan X, Nakashima K, Musser JM. Distribution of streptococcal inhibitor of complement variants in pharyngitis and invasive isolates in an epidemic of serotype M1 group A *Streptococcus* infection. J Infect Dis 2001;183:633-9.

Sumby P, Madrigal AG, Barbian KD, Porcella SF, Ricklefs SM, Virtaneva K, Sturdevant DE, Graham MR, Vuopio-Varkila J, Hoe NP, Musser JM. Emergence of Severe Invasive Group A *Streptococcus* infections by horizontal gene transfer and clonal replacement. J Infect Dis 2005;192:771-82.

Lamagni TL, Efstratiou A, Vuopio-Varkila J, Jasir A, Schalén C, Strep-EURO. The epidemiology of severe Streptococcus pyogenes associated disease in Europe. Eurosurveillance Monthly 2005;10:179-84.

Siljander T, Toropainen M, Muotiala A, Hoe NP, Musser JM, Vuopio-Varkila J. emm typing of invasive T28 group A streptococci, 1995-2004, Finland. J Med Microbiol 2006; 55:1701-6.

3.6.8. Epidemiology of food related bacteria

Project leader: Anja Siitonen, PhD and Kaisa Haukka, PhD

Description

Campylobacter are the most common bacteria causing intestinal infections in humans with 3500 to 4000 annual cases in Finland. However, their epidemiology and sources are still largely unknown. According to the new Zoonoses Directive, *Campylobacter* is included in the list of zoonotic bacteria of statutory monitoring. It aims at obtaining new information about phenotypic and molecular characteristics of a large set (2600 strains) of patient isolates collected in collaboration with clinical microbiology laboratories from 10 hospital districts over a three-year period (June 2002 - July 2005). Molecular typing methods have been developed for epidemiological investigations. These include a PCR-RFLP assay and pulsed-field gel electrophoresis (PFGE). Analyses of the collected material are progressing and comparison of the phenol- and molecular types of human and poultry isolates have been started in collaboration with the Finnish Food Safety Authority Evira.

More than 500 *Yersinia enterocolitica* (YE) infections are notified annually in Finland. In addition, several infections by YE -like *Yersinia* species and one or several large epidemics (30-400 infected people in each), mainly caused by *Yersinia pseudotuberculosis* but sometimes also by *Y. enterocolitica*, are detected every year. In general, *Y. pseudotuberculosis* strains isolated from humans are virulent but the degree of virulence of YE and YE-like strains varies. In the current YE project we identify clinical YE and YE-like isolates by their phenotypic and genotypic characteristics, their source, and the symptoms they cause to patients, as well as the potential sequelae. The laboratory-based identification results are combined with the epidemiological case-control study in order to assess the clinical significance of the various types and species of the isolates as well as risk factors for YE infection. With current funding the project will continue until the end of 2008, when we expect to provide the Finnish clinical microbiology laboratories with new guidelines for isolation and recognition of clinically significant *Yersinia* isolates. For *Y. pseudotuberculosis* we develop improved methods for comparing human, animal, food and environmental isolates to track down the transmission routes as reliably as possible.

FOOD-BUG research project

FOOD-BUG is an acronym for the project entitled "Infections caused by food-borne bacteria - Retrospective study on association of morbidity and mortality of Finns, prospective study on tracing of domestic cases and risk assessment". The project is part of the 4-year-long multidisciplinary Research Programme on Nutrition, Foods and Health (ELVIRA) coordinated by the Academy of Finland. In the project we study the risks of food-borne bacteria to public health in general, as well as trace and characterize salmonella and EHEC strains in particular. *Salmonella* is one of the most commonly reported food-borne pathogens and enterohaemorrhagic *Escherichia coli* (EHEC) is one of the most dangerous food-borne pathogens. The project has three parts: 1) a retrospective registry-based study, 2) a prospective real-time surveillance and population-based study, and 3) risk assessment.

The retrospective study will determine the morbidity and mortality associated with food-borne gastrointestinal infections caused by species of *Salmonella*, *Campylobacter*, *Shigella* or *Yersinia* in Finland since 1995 using register linkage to control for comorbidities. In the prospective study we will trace the source and transmission routes of domestic food-borne *Salmonella* and EHEC infections by using various phenotypic and molecular biology techniques, by case-control studies, and by comparing human isolates with the isolates obtained from the animal and food sources. Thus, the most common sources and transmission routes of the pathogens should be revealed in this project. Finally, a new model for risk assessment will be created. The model will combine the results obtained with the novel laboratory techniques together with data from the National Register of Infectious Disease and other registers, food-borne outbreaks and food production estimating the total risk of a Finnish consumer to get salmonella or EHEC from food available in Finland. Knowing the true impact of the food-borne infections will give us a chance to model the effect and cost-benefits of possible new precautionary actions for the public health. The project started in 2007.

Major achievements

1) PCR analyses revealed that the phenotypic identification test (hippurate hydrolysis), currently used in routine diagnostic laboratories for *Campylobacter* species identification, gives 5% false-positive and 11% false-negative results. Standardization of the test eliminated false-positive results. This finding suggests that reliable species identification of *Campylobacter* strains can be achieved with a combined approach: a standardized hippurate test is done in routine laboratories and hippurate-negative strains are sent to reference laboratory for verification by PCR.

2) Data on travelling history of the patients combined with the epidemiological and typing data of the strains indicate that the seasonal peak of *Campylobacter* infections in summer is mostly caused by domestic *Campylobacter jejuni* strains. We have also found that the distribution of serotypes of the domestic strains differs from that of the strains of foreign origin. This finding is important and will be of great help when the sources of infections are traced.

3) In 2006, 462 YE and YE-like strains were received from 10 clinical microbiology routine laboratories located in different parts of Finland. The majority (65 %) of all these strains belonged to YE biotype 1A, which is non-invasive and traditionally considered apathogenic. Only 18 % of the strains belonged to YE bio-/serotypes 4/O:3 and 2-3/O:9 that are generally considered pathogenic. The remaining 17 % consisted of other *Yersinia* species. For the first time now, we have a clear picture on the distribution of different *Yersinia* types among Finnish *Yersinia* findings, since in the National Infectious Diseases Registry all the isolates are mainly registered merely as *Yersinia*. The symptoms of the patients with either biotype 1A or 4/O:3 of YE finding were rather similar concerning abdominal pain and diarrhoea but there was a statistically significant difference in appearance of fever in the patients with YE 4/O:3 finding and vomiting in the patients with YE BT 1A finding.

4) During several consecutive years, *Y. pseudotuberculosis* strains that are indistinguishable from each other have caused large epidemics. These epidemic strains are similar to the ones found in vegetable and environmental samples.

Key publications

Fredriksson-Ahomaa M, Hallanvuo S, Korte T, Siitonen A, Korkeala H. Correspondence of genotypes of *Yersinia enterocolitica* bioserotype 4/O:3 strains from human and porcine sources. Epidemiol Infect 2001;127:37-47.

Hallanvuo S, Skurnik M, Asplund K, Siitonen A. Detection of a novel repeated sequence useful for epidemiological typing of pathogenic Yersinia enterocolitica. Int J Med Microbiol 2002;292:215-25.

Nakari U-M, Laaksonen K, Korkeila M, Siitonen A. Comparative typing of *Campylobacter jejuni* by heat-stable serotyping and PCR-based restriction fragment length polymorphism analysis. J Clin Microbiol 2005;43:1166-70.

Hallanvuo S, Peltola J, Siitonen A. Simplified phenotypic scheme evaluated by 16S rRNA sequencing for differentiation between *Yersinia enterocolitica* and *Y. enterocolitica*-like species. J Clin Microbiol 2006; 44:3:1077-80.

3.6.9. Epidemiology of reactive arthritis caused by bacteria

Project leaders: Anja Siitonen PhD

Description

ReA is a non-purulent joint inflammation, which can be triggered by infections in the gastrointestinal or urogenital tracts. Enteric bacterial pathogens, such as different serotypes of *Salmonella enterica*, *Campylobacter jejuni, Yersinia* spp., and *Shigella flexneri*belong to the frequent triggering agents. The first-mentioned three bacterial species are the most common bacterial causes of enteric infections acquired domestically as well as associating with travelling abroad, the latter one is mainly from travellers abroad.

The prevalence of antigen HLA-B27 in Finns is higher (14%) than in other European populations (5 - 9%), and it has been estimated that HLA-B27 positive subjects have about 20 fold risk to develop ReA when infected with triggering agent compared to HLA-B27 negative subjects. We have investigated the occurrence and clinical picture of ReA in Finns triggered by the pathogens mentioned above. For that, nation-wide population-based case-control studies and studies associated with outbreak situations have been carried out. At present, data on about 1000 patients with salmonellosis are being analyzed, and we hope to get the answers e.g. to the following questions: 1) does the antimicrobial treatment of an outpatient effect on the development of ReA and other musculoskeletal symptoms, 2) are there immunological or genetic markers that could be exploited in predicting the development of ReA in a patient. These studies have been carried out in collaboration with clinicians from the Helsinki University Hospital.

Major achievements

1) Reactive arthritis occurred in 7% of the Finns after *Campylobacter* infection, with annual incidence of 43/1 000 000 population. The clinical picture was mild. HLA-B27 antigen was positive in 14% of the patients with ReA.

2) Reactive arthritis occurred in 7% of the Finns after *Shigella* infection, with annual incidence of 1.3/1 000 000 population. *S. flexneri* has previously been reported to trigger ReA but we showed that also *S. sonnei* and *S. dysenteriae* can do that. HLA-B27 antigen was positive in 36% of the patients with ReA.

3) Reactive arthritis occurred in 12% of the patients who became ill in an widespread outbreak caused by *Y. pseudotuberculosis* O:3 strain in 1998. The clinical picture was severe.

Key publications

Hannu T, Mattila L, Siitonen A, Leirisalo-Repo M. Reactive arthritis following an outbreak of *Salmonella* Typhimurium phage type 193 infection. Ann Rheum Dis 2002;61:264-6.

Hannu T, Mattila L, Rautelin H, Pelkonen P, Lahdenne P, Siitonen A, Leirisalo-Repo M. Campylobacter-triggered reactive arthritis: a population-based study. Rheumatology 2002;41:312-8.

Hannu T, Mattila L, Nuorti P, Ruutu P, Mikkola J, Siitonen A, Leirisalo-Repo M. Reactive arthritis after an outbreak of *Yersinia pseudotuberculosis* serotype O:3 infection. Ann Rheum Dis 2003;62:866-9.

Hannu T, Mattila L, Siitonen A, Leirisalo-Repo M. Reactive arthiritis attributable to *Shigella* infection: a clinical and epidemiological nation-wide study. Ann Rheum Dis 2005;64:594-8.

3.6.10. Urinary tract infections

Project leader: Anja Siitonen, PhD

Description

Urinary tract infections (UTIs) burden the health care services more than any other bacterial disease. *E. coli* is the most common cause of UTI both in children and adults. The research on *E. coli* strains isolated from UTIs and other extra-intestinal infections have belonged to the long-term research programmes of the KTL since 1970's and until 2002. The studies have mainly focused on virulence-associated characteristics of urinary and blood isolates of *E. coli* with special aims to 1) identify the virulence factors which individually or in combination associate with acute cystitis, pyelonephritis or persistent UTIs and 2) obtain detailed knowledge of P-fimbrial genotypes of the *E. coli* strains that cause acute pyelonephritis, urosepsis and recurrent UTI in subjects with and without predisposing factors for UTI. The knowledge of the virulence-associated characteristics of the particular *E. coli* strains was also exploited in *in vitro* studies where coating materials for urinary catheters and medical stents were developed. The studies were carried out in collaboration with clinicians and other experts working at the Finnish universities and at the University of Michigan School of Public Health.

Major achievements

1) In the majority of infants, after their first episode of pyelonephritis, recurrent UTIs were caused by genetically indistinguishable or highly similar *E. coli* strains. This suggested that recurrent UTIs are relapses rather than true reinfections caused by new strains from colonic flora of the patient.

2) *E. coli* without any of the *papG* alleles encoding P fimbriae, were shown to be common cause of UTIs in infants with major urinary tract abnormalities. In contrast, *E. coli* with P fimbriae encoded by class II *papG* alleles caused UTIs in infants with normal anatomy. These *E. coli* were also able to cause pyelonephritis, urosepsis or bacteremia in non-compromised adults. These diagnostic data can be utilized when the length, whether short- or long-term, of the treatment is considered.

3) KTL described the epidemiological association of the *usp* (uropathogenic specific protein that is *Vibrio cholerae zot* gene homologue), *iha*(IrgA homologue adhesin that is a nonhemagglutinating adhesin) and $iroN_{E.\ coli}$ (a catechole siderophore receptor homologue) genes with virulence of uropathogenic *E. coli*. In comparison with normal faecal isolates, the*usp*gene occurred more frequently in isolates from patients with pyelonephritis ($P<0.001$), in periurethral isolates ($P=0.001$), and in isolates from patients aged 40 - 65 years ($P=0.004$). In contrast, the $iroN_{E.\ coli}$ gene was more common among urinary isolates than faecal isolates ($P<0.001$). We also found that the *iha* gene did not associate with UTI.

4) KTL demonstrated that the expression of a novel fimbrial type, *matB* (meningitis-associated and temperature regulated), was associated with the O18ac:K1:H7 clonal group of *E. coli*, which cause newborn septicaemia and meningitis.

5) Silver nitrate or ofloxacin blended caprolactone-L-lactide copolymer coating was found to prevent *in vitro* the adherence of various uropathogens onto certain biodegradable prostatic stents. This finding will bring real benefits for patients carrying e.g. permanent catheters.

Key publications

Jantunen M, Siitonen A, Koskimies O, Wikström S, Kärkkäinen U-M, Salo E, Saxén H. Predominance of class II *papG*allele of *Escherichia coli* in pyelonephritis in infants with normal urinary tract anatomy. J Infect Dis 2000;181:1822-4.

Jantunen M, Saxén H, Lukinmaa S, Ala-Houhala M, Siitonen A. Genomic identity of pyelonephritogenic *Escherichia coli* isolated from blood, urine and feces of children with urosepsis. J Med Microbiol 2001;50:650-2.

Jantunen M, Siitonen A, Ala-Houhala, Ashorn P, Föhr A, Koskimies O, Wikström S, Saxén H. Predictive factors associated with significant urinary tract abnormalities in infants with pyelonephritis. Pediatr Infect Dis 2001;20:597-601.

Pouttu R, Westerlund-Wikström B, Lång H, Alsti K, Virkola R, Saarela U, Siitonen A, Kalkkinen N, Korhonen TK. matB, a common fimbrillin gene of *Escherichia coli* expressed in a genetically conserved, virulent clonal group. J Bacteriol 2001;183:4727-36.

Jantunen ME, Saxén, Salo E, Siitonen A. Recurrent urinary tract infections at infancy: relapses or reinfections? J Infect Dis 2002;185:375-79.

3.7. Subacute complications and long-term consequesces of infections and inflammation

Association of microbes and human beings is known to show several different patterns as regards time between onset of infection and presentation of clinical symptoms. The term "acute infection" usually refers to a disease with acute symptoms. Termination of symptoms does not, however, always mean that the infectious agent has been eliminated. Rather, it may persist in the body for extended periods up to the rest of life, and may cause a disease similar to or completely different from the possible acute phase disease. In principle, it is also possible that an acute infection triggers a pathogenetic chain of events in the body and thus contributes to the etiology of a disease even without persisting in the body itself. In some cases subacute complications of an acute infection or different disease later in life are well documented (enteric bacteria - reactive arthritis; hepatitis B and C - chronic hepatitis and hepatocellular carcinoma; papillomaviruses - carcinoma of cervix uteri), while in others further research is needed to confirm the association (various microbes - cardiovascular disease; enteroviruses - type 1 diabetes; respiratory infections - asthma etc.). This research is important because, if even a fraction of these common chronic diseases would turn out to be caused by infections, vaccination or antimicrobial treatment could be used to prevent a significant part of the disease. In the following, major KTL projects relevant to this topic will be presented.

3.7.1. Chlamydia pneumoniae -infections and chronic diseases

Project leader: Maija Leinonen, PhD

Description

Chlamydia pneumoniae is a common respiratory pathogen and obviously everybody gets infected at least once during the life time. Persistent *C. pneumoniae* infection has been associated to several chronic disease processes like asthma, chronic obstructive pulmonary disease, lung cancer and atherosclerotic diseases. Evidently, both genetic and environmental factors determine the outcome of infection in the host. The objectives of the group have been to study pathogenetic mechanisms in animal models and cell cultures, to develop methods for the diagnosis of chronic infections, to find drugs or combinations of drugs effective against chronic infection and to study genetic susceptibility to infection. The studies on the association of persistent *C. pneumoniae* infection with cardiovascular diseases and asthma have been done in collaboration with Universities of Oulu and Helsinki, Oulu and Helsinki University Hospitals and Karolinska Institute, Sweden.

Major achievements

1) Treatment of acute *C. pneumoniae* infection in mice with different antibiotics prevents atherosclerotic lipid changes in aorta, but has no effect on chronic infection.

2) Both lipophilic simvastatin and several flavonoids decrease pulmonary infection in mice. Several flavonoids, aspirin and rapamycin affect chlamydial growth in cell cultures.

3) A novel type EIA method for quantification of chlamydial lipopolysaccharide (cLPS) in serum has been developed. cLPS concentrations during acute coronary event correlate with acute phase proteins (CRP and SAA) and troponin T (marker of myocardial damage) in Finnish and Swedish patients. The individual susceptibility of monocyte-derived macrophages is highly variable and sex-dependent. Several gene polymorphisms, e.g. in CD14, MBL2 and GPRA (NPSR1, asthma gene) genes affect the susceptibility to *C. pneumoniae* infection.

4) In North Finland Birth Cohort, *C. pneumoniae* antibodies and slightly elevated CRP levels (hsCRP, marker of low-grade systemic inflammation) are associated with obesity and markers of metabolic syndrome and *C. trachomatis* antibodies and hsCRP affect reproductive health

5) C. pneumoniae infection, but not *Actinobacillus actinomycetemcomitans*, induces liver steatosis in mice and rabbits

Key publications

Huittinen T, Leinonen M, Tenkanen L, Virkkunen H, Mänttäri M, Palosuo T, Manninen V, Saikku P. Synergistic effect of persistent *Chlamydia pneumoniae* infection, autoimmunity, and inflammation on coronary risk. Circulation 2003;107:2566-70.

Törmäkangas L, Erkkilä L, Korhonen T, Tiirola T, Bloigu A, Saikku P, Leinonen M. Effects of repeated *Chlamydia pneumoniae* inoculations on aortic lipid accumulation and inflammatory response in C57BL/6J mice. Infect Immun 2005;73:6458-63

Erkkilä L, Jauhiainen M, Laitinen K, Haasio K, Tiirola T, Saikku P, Leinonen M. Effect of simvastatin, an established lipid-lowering drug, on pulmonary *Chlamydia pneumoniae* infection in mice. Antimicrob Agents Chemother 2005;49:3959-62.

Alvesalo J, Vuorela H, Tammela P, Leinonen M, Saikku P, Vuorela P. Inhibitory effect of dietary phenolic compounds on *Chlamydia pneumoniae* in cell cultures. Biochem Pharmacol 2006;71:735-41.

Tiirola T, Sinisalo J, Nieminen MS, Silvennoinen-Kassinen S, Paldanius M, Saikku P, Jauhiainen M, Leinonen M. Chlamydial lipopolysaccharide is present in serum during acute coronary syndrome and correlates with CRP levels. Atherosclerosis 2006; Sep 13; Epub.

3.7.2. Chlamydia trachomatis infection and tubal infertility

Project leader: Heljä-Marja Surcel, PhD

Description

Occurrence of sexually transmitted *Chlamydia trachomatis* (CTR) infection increases steadily in western countries and in Finland especially in young population and is considered as the most important causative agent of pelvic inflammatory disease, adverse pregnancy outcome and tubal factor fertility (TFI) in women. Our research is focused on immunopathogenesis of CTR induced TFI. We study CTR specific cell mediated immune responses including gene polymorphism and secretion of the cytokines that are central in regulating host responses to CTR. Epidemiologic analysis of chlamydial seroprevalence over 1983-2007 and linkage of this data with the incidence data (Hospital Discharge Register) of the CTR associated complications will give population based information for the causal role of CTR and female reproductive tract morbidity. The study is performed in close collaboration with Helsinki University Hospital and is supported by EVO grants of HUS and participates in EpiGenChlamydia consortium (EU proposal No 037637).

Major achievements

1) Immune response to *C. trachomatis* or to chlamydial heat shock protein 60 (CHSP60) is found as genetically regulated cytokine secretion profiles (Interleukin-10 and Interferon-γ). Especially IL-10 -1082 polymorphism is strongly associated with the intensity of CTR specific cell mediated immune response and secretion of proinflammatory cytokines IFN-γ and TNF-α, which may be linked with tissue injury leading to TFI.

2) TFI prediction model which is generally based on CTR specific antibody analysis, can be improved by combining tests for humoral and cell mediated response to chlamydial antigens. The prediction model is valuable in clinical diagnostics and management of patients referred for subfertility.

Key publications

Kinnunen A, Molander P, Laurila A, Rantala I, Morrison R, Lehtinen M, Karttunen R, Paavonen J, Surcel H-M. C. trachomatis reactive T lymphocytes in genital tract tissue specimens. Hum Reprod 2000;15:1484-9.

Kinnunen A, Surcel H-M, Lehtinen M, Karhukorpi J, Tiitinen A, Halttunen M, Bloigu A, Morrison RP, Karttunen R, Paavonen J. HLA-DQ alleles and interleukin-10 polymorphism associated with *C. trachomatis* -related tubal infertility: a case control study. Hum Reprod 2002;17:2073-8.

Kinnunen A, Surcel H-M, Halttunen M, Tiitinen A, Morrison RP, Morrison SG, Koskela P, Lehtinen M, Paavonen J. C. trachomatis heat shock protein-60 induced interferon-g and interleukin-10 production by peripheral blood lymphocytes in infertile women. Clin Exp Immunol 2003;131:299-303.

Tiitinen A, Surcel H-M, Halttunen M, Birkelund S, Bloigu A, Christiansen G, Koskela P, Morrison SG, Morrison RP, Paavonen J. C. trachomatis and chlamydial heat shock protein 60 specific antibody and cell mediated responses predict tubal factor infertility. Hum Reprod 2006;21:1533-8.

Öhman H, Tiitinen A, Halttunen M, Birkelund S, Christiansen G, Koskela P, Lehtinen M,Paavonen J, Surcel H-M. IL10 polymorphism and cell mediated immune response to *C. trachomatis*. Genes and Immun 2006;7:243-9.

3.7.3. Enterovirus infection and chronic diseases

Project leader: Merja Roivainen, PhD

Description

The large collaborative prospective cohort studies carried out in Finland suggest that common enterovirus infections typically associated with acute diseases are risk factors for chronic diseases, like type 1 diabetes (T1D) and myocardial infarction. In the case of T1D, enterovirus infections appear to be able to initiate or facilitate the pathogenetic processes progressively leading to type 1 diabetes, and sometimes also to precipitate overt clinical disease. We have been concentrating on mechanisms by which enteroviruses are capable of destroying insulin producing ß-cells, a phenomenon characteristic of the disease.

Major achievements

1) In a collaborative study the first documented report of enterovirus infection in pancreatic islets of T1D patients. The finding suggests that during systemic EV infections, the virus may reach pancreatic islets and cause direct beta-cell damage.

2) Demonstration of a definite islet cell tropism of enterovirus infections in humans and an important species difference between men and mice in the cell type specificity of pancreatic enterovirus infection. In experimental infections in mice, the coxsackieviruses infect the exocrine tissue, in particular, while even in lethal cases the islets remain unaffected.

3) Demonstration of susceptibility of primary human insulin-producing beta-cells kept in culture to infections caused by several enterovirus serotypes, representing different genetic subgroups and known to act through a number of different receptor families. Thus, human islets in culture provide an excellent model for studies on pathogenesis of T1D, and to determine changes in islets that enteroviruses may cause.

4) Systematic characterization of prototype strains of EVs for beta-cell tropism revealed that consequences of virus replication on beta-cell survival and beta-cell specific function appear to be strongly serotype-dependent ranging from rapid cytolysis coinciding with the severe functional damage of the surviving cells to subtle morphological changes sometimes associated with enhanced insulin release after proper stimuli. However, analyses of field isolates revealed that all studied serotypes appear to include strains with the definite capability to damage beta cells.

5) Identification of cell surface proteins of human beta-cells recognized by the selected enteroviruses as their receptors. The receptor specificity of islet cell-replicating echoviruses remained to be undiscovered since no evidence was found for the cell surface expression of the decay-accelerating factor known to act as a receptor for several echoviruses in established cell lines.

Key publications

Roivainen M, Rasilainen S, Ylipaasto P, Nissinen R, Ustinov J, Bouwens L, Eizirik D, Hovi T, and Otonkoski T. Mechanisms of coxsackievirus induced damage to human pancreatic beta cells. J Clin Endocrinology and Metabolism 2002;85:1-9.

Roivainen M, Ylipaasto P, Savolainen C, Galama J, Hovi T, Otonkoski T. Functional impairment and killing of human beta cells by enteroviruses - The capacity is shared by a wide range of serotypes, but the extent is a charachteristic of individual virus strains. Diabetologia 2002;45:693-702.

Ylipaasto P, Klingel K, Lindberg M, Otonkoski T, Kandolf R, Hovi T, Roivainen M. Enterovirus infection in human pancreatic islet cells. Islet tropism in vivo and receptor involvement in cultured islet beta-cells. Diabetologia 2004;47:225-239.

Al-hello H, Davydova B, Smura T, Kaijalainen S, Ylipaasto P, Saario E, Hovi T, Rieder E, Roivainen M. Phenotypic and genetic changes in coxsackievirus B5 following repeated passage in mouse pancreas in vivo. J Med Virol 2005;75:566-74.

Ylipaasto P, Kutlu B, Rasilainen S, Rasschaert J, Salmela K, Teerijoki H, Korsgren O, Lahesmaa R, Hovi T, Eizirik DL, Otonkoski T, Roivainen M. Global profiling of coxsackievirus- and cytokine-induced gene expression in human pancreatic islets. Diabetologia 2005;48:1510-1522.

3.7.4. Human papillomaviruses and cervical cancer

Project leader: Matti Lehtinen, MD, PhD

Description

Studies on the etiology and prevention of high risk (hr) human papillomavirus (HPV) associated genital cancer have been conducted at the KTL Departments of Infectious Disease Epidemiology, and Microbiology and Immunology (Oulu unit) in collaboration with University of Tampere, where the project leader has had a part time position. These studies comprise: 1) Evaluation of relative risk and population atributable frcation of hrHPVs in cervical and other anogenital cancers, 2) Design and conduction of long-term immunogenicity and efficacy studies on hrHPV vaccination, and 3) Design, modelling and conduction of phase IV, effectiveness studies on hrHPV vaccination.

Major achievements

1) The project leader was the founder and first coordinator of the Nordic Biological Specimen Banks for Cancer Causes and Control consortium, which conducted the first and largest longitudinal epidemiological studies on hrHPV infections as causes of cervical cancer, other anogenital cancers and head-neck cancers. In the hierarchy of evidence these studies comprise an important step between cross-sectional case-control studies and intervention studies. Being population based, these studies enabled unbiased determination of the PAF of hrHPVs in the anogenital cancers. This has been pivotal for the design of intervention studies. These studies also showed that natural infections with low risk HPV types protects against cervical cancer - indicating the potential of HPV vaccination.

2) The project leader has been the principal investigator of two Merck&Co. Inc. and three GSK Biogicals sponsored phase II - Phase III vaccination studies. The superb immune response of early adolescents compared to older women, and highly efficient boostering after 5 years have been demonstrated. To enable determination of vaccine efficacy (VE) not only against hrHPV infection and associated cancer precursors, phase III studies with long-term follow-up were designed. These were conducted in a population-based fashion and with linkage to country-wide Finnish Cancer Registry. At present 3 500 HPV16/18 vaccinated, 3500 placebo vaccinated, and 17 000 unvaccinated young women comprise a joint cohort for the determination of HPV vaccine efficacy against cervical cancer. 3) Since it was already some time ago likely that hrHPV vaccines will be highly efficacious at the individual levels it was important to start to design and model phase IV

study on the effectiveness of HPV vaccination so that this could be undertaken at the time of vaccine licensure in "uncontaminated" populations of early adolescents. Population-based Finnish data on sexual behaviour changes, HPV prevelance/incidence trends and cervical cancer incidence trends during the last 25 to 35 year have been utilized in the modelling. A phase IV study involving 60 000 Finnish early adolescents on the effectiveness of vaccinating early adolescent girls or both girls and boys has started in Finland. It is very important that the population level safety (type-replacement of hrHPV types following vaccination) is being evaluated monitored, partially based on the distribution of hrHPV and cervical cancer susceptibility genes in Finland.

3) Design and conduction of phase II (immunogenicity), phase III (efficacy) and phase IV (effectiveness) studies on HPV vaccination. Ongoing long-term follow-up of HPV vaccine efficacy against cervical cancer in a joint cohort of 22 000 originally 16-19 young women, and start of a phase IV effectiveness study involving 60 000 early adolescents.

Key publications

Mork J, Lie A-K, Glattre E, Clark S, Hallmans G, Jellum E, Koskela P, Moller B, Pukkala E, Schiller J, Wang Z, Youngman L, Lehtinen M, Dillner J. A prospective study on human papillomavirus as a risk factor for head and neck cancer. N Engl J Med 2001;344:1125-31.

Lehtinen M, Pawlita M, Zumbach K, Hakama M, Jellum E, Koskela P, Lie AK, Luostarinen T, Paavonen J, Pukkala E, Sigstad E, Thoresen S, Dillner J. Evaluation of antibody response to human papillomavirus early proteins in women who developed cervical cancer 1-20 years later. Am J Obstetr Gynecol 2003;188:49-55.

Lehtinen M, Herrero R, Mayaud P, Barnabas R, Dillner J, Paavonen J, Smith PG. Studies to assess long-term efficacy and effectiveness of HPV vaccination in developed and in developing countries. Vaccine 2006;24:233-41.

Barnabas R, Laukkanen P, Koskela P, Kontula O, Lehtinen M, Garnett G. The epidemiology of HPV16 and cervical cancer in Finland and the potential of vaccination: mathematical modelling analyses. PLoS Medicine 2006;3:e138.

Lehtinen M, Kaasila M, Pasanen K, Patama T, Palmroth J, Laukkanen P, Pukkala E, Koskela P. Seroprevalence ATLAS of HPV infections in Finland in the 1980's and 1990's. Int J Cancer 2006;120:2612-9.

3.7.5. Periodontitis

Project leader: Eija Könönen, DDM, PhD

Description

The oral cavity is an important portal of entry for various microorganisms to other sites of the body, which can cause some adverse effects on the general health. Persistent infections in the mouth are of public health concern by exposing an individual to an increased risk for several types of chronic disorders/diseases, including cardiovascular diseases, metabolic disorders, infections of the respiratory tract, and deteriorated birth outcome. Periodontitis is a chronic infection in tooth-supporting tissues. Epidemiological data from different parts of the world have revealed that periodontitis is among the most important conditions affecting the oral health in adult-aged populations. Biological mechanisms which could explain the plausible relationship between periodontitis and chronic systemic disorders/diseases include direct effects of periodontal pathogens and inflammatory mediators triggered by those pathogens released to circulation, and mounted immune response to them. In two national population-based surveys, 'Health 2000' and 'Finrisk 2007', KTL is investigating these above-mentioned aspects.

Major achievements

1) In 'Health 2000', in addition to blood, oral specimens were collected from subjects representing the population aged 30 years or more steadily living in southern Finland as well as from subjects in other parts of Finland attending a satellite study on cardiovascular events in the university central hospitals. For the study, new methods have been set up, including multiplex PCR and quantitative PCR, to perform microbiological analyses. The present study group includes researchers with various expertise areas (periodontology, microbiology, biochemistry, epidemiology, cardiology, dental radiology).

2) A recently published study on carriage rates of periodontal pathogens in adults living in southern Finland presents the first true population-based data in the current literature. The results suggest that distinct species have a different carriage profile, depending on variables, such as age, educational level, and periodontal status.

3) In a satellite study SOKRAS of 'Finrisk 2007'on fat and sugar metabolism, oral samples have been collected from study subjects aged 25-74 years for analyses of microbiology and selected inflammatory markers. A clinical examination will be conducted later this year to gather detailed information on periodontal health status.

Key publications

Könönen E, Paju S, Pussinen PJ, Hyvönen M, Di Tella P, Suominen-Taipale L, Knuuttila M. Population-based study on salivary carriage of periodontal pathogens in adults. J Clin Microbiol 2007;45: Jun 13 Epub ahead of print.

4. RESOURCES

A substantial part of all expenses of KTL, as a research institute under the Ministry of Social Affairs and Health, is covered by a dedicated allocation in the governmental budget, annually decided upon by the Finnish parliament.

The total sum, excluding vaccine purchases for the national programme but including rents for working facilities, has increased from about 26 million in 2000 to about 35 million Euros in 2006. Most of the increases are based on transfer of units from other institutes or starting new units in KTL outside the CD cluster.

In KTL, Director General annually decides upon distribution of this governmental budget money to the departments. The direct budgetary support to the CD cluster has remained rather constant through the study period, presently being slightly less than 8 million euros or 22 – 23% of all KTL basic budget money. These sums include salaries for persons working in the CD cluster departments, and running costs (not institutional overheads or administration).

Although the departments have relatively much freedom in deciding how to use this basic budget money, the salaries are centrally strictly regulated in KTL and e.g. hiring new persons for permanent positions is based on decisions of the DG. The director of a department again annually decides how the basic budget money is divided between different units or research groups in his or her department. The basic budget money is mostly used for various public health functions and for maintaining the research infrastructure rather than for direct research costs, but the departments show variation here to some extent.

On top of the basic budget money, research groups and scientists at KTL are entitled and recommended to search for outside money to cover the costs of desired research activities. The Academy of Finland, TEKES (a governmental body for technology advancement), national and international foundations, and European Commission are major sources of research grants in the CD cluster. Research contracts with industry are also used for certain topics.

The proportion of outside money varies quite a lot between different departments and units, largely because of the varying nature of main activities. Outside resources for public health functions are much more difficult to find but the Ministry of Social Affairs and Health annually allocates KTL/CD about 0.56 million Euros for methods development, epidemiological studies and other public health relevant projects. Support to some activities has also been obtained from EC or WHO.

The following tables and figure show trends in costs and person-years since year 2000 (Source: Annual Reports of KTL). Costs here include institutional overheads due to rents, administration and basic services.

Year	KTL basic budget k€	KTL total costs k€	CD cluster total costs k€	Percentage CD/KTL	CD person-years
2000	25,633	43,515	15,441	35	283
2001	26,721	44,609	17,054	38	286
2002	27,745	48,037	17,737	37	289
2003	28,855	47,370	17,354	37	287
2004	33,387	52,198	17,326	33	279
2005	34,201	53,818	18,576	35	296
2006	35,279	57,230	20,085	35	321

The break down of person years dedicated to and source of direct costs in the four departments of the KTL CD cluster is available from years 2005 and 2006, respectively. One should note that these figures based on resources processed by KTL fiscal office, and the proportion of external sources of salary is somewhat higher in the true life because e.g. Research fellows of the Academy of Finland are directly paid by the Academy and the corresponding sums are not included here.

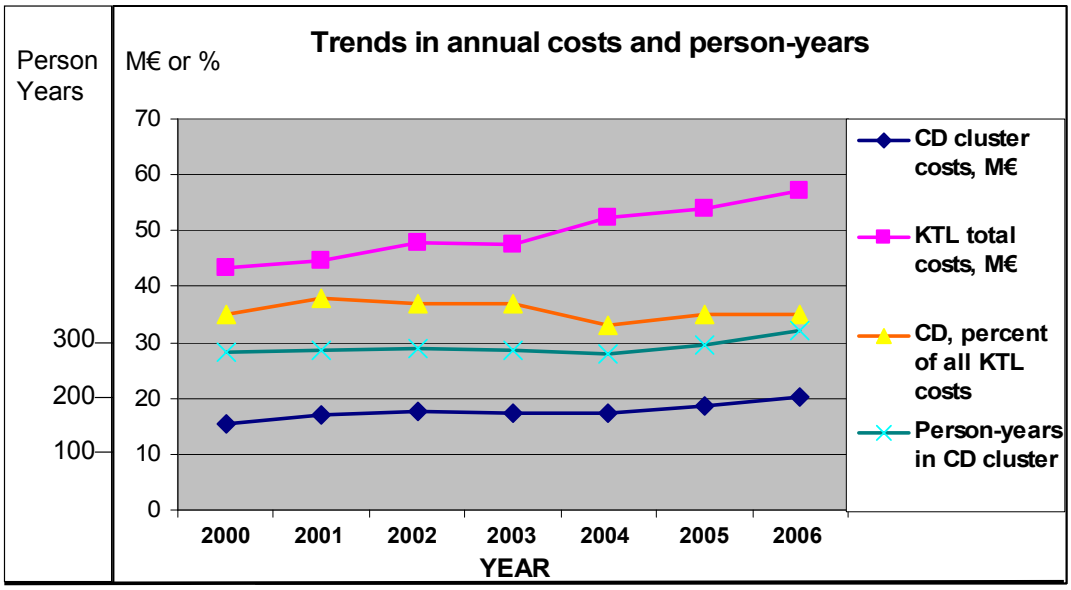
Person years (direct*) and source of salary in 2005					**Person years in 2006**
Department	KTL budget	External sources	Total	% from outside	
BATO	61.6	12.3	73.9	16.6	74.9
INFE	21.3	10.9	32.2	33.9	29.8
ROKO	23.9	28.3	52.2	54.2	65.1
VIMO	65.1	35.7	100.8	35.4	103.3
Total	**171.9**	**87.2**	**259.1**	**33.7**	**273.1**

*These figures represent persons actually working in the indicated department

Department	**Direct costs in 2006, 1000€**		
	Total	***KTL budget***	***External sources***
BATO	3 576	2 763	813
INFE	1 844	1 317	527
ROKO	3 215	1 222	1 993
VIMO	5 858	3 407	2 451
Total	**14 493**	**8 710**	**5 783**

Job categories in 2006							
Dept	Research	Expert functions* (incl.res.)	Lab. work	PC-help, data manag. or biostat.	Secret. work	Not reported	Total
BATO	41	0	36	0	7	0	84
INFE	5	13	5	4	4	1	32
ROKO	21	13	22	9	6	0	71
VIMO	49	1	48	3	7	0	108
Total	116	27	111	16	24	1	295

* This is a relatively new category and it is likely that in BATO and VIMO, several positions now listed in the Research category should also be transferred here



5. FUTURE CHALLENGES AND PROSPECTS

Challenges

Infectious disease will remain an important domain for public health. New infectious agents will be recognised, most of them previously existing but undetected, but also truly new pathogens will emerge. Factors such as travelling, changes in individual behaviour, aging of the population and aggressive modalities of treatment compromising infection resistance will contribute to further diversify the challenges. Previously known pathogens will develop new properties which may circumnavigate previously effective prophylactic and treatment modalities, such as vaccines and antibiotics, making them less effective.

Emerging infections include the detection of infectious causes for an increasing number of diseases previously thought as non-infectious. These, mostly chronic infections and health consequences, will open new possibilities for interventions of public health importance.

Many of the new challenges are related to the rapid 'globalisation' of infectious disease, eg more rapid international dissemination in ever larger numbers of travellers, requiring more intense international collaboration and measures.

In Finland, in addition to the general factors above, rapid changes in the health care service and other systems pose continuous and constantly changing challenges for KTL to create and adopt newest scientific knowledge in recommendations on surveillance and control to cope with the changing functional environment.

Prospects for KTL to cope with the challenges

KTL will continue to develop the surveillance systems to be able to provide a solid knowledge base on the burden of infectious disease. This will require intense collaboration with the health care service sector on all its levels as well as the environmental and veterinary sector for zoonotic diseases, exploitation of rapidly developing national health care information systems for automated collection of relevant data, and utilization of the latest developments of microbiology, in order to ensure the effectiveness of existing control programmes and to describe the epidemiology and causes of emerging disease in sufficient detail to base interventions on.

KTL needs to implement frontline research in applied epidemiology and interventions on prioritised problems in infectious diseases of considerable public health importance, and strategic basic or methodological research that directly support this work. Applied epidemiological research will include maximal utilization of the multiplicity of high quality national health-related registers. Large scale clinical vaccine trials will be implemented to feed into the scientific basis of guiding development of National Immunization Programme. Research on human microbiota and on inflammatory mechanisms will continue in key areas to contribute to development of new interventions.

KTL expert staff will translate the newest national and international scientific knowledge into advice on policy for the Ministry of Social Affairs and Health, and practical recommendations to the health care services. This requires a sustained strong combination of high quality research and a good understanding the general working environment as well as major public health issues, in the same persons or units, to be successful.

Supplement

List of guidelines and recommendations on communicable diseases for health care personnel (In Finnish)

Ohjeita ja suosituksia tartuntataudeista terveydenhuoltohenkilöstölle

1. EHEC: Suositukset toimenpiteistä EHEC-tartuntojen yhteydessä
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2007

2. GBS-taudin ehkäisy vastasyntyneillä
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2006

3. Hepatiitti A: Suositus toimenpiteistä hepatiitti A -tartuntojen ehkäisemiseksi
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

4. Hiv: Hiv-seulonta äitiysneuvoloissa - tietopaketti perusterveydenhuollossa toimiville
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 1997

5. Influenssaepidemian ehkäisy ja torjunta terveydenhuollon laitoksissa
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2007

6. Isorokko (Smallpox)
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

7. Kansallinen varautumissuunnitelma influenssapandemiaa varten
Tartuntataudit, Ohjeet ja suositukset, Muu kuin KTL, 2007

8. Kurkkumätä: toimenpideohje torjuntatoimista kurkkumätätapausten yhteydessä
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2005

9. Lintuinfluenssa ohjeita terveydenhuoltohenkilöstölle, 2004

Tapausmääritelmä, lintuinfluenssa A/H5N1 -epäily ihmisellä

Mikrobiologiset tutkimukset lintuinfluenssa A/H5N1 -epäilyssä

Virusviljelyn turvatasovaatimukset

Hengityssuojainten käyttö terveydenhuollossa

Hengityssuojaimen pukemisohje

Varotoimiluokat

Ohje siipikarjan tai luonnonlintujen lintuinfluenssaepidemiassa

Oseltamiviiriprofylaksian käyttö altistustilanteissa

Yleiset hygieniaohjeet

10. Listeriainfektio (Listerioosi)
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2005

11. Meningokokkitapaus: Toimenpideohje estolääkityksestä ja rokotteen käytöstä meningokokkitapausten yhteydessä
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2005

12. MRSA - Metisilliinille Resistentti Staphylococcus Aureus. Potilasohje
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2004

13. MRSA: Ohje metisilliiniresistenttien Staphylococcus aureusten torjunnasta 2004
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2004

14. Norovirus: toimenpideohje norovirus-tartuntojen ehkäisemiseksi
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2007

15. Pernarutto (Anthrax)
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2001

16. Pernarutto: Ohje terveydenhuoltohenkilöstölle - Toiminta pernaruttoepäilyn tai pernarutolle altistumisen yhteydessä
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2002

17. Pernarutto: Toimenpiteet tilanteissa joissa epäillään pernaruttoaltistusta
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2001

18. Poliovirukset pois Suomesta
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

19. Puutiaisaivokuumeen torjuminen yleisellä rokotuksella Ahvenanmaalla
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2005

20. Rabieksen ennaltaehkäisy ja altistuksen jälkeinen hoito
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2007

21. Ruokamyrkytys- tai vesiperäinen epidemia: Menettely ilmoitettaessa epäillystä ruokamyrkytys- tai vesiperäisestä epidemiasta (epäilyilmoitus)
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 1997

22. Ruokamyrkytysepidemia/Vatsatautiepidemia: Mikrobiologiset tutkimukset vatsatautiepidemian selvittämiseksi - toimenpideohje
Tartuntataudit, Ohjeet ja suositukset, Virustautien ja immunologian osasto VIMO, 2005

23. Salmonella: Toimenpideohje salmonellatartuntojen ehkäisemiseksi
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2007

24. Sars: Hengityksensuojainten ja suu-nenäsuojusten käyttö terveydenhuollossa
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

25. Sars: Menettely sars-tapausten tutkimuksissa ja hoidossa
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

26. Sars: Ohjeita majoitusliikkeille sars-epidemia alueelta saapuvien matkustajien varalle
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

27. Sars: Sars – uusiin uhkiin valmistautumista
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2004

28. Sars: Sars-epäily - torjuntaohjeet sairaalassa
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

29. Sars: Sars-epäilypotilaiden laboratoriotutkimukset
Tartuntataudit, Ohjeet ja suositukset, Virustautien ja immunologian osasto VIMO, 2003

30. Sars: Suositus mikrobiologian laboratorioille sars -koronavirusviljelystä
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

31. Sars: Tiedote sars-tartuntaan varautumisesta poliisihallinnossa
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

32. Sars: Toimenpiteet epäillyn sars-potilaan kotihoidossa
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

33. Sars: Toimenpiteet sars-epäillyn lähikontaktien seurannassa
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

34. Sars: Toimintaohje epäiltäessä sars-tapausta epidemia-alueelta saapuvalla aluksella
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

35. Sars: Yleistietoa Sars-epidemiasta
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2004

36. Tartuntatautien ilmoittaminen - Ohjeet lääkäreille, terveyskeskuksille ja sairaanhoitopiireille
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

37. Tartuntatautien ilmoittaminen - Ohjeet laboratorioille
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2003

38. Tuberkuloosi, Riskiryhmiin kohdistuva tuberkuloosin torjunta
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2005

39. Tuberkuloositartunnalle altistumisen aiheuttamat toimet
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2004

40. Tuberkuloositartunnan torjunta sairaalassa
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 2004

41. Valtakunnallinen tuberkuloosiohjelma 2006
Tartuntataudit, Ohjeet ja suositukset, Muu kuin KTL, 2006

42. VRE: Ohje vankomysiinille resistenttien enterokokkien torjunnasta
Tartuntataudit, Ohjeet ja suositukset, Infektioepidemiologian osasto INFE, 1997

43. Tulossa: Pertussis: Toimenpideohje torjuntatoimista hinkuyskätapausten yhteydessä

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