

EPIDEMIOLOGY AND MICROBIOLOGY AT THE NATIONAL INSTITUTE OF PUBLIC HEALTH, PRAGUE, CZECH REPUBLIC

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HISTORY

The National Institute of Public Health was inaugurated on November 5, 1925. Since the very beginning it included four Departments: Department for the manufacture of sera and bacterial vaccines, Department for the manufacture of smallpox vaccine, Department for the Pasteur vaccination against rabies and Department for bacteriological diagnosis. All of these Departments closely cooperated. The manufacture of vaccines, sera and diagnostic agents was at the European level, not only in terms of quality but also in terms of the rapidity with which new advances in research were introduced into practice. For instance, the manufacture of the vaccine against diphtheria described by Ramon in 1923 was started at the Institute from its establishment. In addition, one of the first meningococcal vaccines in the world was manufactured at the Institute in the 1930's.

In 1939, Dr. Karel Raška who started his career as a pathologist, microbiologist and epidemiologist and later became Professor of the Faculty of Medicine was appointed head of the Department of Epidemiology and Microbiology. His wide background was an ideal point of departure for his scientific and academic activities. During World War II, based on sketchy information on a newly discovered blood antigen, the so-called Rhesus factor, Professor Raška and his colleagues prepared the sera for determination of the Rh factor and were the first in Europe to be able to diagnose fetal erythroblastosis.

Just before the end of World War II in response to the emerging news about the increasing incidence of suspect disease in the Terezin Small Fortress, Professor Raška managed to screen the sera from Terezin prisoners forced to dig trenches. After identification of the causative agent of epidemic typhus he went to Terezin and engaged in difficult and risky negotiations to be allowed to enter the concentration camp in order to take emergency measures. Under his leadership, a team from the National Institute of Public Health, physicians, nurses and medical students were able to control this outbreak in 1945. Until recently one of the researchers involved in these activities, Dr. Eva Aldová, still worked at the Institute. She significantly

contributed to the development of the Czech microbiology, among others, by identifying and describing two novel bacterial genera *Budvicia* and *Pragia*, with two novel species: *Budvicia aquatica* and *Pragia fontium*. In her honor a novel species described by Bercovier et al. was named *Yersinia aldovae*.

On January 1, 1949, the Department of immunological products was separated from the Institute to be converted to the State Company for Sera Production (currently called Sevapharma). On February 23, 1949, the National Institute of Public Health was split into five Departments including the Department of Microbiology and Epidemiology headed by Professor Raška and further divided into six units: microbial research, microbial and serological diagnosis, manufacture of diagnostic products, research on and diagnosis of viral infections, research on and diagnosis of tuberculosis and health statistics.

Shortly after the liberation, the Department of Microbiology and Epidemiology became a basis for the creation of new branches of the National Institute of Public Health in the Czech regions. The Department provided not only training in microbiology and epidemiology to physicians and technicians but also material and personnel assistance in building up the laboratories in Brno, Ostrava, Přerov, Uherské Hradiště, Ústí nad Labem, Karlovy Vary, Plzeň, Jihlava, Havlíčkův Brod, Tábor, Liberec and other cities. The Department manufactured diagnostic sera and antigens and issued recommendations for standardization of microbiological diagnosis. These activities were essential for the development of microbiological diagnosis in the field. A national collection of pathogenic microorganisms was created within the Department. Mobile laboratories utilized to control epidemic outbreaks and to solve complicated epidemiological problems also provided methodical guidance to the newly created laboratories.

In 1952, the Institute of Epidemiology and Microbiology (IEM) was established. Professor Karel Raška, MD, DSc, was appointed director of the Institute and in 1963 also became director of the Division of Infectious Diseases of the World Health Organization in Geneva.

On January 1, 1971 the separate institutes were reintegrated into the Institute of Hygiene and Epidemiology (IHE), with Professor František Janda being appointed director. The Institute of Epidemiology and Microbiology became the Centre of Epidemiology and Microbiology (CEM). After being removed from his post in Geneva in November 1970, Professor Raška was not allowed to continue to head the CEM and was dismissed from the Institute in 1972. Assoc. Prof. Lubomír Syrůček, MD, DSc. was appointed head of the CEM in January 1971 but ceded his position to Assoc. Prof. Josef Pečenka, MD, DSc. in November 1972 who headed the CEM until his tragic death in March 1976. His successor was Jaroslav Helcl, MD, DSc. who headed the CEM until November 1, 1992 when Assoc. Prof. Bohumír Kříž, MD, DSc. was appointed head of the CEM.

SCOPE OF ACTIVITIES

Both the routine and research activities of the Institute of Epidemiology and Microbiology were decisively influenced by the personality of Professor Karel Raška, his background, education and human qualities, in particular his enthusiasm and determination to achieve the goal regardless of personal risk. Medical experience gained in the Army, knowledge of pathology, microbiology and epidemiology coupled with his creative thinking were a source of challenging ideas and projects; it was up to his collaborators to show feasibility of such projects which was not always easy. Nevertheless, their efforts were often crowned with success at the international level. Outstanding achievements of his team are often linked to his personality. In 1984 Professor Raška won the Jenner award for his lifetime contribution to the development of epidemiology and microbiology, the highest and most prestigious award in this field.

Influenza research started at the Institute in 1948 and was headed by Dr. Galia. Under his management, the first batches of formolized influenza vaccine were prepared and immunological surveys were conducted. Since 1951, the incidence and persistence of influenza viruses among the population of Czechoslovakia have been monitored. Many priority results were achieved, e.g., A2 influenza strains reported by this laboratory in 1957 were the first to be isolated in Central and Western Europe, as was also true of type B influenza virus isolated two years later. Dr. Tůmová's influenza laboratory isolated a novel influenza virus from horses with respiratory infection which was recognized internationally, included among animal influenza viruses and named A-equi/Prague 1/56.

Measles research was focused on the antibody status in the population and evaluation of measles vaccines manufactured by the Institute of Vaccines and Sera. The

first controlled field studies providing data on protective effects of different vaccines were carried out in cooperation with field health workers. A long-term surveillance program conducted by Assoc. Prof. J. Strauss and his colleagues was crowned with success in 1986 when transmission of measles virus in the Czech lands was discontinued.

Hepatitis research was focused on the elucidation of epidemiological characteristics of this infection. In 1952-53, several studies were performed to find out whether or not normal human gammaglobulin is involved in prophylaxis of hepatitis, and if so, to what extent. These studies ranked among the top European projects. Further studies dealt with the collection of more accurate data in an attempt to map the incidence of infectious and serum hepatitis and to elucidate principles of their spread. New diagnostic methods were being implemented on an ongoing basis with only a small delay compared to industrialized countries.

Dr Galia also laid the foundations for research of tick-borne encephalitis (TBE) in Europe. In 1948, he isolated the first TBE viral strains from human clinical specimens and in 1949, together with Dr. Rampas, they detected the TBE virus in *Ixodes ricinus* ticks originating from Central Bohemia. The main focus was on serological and culture diagnosis of TBE. The results obtained became part of the background information for delineation of TBE as a nosological entity. A world priority was also demonstration of food-borne transmission of TBE virus to humans following ingestion of raw or poorly pasteurized milk. This finding resulted from epidemiological analysis of a large TBE outbreak in Rožňava in 1952 made by Prof. Raška, Prof. Blaškovič, Assoc. Prof. Bárdoš and others. Further studies in TBE endemic regions contributed to elucidation of the TBE virus circulation in nature. It was found that not only small rodents but also birds might be involved in the spread of TBE virus.

In the 1950, great efforts were made to elucidate the etiology of "atypical pneumonia" among chicken farm workers. The first isolation of the causative agent of ornithosis from sputum in 1953 was prerequisite for implementation of serodiagnosis. One of the first isolations of the causative agent of ornithosis in ducks and geese in Europe (except the USSR) provided the missing link in the spread of ornithosis in Czechoslovakia. This finding was confirmed later in all of the border Central European countries. Since 1955 ornithosis became the most widespread anthroponosis in Czechoslovakia for a certain time. Thanks to the researchers of the Institute, as many as 1072 cases of ornithosis were diagnosed by 1960. Experimental studies searched for more effective specific means for prevention of ornithosis.

The first cases of Q-fever in Czechoslovakia were diagnosed by the researchers of the Institute in 1952. In

the following years, intensive research was conducted in the most afflicted region of north-western Bohemia to confirm Prof. Raška's hypothesis that this infection was imported to Czechoslovakia after World War II. Q-fever as a typical anthroponosis spread into biocenosis of the given region: it was possible to observe the emergence of a natural focus in a reversed manner. Assoc. Prof. Lubomír Syřůček was involved in this research by providing laboratory diagnosis. In the following years, he specialized in high risk infections such as plague, cholera, typhoid fever and variola. After the emergence of HIV/AIDS he focused on this infection and took the necessary steps to establish an AIDS laboratory within the Centre of Epidemiology and Microbiology, where he spent most of his professional life, in 1985. After his retirement, Dr. Brůčková, his pupil and collaborator, became the head of the National Reference Laboratory (NRL) for AIDS. She was highly skilled and prepared to face the difficult task. She got familiarized with HIV/AIDS diagnosis in the leading laboratories world-wide, implemented the most advanced diagnostic tests in the NRL and provided training to many specialists from extramural laboratories involved in the QA/QC system. The rapidity and high quality with which these activities were organized and conducted contributed substantially to good outcomes in the field of HIV/AIDS at the national level. Both the research and diagnostic activities of the HIV/AIDS laboratory are top level.

Toxoplasmosis is another infection whose laboratory diagnosis was implemented and studied on an ongoing basis at the Institute of Epidemiology and Microbiology. For years, the parasitology laboratory headed by Dr. Havlík was the only one to provide this diagnosis in Czechoslovakia. In 1953, it also reported the first isolation of a *Toxoplasma gondii* strain from a human case in Czechoslovakia. The diagnosed human cases were characterized epidemiologically and epizootologically in a comprehensive manner. In many instances, the source of disease could be elucidated. The epidemiology of this infection then unclear was studied mainly from the point of view of the role of different animal species as possible sources of infection to humans.

In the 1950's, brucellosis surveillance was conducted in both human and animal populations. Serological reactions were used to investigate the seropositivity rates not only in humans but also in animals. The obtained results allowed to achieve higher accuracy in epidemiology and diagnosis of brucellosis in practice and thus also contributed to the elimination of this infection in Czechoslovakia.

The Czechoslovak Reference Laboratory for Salmonella Typing started its activities as the first reference laboratory of the National Institute of Public Health in 1939. By 1960, the laboratory identified 1100 strains be-

longing to 90 serovars. Among further important activities was efficacy testing of different types of anti-typhoid vaccines. Salmonellosis as a typical anthroponosis whose spread among animal and human populations is markedly influenced by human activities was the subject of extensive study in the second half of the last century. While in 1945 seven serovars were detected in Czechoslovakia, 40 serovars were reported in 1952 and twenty years later their number was four times as high. The laboratory clearly demonstrated at the turn of the 1950's that the progressive increase in the newly detected *Salmonella* types resulted from the use of imported animal fodder contaminated with *Salmonella*.

From its establishment in the 1950's, the Reference Laboratory for *Shigella* studied distribution of *Shigella* types and subgroups among the population and their resistance to sulfonamides, which were then considered as the drug of choice. The laboratory also prepared bacteriophages to cover practically all strains found in Czechoslovakia. Phages were also supplied to the Institute of Sera and Vaccines to be further processed and used dried for therapeutical purposes. These bacteriophages were very helpful in controlling outbreaks of dysentery.

Staphylococci as ones of the leading causative agents of hospital infections were in focus as well. Epidemiological analysis of the incidence of different staphylococcal phagotypes, production of toxins and susceptibility to antimicrobials provided valuable data usable in practice. Monitoring the resistance of thousands of strains enabled prediction of negative effects of an excessive or inadequate use of antibiotics and at the same time provided valuable data to clinicians. Noteworthy was also the finding that exclusion of groups of antibiotics similar in biological and chemical nature for more than one year led to changes in staphylococcal susceptibility which could return to baseline levels. The study of the staphylococcal phages resulted in the discovery of a new treatment for serious life-threatening staphylococcal infections with phage lysate. The reference laboratories for *Salmonella*, *Staphylococcus* and *Shigella* were among the first laboratories established at the National Institute of Public Health and were headed by Dr. Dobromila Matějovská, Dr. Věra Matějovská and Dr. Eva Aldová, respectively.

As for air-borne bacterial infections, those caused by streptococci were the first to be studied. In the 1960's, the NRL for Streptococci was established to be designated as the WHO Collaborating Centre for Streptococci as one of the first laboratories world-wide. Both of the laboratories and the respective research group were headed by Dr. Rotta. In the 1970's, the laboratory for meningococci joined this research group.

Research of pertussis, one of the most serious infections in children, was at a top level from the very begin-

ning in the 1950's. The vaccine prepared by the Institute of Sera and Vaccines from strains isolated from patients in the field and provided by the Institute of Epidemiology and Microbiology was highly immunogenic, causing only slight local reactions. Thorough vaccine efficacy testing and monitoring of the immune status of children were conducted to detect failures in the vaccine manufacture and administration and led to rapid elimination of pertussis as a healthcare problem. Assoc. Prof. Vysoká's endeavours in this field will be indelibly imprinted in our memory.

Rabies research resulted in isolation of almost thirty viruses immunologically linked to rabies viruses, pathogenic to laboratory animals, dogs and foxes, from small wild rodents. These findings were confirmed internationally and recognized as priority results.

The Department of Statistics also played an important role in building up the Institute of Epidemiology and Microbiology. Both theoretical and practical statistics underwent rapid development in post-war years and with the advent of cybernetics new possibilities and directions opened up for the research methodology in general and for dynamic application of statistical methods in biology and medicine in particular. Research data processing was no longer thinkable without cooperation with skilled statisticians. Carrying out controlled field or clinical studies has become a common part of epidemiological work.

Apart from conducting research and reference activities and providing methodical guidance, the Institute of Epidemiology and Microbiology was engaged from the very beginning in both pregraduate and postgraduate teaching, in cooperation with the Medical Faculty of Hygiene and the Institute for Postgraduate Medical Education, respectively.

INTERNATIONAL COOPERATION

Czech microbiology and epidemiology always were and continue to be appreciated in the international context. Many priority results were achieved in the field of vaccination strategy based on the monitoring of the vaccination coverage via the so-called serological surveys. For illustration, at the turn of the 1950's, the American researcher Albert S. Sabin collaborated with researchers of the Institute of Sera and Vaccines and the Institute of Epidemiology and Microbiology in Prague on the manufacture and testing of live poliovaccine, subsequently used in a nation-wide vaccination campaign in 1962 to stop the spread of this infection among the Czech population. Twenty years later, nine epidemiologists who worked or have been working at the National Institute of Public Health made history by being involved in the variola eradication campaign. The idea of eradicating

variola was Professor Raška's; he pushed it in the WHO in 1964 while in post.

In 1960, an important part of the Institute of Epidemiology and Microbiology became the WHO Serum Reference Bank, one of three WHO serum banks in the world. Sera from seventeen European, African and Asian countries were (and in part have been) deposited there. The WHO Serum Reference Bank played an important role, along with the respective reference laboratories involved in antibody testing, in the nationwide immunization programs organized by the WHO or national governments.

Since 1960 the cooperation with the WHO became more extensive and several international conferences, workshops and courses were organized at the Institute of Epidemiology and Microbiology every year. The International Courses of Epidemiology organized by the WHO in Prague and continued in New Delhi were more than successful.

Currently, cooperation with the WHO and the European Union (EU) is priority for the Centre of Epidemiology and Microbiology. Practically all of the National reference laboratories have been involved in international cooperation. Three WHO Collaborating Centres are currently operating at the Centre of Epidemiology and Microbiology: Centre for Streptococci, Centre for Mycobacteria and Centre for Lyme Disease, the first one being established in the 1960's as one of the first WHO Collaborating Centres in the world.

The accession of the Czech Republic to the EU also means new commitments in the field of infectious diseases. Based on Resolution No 2119/98/ES of the European Parliament and Council, Czech specialists joined the international surveillance networks for selected infections (EISS, FLUNET, ESWI, SALMNET, ENTERNET, EARSS, EuroHIV, SPREAD, EUROVCT, EuroTB, EMGM, MenNet, Strep-EURO, EUIBIS, DiphNet, ESEN, WFCC, ECCO, CEPA, ESSA, SBFGS, EQA, Eurosurveillance, BSN). These networks also collect data from regular reporting of cases and outbreaks of reportable diseases. The first steps towards a unified international surveillance of infectious diseases were the formulation and legal establishment of case definitions. The microbiological laboratories of the Centre of Epidemiology and Microbiology carry out collection of microbial strains, their typing, antibiotic susceptibility testing and molecular biological analyses to provide the obtained data to the international network databases. These laboratories have been involved in the External Quality Assessment (EQAS) and cooperation on the development and testing of diagnostic methods. Additional funding is currently required for these extra activities.

CURRENT SITUATION

The Ministry of Health of the Czech Republic established 24 national reference laboratories for the most relevant infections within the Centre of Epidemiology and Microbiology. They provide methodical guidance as well as consultation, reference and research activities in their respective fields. They also carry out further identification, typing, antibiotic susceptibility testing and molecular biological characterization of isolates from field laboratories for the diagnostic, epidemiological and forensic purposes. They have been involved in the EQAS at both the national level (by supervising QA/QC in 421 microbiological laboratories in the Czech Republic) and international level (by participating in the EQAS organized by the EU and WHO). NRL activities also include the development and efficacy testing of new diagnostic methods and procedures, advisory activities for the national authorities, preparation of the background information for the law-making authorities, including draft standard operating procedures, methodical guidance and instructions. The NRL provide diagnosis of emerging and re-emerging infectious diseases, for which new and more costly diagnostic methods and procedures have to be used.

The involvement of these reference laboratories in international cooperation with the leading microbiological laboratories, e.g. on analysis of characteristics of streptococcal strains isolated from cases of necrotizing fasciitis in the UK, identification of a novel meningococcal serotype and valid publication of three novel *Acinetobacter* species, is also illustrative of their top level quality.

Outstanding results were achieved in the nation-wide antibiotic policy. The antibiotic resistance monitoring organized, conducted and evaluated by the respective NRL is a vital part of this policy. The NRL issues recommendations and guidelines for reasonable and targeted prescription of antibiotics, thanks to which relatively good susceptibility of clinically important bacterial species could be maintained in the Czech Republic compared to other European countries.

In the 1990's, the epidemiological part of the Centre of Epidemiology and Microbiology was reorganized in view of the emerging challenges. The socio-economic changes at the national and global levels, current international situation, social differentiation, integration of different population and ethnic groups, unemployment, legal and illegal migration from all climatic zones and emergence and re-emergence of infections are associated with multiple previously unknown serious problems which need to be identified and solved. Since the available reporting system for infectious diseases did not meet the current needs, the epidemiologists in

cooperation with their colleagues from the Department of Biostatistics and Informatics of the National Institute of Public Health and Public Health Service designed a new electronic EPI-INFO-based reporting system suitable for rapid data exchange between the field workers and the Centre of Epidemiology and Microbiology. The reporting system along with a monthly epidemiological and microbiological periodical called CEM Newsletter issued in Czech since 1992 and the websites of the Centre of Epidemiology and Microbiology (www.szu.cz/cem/hpcem.htm) are an adequate source of up-to-date epidemiological information relevant to both the national and international specialists. Reports of individual cases are e-mailed weekly to the National Reference Centre for Epidemiological Data Analysis. Comprehensive data on new epidemic outbreaks are reported weekly as well. The occurrence of individual cases or outbreaks of serious infections is reported without delay by phone, e-mail or fax. Annually, the incidence of epidemic outbreaks and the numbers of cases within each outbreak as recorded by the National Reference Centre for Epidemiological Data Analysis are reported to the UN International Agency for the Control of the Observance of the Bacteriological (Biological) and Toxin Weapons Convention Protocol. The epidemiological groups organize surveillance programs for most infections and are involved in these programs and WHO eradication campaigns.

Recently, the risk of terrorist attacks using conventional and biological weapons has been increasing. Over the last two years, the laboratory of the Centre of Epidemiology and Microbiology screened as many as 404 specimens for the presence of anthrax spores. If the abuse of biological agents were suspected, it would be reported to the respective international organizations. One year prior to the accession of the Czech Republic to the EU, the surveillance programs in the Czech Republic were audited by the EU experts. Although the auditors' conclusions were positive in general, many new tasks emerged in this field. The subsequent audit in April 2004 was focused not only on the fulfilment of the tasks resulting from the last audit but also on further activities which were newly implemented throughout the last year. Except for one failure to meet the construction requirements, the auditors concluded that the EU standards have been met in the field of surveillance of infectious diseases in the Czech Republic.

The increasing requirements for higher quality of work in microbiological laboratories, possible importation of emerging highly virulent infectious agents, along with legislation on biological safety, occupational safety and protection, and more stringent conditions of international cooperation led the management of the Centre of Epidemiology and Microbiology to the conclusion that

the NRLs needed accreditation. This difficult task was fulfilled three years later thanks to great efforts made by the laboratory staff: based on the audit of the Czech Accreditation Institute, all of the NRLs have become holders of the accreditation certificate ISO 17025. Recently, on February 7, 2005, 21 National Reference Laboratories in CEM obtained another accreditation certificate from the Czech Accreditation Institute as “Public Health Laboratory No. 8002” according to ČSN ISO 15189. With the respective EU standard being in force since May 2004 only, NRLs CEM are the second laboratory complex accredited in the Czech Republic.

Research is an important part of the activities of the Centre of Epidemiology and Microbiology. Researchers of the Centre have been involved in multiple grant

projects funded by both the Czech and international grant agencies. Between 1993 and 2004, they were involved in as many as 95 grant projects whose list is available on the Centre websites along with the list of publications.

Unfortunately, the extent of this communication does not allow to enumerate all achievements of the former Institute and then Centre of Epidemiology and Microbiology and to mention the names of the dozens of researchers who contributed to these achievements. The authors apologize to all outstanding colleagues whose names have not been mentioned.

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