SEVERE INFECTIONS IN CHILDREN – PRAGMATIC ASPECTS OF RESEARCH

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Historically, humanity has experienced many epidemics and pandemics, but is still not prepared for every kind of event. The COVID-19 pandemic is an example of an event that has medical, social, and economic impacts and touches our moral and ethical values at the core. This is a time when public trust in science is dependent on clear and practical answers to complex problems related to the new situation. Where can these answers be found? Is it in the framework of medical practice, applied or fundamental research? What are the priorities today? There are more questions than answers.

Theoretically, fundamental research can help us understand phenomena and leads us to new knowledge. Applied research focuses on immediate needs-driven applications and the pragmatic aspect of research and strived to solve practical problems in an evidence-based manner. The aim of clinical practice is to care for patients and respond to public health needs using the best technologies, skills and professional experience available. It is not easy to separate basic research from applied research in practice – one of the options is to understand clear research targets and researchers' motivation. Recently, the American Academy of Paediatrics published seven great achievements in paediatric research in the past 40 years: preventing diseases with life-saving immunisations; reducing sudden infant death syndrome (SIDS) with the Back to Sleep campaign; curing common childhood cancer; saving premature babies by helping them breathe; preventing mother-to-baby HIV transmission; increasing life expectancy for children with chronic diseases; saving lives with car seats and seat belts. These achievements give definitive answers to practical health problems affecting children and their families, save lives and improve the quality of medical care.

What is paediatric research in Latvia like? Theoretically, the future of fundamental research is very promising, but in Latvia it is mostly physicians who are the researchers in this field, who are close to patients and try to solve practical problems by applied research. We understand that the funding provided by national research programmes is not stable and that paediatric research in Latvia is relatively underfunded. Short-term grants do not ensure sufficient development of this field, but this does not undermine the activities of researchers on an international level. For us, it is important to change the clinical practice. This article provides some examples from our studies of paediatric infectious diseases.

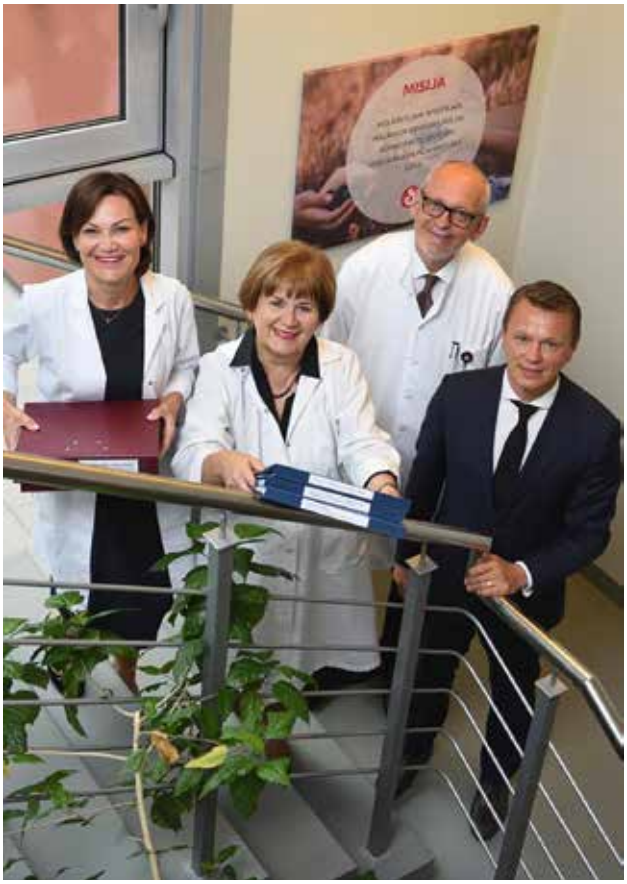
The study started with a large outbreak of gastroenteritis caused by *Salmonella* spp. that occurred among children in Latvia. Over 4000 cases were reported from 1991 through the first quarter of 1998. Approximately 70% of patients were under the age of one, and their condition was moderate to severe with bloody stool and a high fever. The outbreak saw several lethal outcomes. Some of the cases were complicated by extraintestinal infections. In this study, conducted together with peers from Washington University School of Medicine, the St. Louis Children's Hospital and Wyeth-Ayerst Research, New York, we reported a new member of the CTX-M cefotaxime-hydrolyzing β-lactamase family, designated CTX-M-5. The outbreak strain

was resistant to multiple antibiotics, including ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, and cefotaxime, which were commonly recommended and used to treat serious infections caused by Salmonella spp [1]. These strains were uniformly susceptible to ciprofloxacin; however, the extremely young age of most of the patients prevented its use in treatment. The prevalence of this cefotaxime-hydrolyzing β-lactamase among *S. typhimurium* strains in Latvia was possibly related to the increased usage of expanded-spectrum cephalosporins during that time. With the recognition of the high prevalence of resistance, efforts were made to curtail the use of antibiotics in patients with salmonellosis and other gastrointestinal infections to control the spread of *S. typhimurium* infection, which was very successful. The detection of a new member of the CTX-M family in Latvia raised important questions about whether such enzymes arise *de novo* in multiple geographic locations or, alternatively, are transmitted across national borders. The importance of these questions emphasises the need for global surveillance of antibiotic resistance so that appropriate control strategies can be designed and implemented. Later, the changes made to the nation-wide antibiotic policy for children had a significant impact on other infections. Based on our previous experience, we minimised the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed to children and implemented antibiotic stewardship for paediatric patients.

During our participation in the WHO Multicentric (Egypt, Latvia, Brazil, Croatia) Study (The Grasp Study, 2001–2004) and later in the National Research Programme (2008–2009), we investigated diseases caused by Group A beta haemolytic streptococcus (GAS) that have been known since the 19th century [2]. Despite the improvement of socio-economic circumstances and environmental factors in Latvia, prevalence of GAS in aetiology of acute pharyngitis in children was still a pressing matter and the necessity for early diagnosis and treatment with antibiotics was very important due to the risk of late complications – rheumatic fever and poststreptococcal glomerulonephritis. We found that around half of children who had GAS obtained from throat posterior wall cultures, or who had a positive rapid antigen detection test (RADT), were noticed carrying GAS with acute pharyngitis clinical picture of some other unspecified aetiology. This meant that these cases did not need treatment with antibiotics, which was a common clinical practice in the past. We found that GAS strains used in the study had a very high macrolide resistance (78%) – an antibacterial drug which was widely used in outpatient settings. Since then, great attention has been paid to a deliberative strategy of antibiotic use in the population of children in Latvia. The association of antimicrobial resistance with certain GAS emm types was similar to that in other European countries. During the course of the study, a new GAS emm 1.51 subtype was discovered, which is now approved by the Centers for Disease Control and Prevention (CDC, USA). The findings of the study also indicated that certain HLA class II alleles, genotypes and haplotypes are associated with risk/protection from RHD and that these associations are more evident in patients among clinically homogeneous groups. This is a useful tool for predicting clinical outcomes of rheumatic fever.

Staphylococcus aureus is a major cause of purulent infections. The spectrum of staphylococcal infections varies from mild superficial to invasive life-threatening diseases due to the ability of *S. aureus* to produce a wide range of virulence factors, including toxins, for example, Panton–Valentine leukocidin (PVL). Due to PVL positive *S. aureus*, community-acquired necrotising pneumonia is an emerging infection. Pneumonia often arises from the blood-borne spread of organisms from infected tissues and can follow viral respiratory infections, especially influenza. Necrotising pneumonia mainly affects children and young adults and up to 75% of cases are lethal. The isolates collected in our study were typed by spa gene. We found out that the prevalence of PVL positive *S. aureus* in hospitalised children with *S. aureus* infection was 75% and the spread of spa clonal type CC435 *S. aureus* isolates was observed in children treated in hospitals [3]. A new and successful approach to the antibacterial treatment of necrotising pneumonia was introduced following this research.

The Department of Paediatrics is conducting long-term studies on fever, severe bacterial infections and sepsis, which is one of most significant causes of hospitalisation and mortality of children. Between 1995 and 2000, the child mortality rate from sepsis at the Children's Clinical University Hospital was 24.4%. The situation has not improved significantly over a period of almost ten years – a repeated epidemiological survey demonstrated that 21.7% children died from sepsis and only 22.9% children with sepsis were hospitalised on the first day of illness. National research programmes have enabled Rīga Stradiņš University (RSU) to start studies on life-threatening infections in children [4, 5, 6, 7], which demonstrate low awareness in the evaluation process of children with fever in outpatient settings and also during hospital admission as evaluations were mostly based on physicians' personal experience and less on evidence – test results or approved hospital guidelines for sepsis patients. As a result of this study, new inflammatory markers were evaluated and algorithms, guidelines and pathways for outpatient and hospital settings and parents were developed and implemented in 2019 –2020 across all children's healthcare institutions in Latvia with the support of the Ministry of Health. It is very important for paediatric research in Latvia to be a part of an international research team and to cooperate with other countries [8]. In recent years, we have participated in the following Horizon 2020 projects: PERFORM (Personalised Risk Assessment in Febrile Illness to Optimise Real-Life Management across the European Union) and DIAMONDS (Diagnosis and Management of Febrile Illness using RNA Personalised Molecular Signature Diagnosis). The aim of the DIAMONDS project (2020–2024) is to design new diagnostic tests that can quickly and accurately tell what illness a patient has when they come to a hospital with common symptoms such as a fever. This would help give patients the right treatment at the right time ("personalised medicine"). An international and a multi-disciplinary team of researchers and scientists from across 28 institutions and 13 countries (11 out of the 13 being European countries) are working on this project. Besides that, we have studied other infections, including the human bocavirus (HboV) [9], rotavirus



From the left: Associate Professor Jana Pavāre, Dean of the Faculty of Medicine, RSU; Professor Dace Gardovska, Head of the Paediatric Department, RSU; Professor Aigars Pētersons, Rector of the RSU; Valts Ābols, Chair of Board, Children's Clinical University Hospital

[10], tick-born encephalitis [11] and respiratory syncytial virus (RSV) [12, 13] in children. We proved the usefulness of the introduction of a rotavirus vaccine for infants in Latvia and studied evidence of the human bocavirus HBoV in the aetiology of diseases in children, epidemiology and treatment options for RSV bronchiolitis, variations in paediatric hospital antibiotic use and levels of paediatric preparedness for emergency situations in Latvian hospitals [14].

Since SARS-CoV-2 was first identified in December 2019, it has become a global pandemic at an incredible rate. In March 2020, we successfully started studies on COVID-19 and since then we have been conducting an investigation on laboratory-confirmed SARS-CoV-2 infected children in Latvia. This study includes long-term follow-up and evaluation of how COVID-19 affects the quality of life to understand all phases of the disease and its outcomes. We have performed SARS-CoV-2 serological testing

in children with chronic diseases with no COVID-19 clinical evidence to understand the spread of the infection in this population. SARS-CoV-2 seroprevalence is only 1.7% among children with chronic diseases enrolled in the study, which means that this group of children is not protected against SARS-CoV-2 infection and it would be risky and unethical to wait for an asymptomatic natural infection. We have recommended the Ministry of Health to support prioritising the vaccination of family members of children with chronic diseases. In addition, evaluating the health-related quality of life in children with chronic diseases, we found that the emotional health and school/educational activities are most affected by the pandemic. Despite all restrictions, physical health and social activity are less affected. This means that instead of informing adults alone, the information has to contain understandable explanations for children as well.

The most important value of our research projects is to develop a generation of motivated young scientists. Over the last 15 years, eight researchers have defended doctoral theses and been awarded PhDs in the field of paediatric infectious diseases. The next five dissertations are currently being prepared. The RSU Department of Paediatrics has become an internationally recognised centre for the research of paediatric infectious diseases. In close cooperation with the Children's Clinical University Hospital, the RSU Institute of Microbiology and Virology, Department of Human Physiology and Biochemistry, and the RSU Institute of Oncology, E. Gulbis Laboratory Ltd, and our international partners we try to give the best possible input for improving children's health in Latvia.

Where next? In the USA, mortality and prevalence data from nationally representative disease statistics provide the public and policymakers with information that is helpful for understanding research portfolios, the budget and its relationship to public health needs. The budget for paediatric research in National Institutes of Health (NIH) in 2015 was 3632bn USD. The aim of the article is not to compare research budgets in different countries, but rather to be a reminder that the return on investment for paediatric research does not only have a direct impact on improving children's health. It is now recognised that adult health risks and chronic diseases have their antecedent early in life (even before birth) and that paediatric research is really lifespan research. The future of paediatric medicine depends on young scientists who are interested in children's health and research, but in order for this to happen, long-term, sustainable funding for paediatric research must become a priority for the state. We understand that researchers have to meet foreseeable national goals, but sometimes it is not so easy to measure for short period. When Gladstone, the British Chancellor of the Exchequer in the 1850s, asked physicist Faraday whether electricity had any practical value, Faraday replied: "One day, Sir, you may tax it."

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