Summaries Schroten/Wirth: Pediatric Infectious Diseases Revisited

Summary
Rudolf H. Tangermann, Hanna Nohynek and Rudolf Eggers
Global control of infectious diseases by vaccination programs

In both industrialized and developing countries, childhood immunization has become one of the most important and cost-effective public health interventions. National immunization programmes have prevented millions of deaths since WHO initiated the 'Expanded Programme on Immunization (EPI)' in 1974. Smallpox was eradicated in 1979, poliomyelitis is on the verge of eradication, and 2/3 of developing countries have eliminated neonatal tetanus. Global immunization coverage was at 78% in 2004. Through their impact on childhood morbidity and mortality, immunization programmes are contributing to reaching the 'Millenium Development Goal 4' – a 2/3 reduction of under-five mortality by 2015. However, the failure to reach > 20% of the world's children with existing vaccines was responsible for at least 2.5 million of an estimated 10.5 million deaths of children < 5 years, mainly in developing countries. Of these deaths, 1.4 million could have been prevented by vaccines currently recommended by WHO.
Rapid progress in understanding of infectious disease pathogenesis, immunology, and biotechnology has increased the number of candidate vaccine antigens available. Pressures are growing on public health decision makers to establish evidence-based ways to decide which new vaccines should be introduced on large scale into national immunization programmes. The gap in access to new vaccines between the developing and industrialized world is still wide, and wealthy countries are still the first to introduce and use new vaccines.
Interest from countries and partner agencies in vaccination, as one of the most cost-effective public health interventions, continues to be strong**,** also due to rapid progress in biotechnology and vaccine development and the emergence of global infectious disease threats, including HIV/AIDS, SARS, and influenza. The establishment of the Global Alliance for Vaccines and Immunization (GAVI) has focused global activities to support vaccination programs through raising considerable funds, and to assist especially poorer countries in improving and expanding their vaccination programmes. Global efforts concentrate on further reducing the gap in access to all existing vaccines between industrialized and developing countries.

Duncan Steele
Potential impact of rotavirus vaccination on the mortality of children in developing countries

The global burden of rotavirus infection and associated mortality in infants and young children has led to the international prioritization of the development of a rotavirus vaccine. In recent months, two new rotavirus vaccines have been licensed by the multinational pharmaceutical industry and are currently being introduced into routine childhood immunization schedules in the Americas and Europe. However, for the full impact of these rotavirus vaccines to be felt they need to be introduced into Africa and Asia where the bulk of rotavirus associated mortality occurs. Several questions regarding the efficacy of the vaccines in these settings remain, as well as questions of supply and pricing of the vaccines.

Summary
Sieghart Dittmann
Controversially discussed indications for immunization

The indication for immunization in general or indications for selected vaccines are sometimes discussed controversially by parents, the media and even by some parts of the medical community. This controversial discussion can cause confusion for people who want to make decisions about immunization for their children or themselves. There is clearly a need for accurate and evidence-based information about indications and effectiveness of vaccines as well as about the risks from natural diseases compared with potential risks of adverse events following immunization. This chapter deals with

- immunization as a safe and very effective disease prevention measure
- indications for immunization of selected risk groups, and
- contra-indications and false contra-indications.

The first part raises the most controversial questions (many diseases already disappeared due to improved socioeconomic conditions before vaccines were introduced; when a disease is gone there is no need to continue with immunization; natural immunity is better than vaccine-induced immunity; many vaccines are useless and not able to prevent disease; multiple immunizations overload the immune system; some vaccines are not safe and cause more complications than the natural disease) and tries to provide evidence-based answers.
The second part deals with controversially discussed indications/contraindications for selected risk groups such as pregnant and breast-feeding women, pre-term babies, individuals with chronic diseases or immunodeficiency, patients with bleeding disorders and patients receiving anticoagulant medication.
In the last part genuine contraindications against distinct vaccines are discussed as well as health conditions falsely believed by the physician or the health worker to constitute a contraindication.

Summary
Axel Schmidt
Gonorrheal ophthalmia neonatorum: historic impact of Credé's eye prophylaxis

In the pre-antibiotic era gonorrhea showed a high prevalence also in industrialized countries. In Germany, more than 10% of all newborns developed gonorrheal ophthalmia neonatorum. Clinical courses of gonorrheal ophthalmia neonatorum were quite different in their severity but often caused significant impairment of eyesight up to total blindness in more than 5%. This accounted for 25–40% of cases of blindness in Germany. It was Carl Siegmund Franz Credé (1819–1892), a German obstetrician, who introduced the eye prophylaxis of eye drops containing 2% silver nitrate solution to every newborn child in his clinic in Leipzig on June 1st 1880. The incidence of gonorrheal ophthalmia neonatorum immediately decreased from 10% to 0%. Credé actively communicated these results and immediately published them in four publications within a time period of 3 years. These publications, which are discussed here, are written in a very pragmatic and strictly clinical style, ignoring new basic scientific insights into the microbiology of gonorrhea and the discovery of the corresponding pathogen, the "*Micrococcus*" by Albert Neisser, which Credé considered unimportant for his purposes. Against a high degree of opposition by many physicians, Credé put all enthusiasm into the call for education of midwives in this technique. Credé knew that this was the central way to ensure that all newborns could obtain this prophylaxis, including outpatients and home deliveries. Credé's eloquence led to the rapid spreading of "his" eye prophylaxis over the rest

of the world. The concentration of silver nitrate was often reduced from 2% to 1% thereafter and in most countries the performance of this prophylaxis was rapidly enforced by law. By introducing this method, Credé saved or improved the eyesight of millions of people – a significant contribution to obstetrics, neonatology and pediatrics, ophthalmology and mankind. Still today, in the antibiotic era, other topical regimens for antiseptic prophylaxis against ophthalmia neonatorum are often referred to as “Credé's prophylaxis”.

Summary
Susanna Cunningham-Rundles and Deborah Ho Lin
Malnutrition and infection in industrialized countries

Malnutrition is a major cause of immune deficiency that directly affects the acute phase response and leads to greater frequency and severity of common infections. Primary malnutrition is not uncommon in wealthy industrialized societies due to poverty, lack of education, food allergies, inappropriate or limited diet, or eating disorders. Inadequate intake of micronutrients including vitamin A, E, calcium, iron and zinc are prevalent among children under 10 years of age and often unrecognized. Although chronic infectious diseases are less prevalent in industrialized countries, infections with HIV, *Mycobacterium tuberculosis* and hepatitis C virus are significant problems and parasitic infections may appear among immigrant populations. Obesity is becoming increasingly common in children and may enhance risk of serious complications of common infections. Adequate nutrition is critically important for the development of the immune system, immune response to environmental antigens and pathogens, and for the maintenance of host defense. In children with congenital anomalies or medical conditions affecting growth, poor nutrient status will have a disproportionate effect on development, immunity, and susceptibility to infection since nutrients are cofactors in immune response. Defects in T cell immunity lead to increased susceptibility to intracellular pathogens, reactivation of viral infections, and development of opportunistic infections. Zinc deficiency inhibits Th1 cytokine responses, thymic hormone activity, and lymphopoiesis. Vitamin A deficiency is associated with severity of many infections including measles, rotavirus, HIV, and bacterial infections. Selenium deficiency is associated with HIV progression. Nutrient cofactors of innate immune response include 1,25-dihydroxyvitamin D3, which is a direct regulator of antimicrobial responses. The overall impact of chronic subclinical malnutrition in children may determine the quality and duration of immune response to vaccines and may be an important topic for future research.

Summary
Matthew Jukes
Better education through improved health and nutrition: Implications for early childhood development programs in developing countries

Before children reach school age they must negotiate threats from a number of diseases. More than 50% of child deaths are caused by pneumonia, diarrhea, malaria, measles, malnutrition and HIV. For those who survive, health and nutrition can affect children’s development. School readiness depends on cognitive, motor and socio-emotional development, which can be affected by, among other things, undernutrition, iron deficiency anemia and malaria. There is clear evidence of the benefits of preschool health and nutrition interventions to tackle these three conditions. For malnourished children, psychosocial stimulation can be as effective as

nutritional supplementation in compensating for delayed cognitive development. In general, interventions in this preschool age group have substantial and consistent effects on development and education, which are generally larger than for school-age children. Effects are seen in all dimensions of school readiness – cognitive, motor and socio-emotional development – but are perhaps greatest for motor development. They also have a greater impact on the most disadvantaged children and can help to promote equity in educational outcomes. Overall, evidence suggests that early childhood health and nutrition interventions have the potential to make a major contribution to achieving the goal of Education for All.

Summary
Shigenobu Kimura and Yuko Ohara-Nemoto
Early childhood caries [ECC] and childhood periodontal diseases

Dental caries and periodontal diseases are one of the most prevalent diseases affecting adults and children in industrialized countries. The major causative factor in both diseases is the microbial biofilm (dental plaque) formed on teeth and oral epithelial surfaces, and early childhood caries and periodontal diseases are both plaque-induced infectious diseases caused by endogenous bacteria. However, it is also evident that the colonization of the putative pathogenic bacteria in plaque is not sufficient for the initiation and onset of these plaque diseases. In dental caries, it is apparent that the association of dietary fermentable carbohydrates, especially sucrose, is implicated in the etiology. Moreover, recent studies also acknowledge the significant role of the local environmental conditions in plaques. In periodontal diseases, the host response plays a major role in the outcome of the diseases. The present review addresses the pathogenic bacteria and microflora and the etiology of early childhood caries and childhood periodontal diseases.

Summary
Rüdiger Adam, Kwang Sik Kim and Horst Schroten
Role of the blood-brain barrier and blood-CSF barrier in the pathogenesis of bacterial meningitis

Despite significant progress in prevention, diagnosis and therapy acute bacterial meningitis remains an important cause of high morbidity and mortality in the pediatric population with no significant improvement in the outcome in recent years. Further amelioration in treatment can only result from a better understanding of the pathophysiological events that occur after activation of the host's inflammatory pathways secondary to initial bacterial invasion. The need for improved management strategies is highlighted by the observed increase in antibiotic resistance of microbial pathogens and recent developments in the pharmacological treatment of meningitis patients with dexamethasone, which might adversely influence delivery of drugs to the central nervous system (CNS). In this respect the cellular and molecular events at the blood-CNS barriers come to the focus of attention. It has become evident that these anatomical and functional barriers with their differentiated functionality and vast surface area centrally contribute to the development of bacterial meningitis. This holds true not only for their role as a port of entry into the CNS but also as key players in the pathophysiological cascade following bacterial invasion into the brain. Important aspects that have to be considered are the unique anatomical and functional features of the blood-brain barrier and

the blood-cerebrospinal fluid barrier, and their distinct interactions with the variety of pathogens responsible for the development of bacterial meningitis.

Summary
Ian A. Clark and Michael J. Griffiths
The molecular basis of paediatric malarial disease

Severe falciparum malaria is an acute systemic disease that can affect multiple organs, including those in which few parasites are found. The acute disease bears many similarities both clinically and, potentially, mechanistically, to the systemic diseases caused by bacteria, rickettsia, and viruses. Traditionally the morbidity and mortality associated with severe malarial disease has been explained in terms of mechanical obstruction to vascular flow by adherence to endothelium (termed sequestration) of erythrocytes containing mature-stage parasites. However, over the past few decades an alternative 'cytokine theory of disease' has also evolved, where malarial pathology is explained in terms of a balance between the pro- and anti-inflammatory cytokines. The final common pathway for this pro-inflammatory imbalance is believed to be a limitation in the supply and mitochondrial utilisation of energy to cells. Different patterns of ensuing energy depletion (both temporal and spatial) throughout the cells in the body present as different clinical syndromes. This chapter draws attention to the over-arching position that inflammatory cytokines are beginning to occupy in the pathogenesis of acute malaria and other acute infections. The influence of inflammatory cytokines on cellular function offers a molecular framework to explain the multiple clinical syndromes that are observed during acute malarial illness, and provides a fresh avenue of investigation for adjunct therapies to ameliorate the malarial disease process.

Summary
Wilbert Mason
Epidemiology and etiology of Kawasaki disease

Kawasaki disease was first reported in Japan in 1967 by Dr. Tomisaku Kawasaki. It has since been recognized worldwide, and in at the United States and Japan is the most important cause of acquired heart disease in children, surpassing other more recognized conditions such as rheumatic fever, endocarditis and myocarditis. It is primarily a disease of children less than 5 years of age but has been reported in older children and adults. Risk factors for the illness include Asian ancestry, male gender and certain familial predispositions. Observations such as similarity to certain exanthematous infectious diseases, temporal-geographic clustering of cases and seasonality in incidence favors an infectious etiology. Pathology and pathogenesis of the disease indicate that it is a medium-sized artery vasculitis that results from a dramatic immune activation that in most cases reversed by immune modulating agents such as intravenous immunoglobulin. Unfortunately, the etiology of the illness remains obscure, although recent studies favor a possible viral etiology.

Summary
Hien Q. Huynh
***Helicobacter pylori* infection in children**

Helicobacter pylori is generally acquired in childhood, and the prevalence of this infection varies between and within populations and is decreasing in the developed world. The clinical manifestation of diseases is dependent on the interaction between host, environmental and bacterial factors. The mode of transmission is likely person to person. Strong evidence has accumulated, establishing the causal link between peptic ulcer disease, gastric cancer and mucosal associated lymphoma with H. pylori infection. The association with refractory iron deficiency anemia and idiopathic thrombocytosis purpura are compelling but need more studies. New indications for the eradication of H. pylori are emerging – such as those with strong family history of gastric cancer. Prevention of gastric cancer may require eradication of this bacterium in childhood prior to the development of precancerous lesions. A test-and-treat strategy is not indicated for those with recurrent abdominal pain. In addition, the rate of antibiotic resistance has increased in some populations. Novel eradication strategies need to be developed. Improving the children socioeconomic situation, such as better housing, sanitation and hygiene, remains one of the major pillars in reducing the prevalence of H. pylori children and its diseases burden.

Summary
Adilia Warris and Ronald de Groot
Human metapneumovirus infection

Initially, human metapneumovirus (hMPV) was isolated from children with clinical symptoms of respiratory syncytial virus (RSV) infection in whom RSV could not be detected. Since then, numerous reports have described the detection of hMPV in clinical specimens from children, adults and the elderly (both immunocompetent and immunocompromised patients), diagnosed with an acute respiratory illness all over the world. hMPV is associated with a substantial number of respiratory tract infections in otherwise healthy children, with clinical illnesses similar to those associated with other common respiratory viruses. Serological surveys have shown that hMPV is a ubiquitous virus that infects all children by the age of 5–10 years and has been circulating in humans for at least 50 years. hMPV is a member of the Metapneumovirus genus of the Paramyxoviridae family, a group of negative-stranded RNA viruses. Genetic studies on hMPV have demonstrated the presence of two distinct hMPV serotypes each divided in two subgroups. Diagnosis is made by RT-PCR assays on respiratory secretions. Rapid antigen detection tests are not yet available and its growth in cell cultures is fastidious. No vaccines, antibodies (monoclonal or polyclonal), or chemotherapeutic agents are currently licensed for use to prevent or treat hMPV infections. The contribution of hMPV to pediatric respiratory tract infections suggests that it will be important to develop a vaccine against this virus in combination with those being developed for RSV and parainfluenza viruses. Reverse genetics technology is currently used to develop multivalent vaccines against hMPV and a variety of other important respiratory viruses such as RSV. Additional research to define the pathogenesis of this viral infection and the host' specific immune response will enhance our knowledge to guide the search for preventive and therapeutical strategies.

Summary
John V. Williams
Avian influenza viruses: a severe threat of a pandemic in children?

Influenza virus is a leading cause of human respiratory illnesses, causing significant annual morbidity and mortality. The greatest severity of illness due to seasonal influenza occurs in infants less than 6 months of age and the elderly. In recent years, avian influenza virus infections with high mortality have occurred in humans. Many of these avian influenza virus infections have occurred in children, and unlike seasonal influenza, the most severe disease and highest death rates have occurred in children and young adults. Treatment and prevention options for avian influenza viruses are limited at present, although much research effort is directed toward these areas. Avian-derived influenza viruses are potential causes of pandemic influenza that could have a dramatic impact on children worldwide.

Summary
Nanette B. Silverberg
Human papillomavirus infections in children

Human papillomavirus (HPV) is a ubiquitous double-stranded DNA virus that infects human squamous cells causing a variety of clinical diseases ranging from plantar or common warts to genital warts to neoplasia of the cervix and genitalia. Over 200 HPV types have been characterized, but only about 20 are commonly identified in pediatric skin lesions. Once infected, the host requires an extended time period to produce antibodies and a cell-mediated immune response against HPV. Two out of three patients will achieve natural immune clearance by 2 years and three out of four by 3 years. Therapy of HPV infections includes agents that destroy the lesion, agents that induce immune response by the host, and removal techniques. For genital HPV, prevention of initial HPV infection is now the therapeutic gold standard and can be achieved by vaccination with a quadrivalent HPV 6, 11, 16, 18 vaccine in three doses introduced before an adolescent's sexual debut. Another problem that may be alleviated long-term by HPV vaccination is the vertical transmission of genital HPV, which can result in pediatric condyloma or juvenile onset recurrent respiratory papillomatosis (juvenile laryngeal papillomatosis). Genital warts in childhood that cannot be documented to have occurred via vertical transmission from an infected mother must be presumed to be sexually transmitted and may be the result of sexual abuse in elementary school children. Until vaccination has become widespread, genital HPV infections must be carefully screened through papanicolaou screening, HPV screening and cytology.

Summary
Patrick Gerner
New treatments for hepatitis B and C in children and adolescents

The treatment of chronic viral hepatitis is a rapidly evolving field. Therapy for chronic hepatitis B is indicated at times of high viral replication, as long as the patient's aminotransferase levels are increased by more than twice the norm, and when hepatitis B e antigen (HBeAg) is positive. The treatment options for chronic hepatitis B include interferon-alpha and the nucleoside analogues lamivudine and adefovir dipivoxil. Between 26% and 38% of patients respond to treatment with interferon-alpha and nucleoside analogues; from

17% to 36% respond with antibodies to HBeAg (anti-HBe) seroconversion after 1 year. With seroconversion, HBeAg disappears and there is a dramatic decrease in HBV-DNA and usually in the aminotransferases. Further development of nucleoside analogues promises to increase the effectiveness of the therapy. Complete recovery, with conversion to antibodies to hepatitis B surface antigen (anti-HBs), occurs in about 5% of patients only after interferon-alpha therapy. The success of treatment is influenced by factors such as the origins of infection, the viral load before therapy, and the intensity of liver inflammation. Without therapy, the rate of seroconversion to anti-HBe ranges from 2.5% to 11% a year. It is becoming evident that patients with fulminant hepatitis B benefit from treatment with lamivudine. In contrast to hepatitis B, the treatment goal for chronic hepatitis C is the patient's full recovery. Currently, depending on the HCV genotype, the combination therapy of interferon-alpha and ribavirin administered for 6–12 months has proven effective. Approximately 80% of children are infected with genotype 1a or 1b. They have a recovery rate of 45%. Genotypes 2 or 3 respond much better to treatment. More than 84% of patients can be successfully treated. Genotype 4 is relatively rare and appears to respond to treatment like genotype 1. Under certain circumstances, unsuccessfully treated patients can be treated a second time, after a number of years, with another interferon-alpha, e.g., natural human alpha interferon (Multiferon®) or consensus interferon (Inferax®) plus ribavirin. In addition, new medications such as protease and polymerase inhibitors are currently being tested in adult patients and should be available in the next few years.

Summary
Andreas H. Groll, Julia Koehler and Thomas J. Walsh
Invasive fungal infections in children: advances and perspectives

Invasive fungal infections are important causes of morbidity and mortality in immunocompromised children. The past two decades have seen a dramatic increase in both number and overall relevance of invasive fungal infections in the hospital. At the same time, however, improved microbiological and imaging techniques together with an increased awareness have shifted the diagnosis of fungal infections from the autopsy theatre to the bedside. Major advances have been made in the definition of fungal diseases, the algorithms of antifungal interventions, the design and implementation of clinical trials and the development of standardized in vitro susceptibility testing. Most importantly, however, an array of new antifungal agents has entered the clinical arena and has made antifungal therapy more safe, more effective, but also more complicated. This article reviews some unique features of invasive fungal infections in infants and children and provides an update on the pharmacology of antifungal therapeutics in the pediatric population.

Summary
Kwang Sik Kim
Pediatric aspects of bioterrorism

Potential microbes for bioterrorism threats include Bacillus anthrax, Yersinia pestis, Francisella tularemia, Clostridium botulinum, variola virus and hemorrhagic fever viruses such as Ebola. This review covers selective topics associated with anthrax and smallpox, such as epidemiology, pathogenesis, clinical presentation, diagnosis, prevention, and therapy, as well as approaches for clinical management of children in suspected exposure to anthrax and

smallpox. Information is lacking regarding weaponized anthrax spores, including LD50, optimal management, alternatives for antibiotic-resistant strains and use of genetically modified strains to escape vaccine protection. The recent US outbreak in 2001 highlights the following features: case fatality rates of 45%, no secondary cases among household contacts of the inhalation anthrax subjects and no cases of anthrax among individuals on antibiotic prophylaxis. Regarding smallpox, discussions have concerned the identification of first response individuals and vaccination of such individuals; however, smallpox vaccine is associated with mortality and morbidity, and current issues include principles and procedures associated with vaccination.

Summary
David Nadal
Pediatric infectious diseases – Quo vadis 2015?

In modern medicine the discipline pediatric infectious diseases is an essential medical specialty. The challenging and complex tasks in the next years include meticulous consolidation and careful extension of existing activities aiming at conducting high level research, offering high standard teaching, and providing high quality patient management. This can only be accomplished by exquisitely dedicated individuals with extraordinary communication and integrative skills following painstaking continued training and formation. Potential careers in the discipline can be envisioned not only in academics, but also in government, public health, and industry, whilst less likely in private practice.

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