

Current views and advances on Paediatric Virology: An update for paediatric trainees (Review)

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Abstract. Paediatric Virology is a bold new scientific field, which combines Paediatrics with Virology, Epidemiology, Molecular Medicine, Evidence-based Medicine, Clinical

Governance, Quality Improvement, Pharmacology and Immunology. The Workshop on Paediatric Virology, which took place on Saturday October 10, 2015 in Athens, Greece, provided an overview of recent views and advances on viral infections occurring in neonates and children. It was included in the official programme of the 20th World Congress on Advances in Oncology and the 18th International Symposium on Molecular Medicine, which attracted over 500 delegates from the five continents. During the Workshop, the topics covered included the challenges of vaccine implementation against human papillomaviruses in countries under financial crisis, strategies for eradicating poliomyelitis and its 60th vaccine anniversary, as well as the debate on the association between autism and vaccination against measles, mumps and rubella. Among the non-vaccine related topics, emphasis was given to viral infections in prematurely born infants and their long-term outcomes, new paediatric intensive care management options for bronchiolitis related to respiratory syncytial virus, the clinical implications of hepatitis B virus and cytomegalovirus genotyping, the Ebola virus threat and preparedness in Paediatric Emergency Departments, oral, oropharynx, laryngeal, nasal and ocular viral infections and Merkel cell polyomavirus as a novel emerging virus of infancy and childhood. In this review, we provide selected presentations and reports discussed at the Workshop.

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Abbreviations: AFP, acute flaccid paralysis; AIDS, acquired immunodeficiency syndrome; ALTO, alternative tumor antigen open reading frame; ASD, autism spectrum disorders; BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; EBV, Epstein Barr virus; ED, emergency department; EEA, endoscopic endonasal approach; ELISA, enzyme linked immunosorbent assay; EV, Ebola virus; HBV, hepatitis B virus; HBcAg, hepatitis B capsid protein; HBeAg, hepatitis B e antigen; hMPV, human metapneumovirus; HPV, human papillomavirus; HRV, human rhinovirus; HSV, herpes simplex virus; IM, infectious mononucleosis; IPV, inactivated polio vaccine; LRTI, lower respiratory tract infection; LT, large tumor; MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; MMR, measles, mumps and rubella; NCRR, non-coding regulatory region; NICU, Neonatal Intensive Care Unit; OPV, oral polio vaccine; PICU, Paediatric Intensive Care Unit; PPE, personal protective equipment; PVSG, Paediatric Virology Study Group; RCPCH, Royal College of Paediatrics and Child Health; RNA, ribonucleic acid; RRP, recurrent respiratory papillomatosis; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome; SNP, single nucleotide polymorphism; sT, small tumor; TLM, transoral laser microsurgery; VP 1-3, viral protein 1-3; VZV, varicella-zoster virus; WHO, World Health Organization; WNV, west Nile virus; WPV, wild-type poliovirus

Key words: Paediatric Virology, viral infections, human papilloma virus, respiratory syncytial virus, hepatitis B, poliomyelitis, Ebola, measles, mumps, rubella, infectious mononucleosis, Merkel cell polyomavirus

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1. Introduction

The history of paediatric infectious diseases closely parallels the history of Paediatrics, as infections remain the major causes of childhood morbidity and mortality (1,2). Viral paediatric infectious diseases are characterised by a great heterogeneity of clinical manifestations due to the unique characteristics of the neonatal period and childhood. Almost 50 years ago, Paediatric Virology was not considered an isolated discipline and was included in the paediatric infectious diseases section of the scientific field of Paediatrics (3). However, during the past two decades, new advances in the field of Clinical Virology and Molecular Medicine have expanded the level of knowledge on the prevention, diagnosis and treatment of viral infections occurring in infancy and childhood. For this reason, although additional subspecialists in several fields may be diminishing (4), Paediatric Virology as a bold new scientific field can combine Paediatrics with Virology, Epidemiology, Molecular Medicine, Evidence-based Medicine, Clinical Governance, Quality Improvement, Pharmacology and Immunology (Fig. 1).

To date, paediatric infectious diseases professionals have achieved a distinct role within the scientific field of Paediatrics and their contribution to tertiary paediatric care is valued (2). Their current clinical and research aims are to resolve important public health issues in both developed and developing countries. Furthermore, new emerging diseases, such as severe acute respiratory syndrome (SARS), west Nile virus (WNV) and Ebola virus (EV) infections, require new prevention strategies and therapeutic protocols. In addition, paediatric infectious diseases professionals are involved in specialised paediatric care and in the follow-up of children with a history of viral infections, such as viral meningitis or acquired immunodeficiency syndrome (AIDS), who survive to adolescent years and beyond, requiring advanced medical care and technological services. Moreover, newfound social issues have arisen, including the recent anti-vaccination wave, the financial crisis and the unprecedented immigration occurring globally and in Mediterranean countries, in particular (5). These developments and changes definitely highlight the demand for the continuous education of paediatric health professionals, informing them of the ongoing advances in paediatric care and management strategies involved in the discipline of Paediatric Virology (6,7).

2. Workshop on Paediatric Virology

The 20th World Congress on Advances in Oncology and the 18th International Symposium on Molecular Medicine was held in Athens (Greece) and was attended by >500 participants from the five continents (8). This annual scientific meeting attracted its largest number of delegates to date and over a period of three days, up-to-date basic and clinical research findings on Molecular Medicine and Oncology were presented and discussed. For the first time this year, during the third day of the meeting, participants had the chance to participate in the Workshop on Paediatric Virology, with the theme 'Paediatric Virology: from the lab to clinical practice' (Fig. 2). This Workshop gathered world experts on Paediatrics, Neonatology, Virology, Vaccinology, Epidemiology, Microbiology and Public Health. It was co-chaired by Professor Anne Greenough, Professor of Neonatology and Clinical Respiratory Physiology at King's

College London in London (UK) and Vice-President of the Royal College of Paediatrics and Child Health (RCPCH), Professor Anna Kramvis, Research Professor of Molecular Virology at the University of the Witwatersrand in Johannesburg (South Africa) and Professor Maria Theodoridou, Professor of Paediatrics at the 'Aghia Sophia' Children's Hospital in Athens (Greece). The Workshop was enthusiastically supported by the Department of Clinical Virology, School of Medicine, University of Crete in Heraklion (Greece) and the First Department of Paediatrics of the School of Medicine at the University of Athens in Athens (Greece).

The initial idea for the birth of this Workshop was inspired in 2007 at the Wirral University Teaching Hospital in Wirral (UK), where cytomegalovirus (CMV)-positive twins were treated at the local Neonatal Intensive Care Unit (NICU) (9), requiring the collaboration of an extended scientific network in Merseyside and Manchester (UK) for the management of this neonatal viral infection. Two years later, in October 2009, during the oral session at the 14th World Congress on Advances in Oncology and the 12th International Meeting in Molecular Medicine, which was devoted to human papilloma virus (HPV) infection in childhood (10) and chaired by Professor Maria Theodoridou, Professor of Paediatrics at the 'Aghia Sophia' Children's Hospital in Athens (Greece), this idea was re-enforced by a group of young paediatric trainees and junior researchers, leading to the creation of the Paediatric Virology Study Group (PVSG). The fundamental aim of the PVSG was to provide an array of scientific and educational activities, bringing together Virology with Paediatrics within a single entity. Covering Basic Sciences and Clinical Medicine, the PVSG was open to scientists interested in the field of Paediatric Virology, either as basic scientists, researchers and virologists or as medical students, paediatric trainees, general paediatricians, paediatric infectious diseases physicians and allied health professionals. Six years later, on October 2015, the PVSG had the great honour to coordinate the 'Workshop on Paediatric Virology' as an official session of the 20th World Congress on Advances in Oncology and the 18th International Meeting in Molecular Medicine. This Workshop was dedicated to promoting international scientific exchange and cooperation of both clinicians and researchers on Paediatric Virology and improving biomedical research and paediatric medical practice on viral infections occurring in childhood. In this review, we present an update on selected topics presented at the Workshop.

3. Update on current views and advances on Paediatric Virology

Viral infections and long-term outcomes of prematurely born infants. Respiratory syncytial virus (RSV) is a common respiratory pathogen in young children (11). Between 1 and 2% of infected children will require hospitalisation and up to 8% of those hospitalised will require mechanical ventilation. Numerous studies (12-16) have demonstrated that infants born at term, who were previously healthy, subsequent to an RSV lower respiratory tract infection (LRTI), develop chronic respiratory morbidity. There are many risk factors for severe acute RSV infection, which include being born prematurely and having developed bronchopulmonary dysplasia (BPD). Greenough *et al* (12) have demonstrated that up to school age,

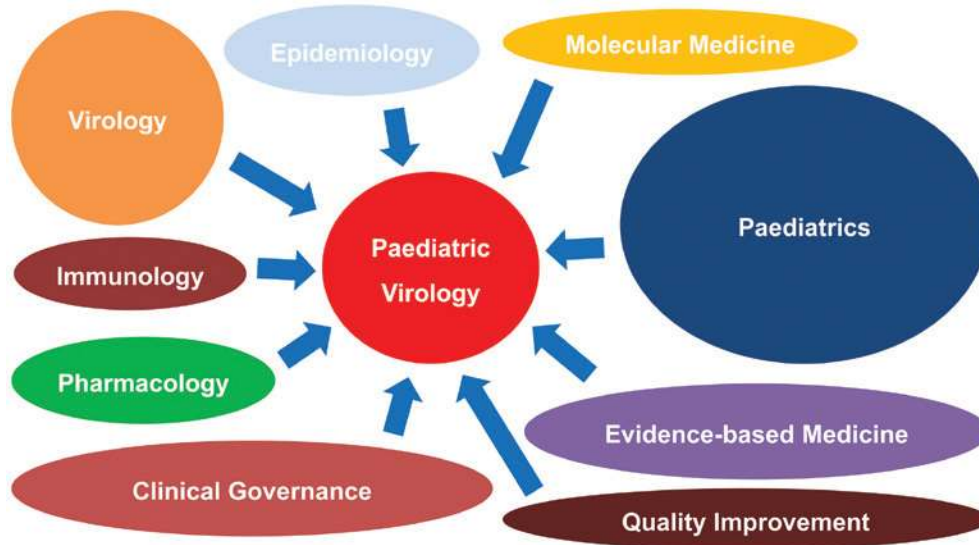


Figure 1. Paediatric Virology involves the scientific fields of Paediatrics, Virology, Epidemiology, Molecular Medicine, Evidence-based Medicine, Clinical Governance, Quality Improvement, Pharmacology and Immunology.

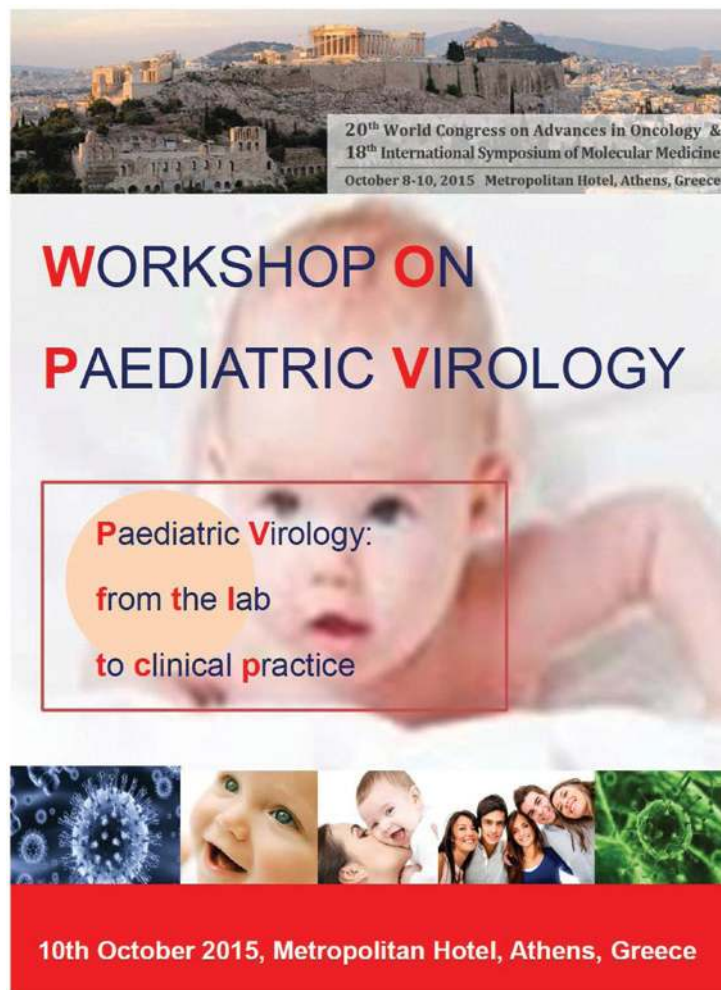


Figure 2. Workshop on Paediatric Virology with the theme 'Paediatric Virology: from the lab to clinical practice', Athens, Saturday, October 10, 2015.

those prematurely born children, who had developed BPD and an RSV LRTI requiring hospitalisation in infancy, had

increased healthcare utilisation and worse lung function, particularly affecting small airways, than children with BPD, who

had not been hospitalised due to RSV. Healthcare utilisation in the first two years after birth was also shown to be increased even in moderately prematurely born infants (32-35 weeks of gestation), who had were hospitalised due to RSV (13). In two prospectively followed cohorts, one very prematurely born cohort (14) and the other, which included pre-term infants of a wide range of gestational ages (24-35 weeks), respiratory morbidity was greater during infancy in those who had had an RSV LRTI (15,16). In the very prematurely born cohort, subsequent respiratory morbidity was increased after an RSV LRTI regardless of whether hospitalisation was required or the infant had BPD (14). The prematurely born infants, who required hospitalisation due to an RSV LRTI, had poorer premorbid lung function (17). It has also been identified that prematurely born infants may have a genetic predisposition to developing RSV LRTIs. In addition, single nucleotide polymorphisms (SNPs) in several genes were found to be associated with chronic respiratory morbidity during infancy and reduced lung function at one year following an RSV LRTI (18). Other respiratory viral infections also adversely influence respiratory outcomes during infancy in those born prematurely, including human metapneumovirus (hMPV) and human rhinovirus (HRV), particularly HRV-C (19).

Defeating polio: Vaccine anniversary (1955-2015).

Poliomyelitis is an acute infectious disease affecting humans, occurring particularly in children, which is caused by small ribonucleic acid (RNA) viruses of the enterovirus group of the family *Picornaviridae* (20-26). Three antigenically distinct strains (strains 1, 2 and 3) are known, with-type 1 accounting for 85% of cases. The clinical manifestations of the disease vary greatly. Most cases are asymptomatic; paralytic illness is rare, affecting <1% of infected individuals. The year 2015 is the 60th anniversary since Jonas Salk launched the inactivated polio vaccine (IPV), enabling children to be protected against the crippling disease of poliomyelitis. With the development of the oral polio vaccine (OPV) by Albert Sabin in 1961, the world was given the tools, with which to stop outbreaks, strengthen and build immunity, to ensure that children can grow up without the threat of polio. The combination of OPV and IPV led to the eradication of polio in the Americas, the western Pacific and Europe. Today, 80% of the world population lives in polio-free regions. Nevertheless, Pakistan, Afghanistan and Nigeria are countries where polio is still categorised as an endemic viral infection. It should be noted that in 2013-2014 an upsurge of polio in areas, which were considered polio-free, occurred. The confirmed circulation of wild-type poliovirus (WPV) in Israel and the outbreak of acute flaccid paralysis (AFP) in Syria mean that there is a high risk of the disease being reintroduced into Europe. Europe should implement a prevention policy, which is based on enhancing the vaccination of resident and refugee populations, strengthening surveillance and being prepared to rapidly respond to the identification of polio. In Greece, there is a national action plan, which includes programmes to sustain high levels of polio immunisation coverage, AFP surveillance and actions in the event of a suspected or confirmed poliomyelitis case. Fighting polio with vaccination has been one of the most successful public health programmes in history, reducing the number of polio cases by 99%, making possible the expectation towards disease eradication.

Clinical implications of hepatitis B virus (HBV) genotypes in Paediatrics. Even though a successful vaccine against HBV has been implemented in 184 countries, the eradication of HBV is still not on the horizon (27). According to the World Health Organization (WHO), there are 240 million chronic carriers of the virus, globally (28). The risk of developing chronic hepatitis ranges from >90% in newborns of hepatitis B e antigen (HBeAg)-positive mothers, 25-35% in children under the age of 5 and <5% in adults (29). HBeAg, a non-particulate viral protein, is conventionally considered a marker of HBV replication (30). This is the only antigen of HBV, which can cross the placenta (31), leading to the specific unresponsiveness of helper T cells to the hepatitis B capsid protein (HBcAg) and HBeAg in newborns of HBeAg-positive mothers (32). HBeAg is tolerated *in utero* and acts as a tolerogen after birth (33). Thus, perinatal transmission is frequent when mothers are HBeAg-positive, whereas it occurs significantly less frequently when mothers are HBeAg-negative (34-36).

Sequence heterogeneity is a characteristic of HBV, the prototype member of the family *Hepadnaviridae* (37). Based on an intergroup divergence of >7.5% across the complete genome, HBV has been classified phylogenetically into at least 9 genotypes. With between ~4 and 8% intergroup nucleotide divergence across the complete genome and good bootstrap support, genotypes A-D, F, H and I are further classified into subgenotypes. HBV genotypes and in some cases subgenotypes have a distinct geographical distribution both globally and locally (37). The different genotypes/subgenotypes can develop different mutations in the regions of the HBV genome, which code for HBeAg and the envelope proteins. These differences can be related to the role of the HBV genotypes, to their mode of transmission, to the clinical manifestation of the disease following HBV infection and to their response to antiviral therapy. Thus, the genotypes/subgenotypes of HBV may be responsible for the different modes of transmission and natural history of infection in children, noted in different regions of the world, where distinct genotypes/subgenotypes prevail.

Implementation of vaccination against HPV in a country under financial crisis. Despite the invention of the Pap smear test by George N. Papanicolaou almost 90 years ago, HPV is considered the most frequent carcinogen in humans, causing approximately 530,000 cases of cervical cancer per annum, with the majority of cases occurring in developing countries (38-40). The link between this deoxyribonucleic acid (DNA) virus and cervical cancer was firstly suspected in the early 1970s by Professor Harald zur Hausen, who in 2008 received the Nobel Prize in Physiology and Medicine (41). In the same year, two vaccines against HPV, the bivalent HPV 16/18 and the quadrivalent HPV 6/11/16/18, were implemented into clinical practice in several countries, worldwide (42). However, despite the significant calculated expected health benefits following the implementation of HPV vaccination programmes, current trends indicate low HPV vaccination uptake among female adolescents in several countries in Europe (43-46). These studies have also focused on potential socio-demographic factors, which influence parents' decisions to decline HPV vaccination to their daughters, including age, ethnicity, receipt of childhood vaccines, knowledge, attitudes, parental and community acceptability. Of note, in Greece, a country under financial crisis since 2010,

in which several health quality indexes have already deteriorated (47), financial reasons have also been elucidated behind non-vaccination against HPV (38). Since data on HPV vaccination among female adolescents in Greece remain limited, the first pilot cross-sectional questionnaire-based study, known as the ELEFThERIA study, was expected to assess HPV vaccination uptake among female adolescents in Greece during the period between 2008-2014 and to investigate socio-demographic reasons for declining HPV vaccination (38). It was designed by the First Department of Paediatrics at the University of Athens and the Department of Clinical Virology at the University of Crete and its name was inspired by 'Eleftheria', the name of the first adolescent, who was recruited in the study. The preliminary findings of this project stress the need to provide and maintain health insurance coverage to children in countries under financial crisis (38). For this reason, urgent health policy responses to the recent financial collapse in Greece are required as the full impact of austerity measures unfolds in the coming years.

Children and Ebola infection. EV was first discovered in 1976 and has caused three outbreaks, two simultaneously in 1976 and one in 2014 (48). The exact mode of transmission of EV remains unknown; however, it seems to be transmitted from the biological fluids of wild animals and subsequently through human-to-human contact (49). According to the WHO, the 2014 west African outbreak claimed a case fatality, which ranged from 25 to 90% and a total number of roughly 10,000 fatalities; the number of children is unknown (49). This fact makes it a potential lethal tool in bio-warfare. If used in residential areas or within the public transportation system, as a biological agent, EV can easily affect the welfare and life of children.

Emergency Departments (EDs) should be ready for such attacks, especially catering for the needs of paediatric victims (50,51). Carley's consensus statement for formulating major incident plans can be quite helpful (52). Local tertiary paediatric hospitals or paediatric units should play an active role by coordinating the care of children. Planning for such events involving children should be carried out by experienced clinicians in Paediatrics. Approximately 10-15% of the equipment used in general hospitals should be suitable for paediatric victims of all ages. Staff training for major incidents should be regular and should include caring for children. While triaging, it is advisable to use modified adult scoring systems. In particular, when triaging a large number of children, the Eichelberger modification to the triage revised trauma score should be used (48). If possible, children's assessment and treatment, as well as transfers, when needed, should be provided by experienced paediatric teams. If allowed by the senior clinician, parents could possibly stay on site near their children. During hospitalisation and following discharge, adequate support should be provided to the families (52). An ED should be ready to accommodate the needs of children following an EV attack by offering personal protective equipment (PPE) to staff, appropriate decontamination and isolation facilities and antidotes, if available, as well as general paediatric equipment. Staff should always suspect bioterrorism if a few or several people present with unusual or unexpected symptoms or if their symptoms do not conform with a certain medical diagnosis. Identify, isolate and inform is the current standard approach to EV suspicion (53). Hopefully, none of this will be actually needed in the near future.

Viral bronchiolitis in Paediatric Intensive Care Unit (PICU). Viral bronchiolitis, mainly caused by RSV infection, remains the leading cause of infant admission to the PICU (54,55). Recent laboratory tools have also confirmed many other viruses to account for bronchiolitis, either as co-infection with RSV or as the only aetiological pathogen. Such viruses are HRV, hMPV, adenovirus, as well as influenza and parainfluenza viruses (56). Even following the anti-RSV post-prophylaxis era, RSV seems to be the most common cause of bronchiolitis in infancy and is responsible for severe clinical manifestations, longer hospitalisation and PICU admissions (57). Severe bronchiolitis is indicated by persistently increased respiratory effort (tachypnoea, nasal flaring, intercostal, subcostal or suprasternal retractions, accessory muscle use and grunting) hypoxaemia, apnoea or acute respiratory failure. Risk factors for severe disease and/or complications of bronchiolitis, even death, are considered to be prematurity (gestational age <37 weeks), age <12 weeks, chronic pulmonary disease, particularly BPD (also known as chronic lung disease), congenital and anatomic defects of the airways, congenital heart disease, immunodeficiency and neurologic disease (58). Though it is a common and old clinical entity, there is a wide variety in clinical practice and the need to clarify each of the therapeutic means has to be done with large, well-designed clinical studies. When it comes to the treatment of critically ill children, there is a paucity of evidence-based guidelines. Fluid replacement, oxygen supplementation and close monitoring are the first steps in the management of the disease. The role of epinephrine and nebulised bronchodilators in combination with systemic corticosteroids is questioned, but can be given on an individualised basis (59). Nebulised hypertonic saline is a new therapeutic agent, which has not been investigated for possible use in the PICU. Although it is recommended, its use remains to be established. Other therapies, such as Heliox, surfactant and ribavirin, are also being examined, with controversial results thus far. As little seems to have been achieved when it comes to treatment, a lot of emphasis has been given to the prevention of the illness. Hygiene measures and education of caregivers, hospital personnel, nurses and doctors on limiting transmission and elimination of the environmental risk factors are strongly recommended in published guidelines (59). Palivizumab prophylaxis is recommended for infants with risk factors, such as chronic illnesses, prematurity and immunodeficiency, as well as other conditions, which are being clarified at the revised published guidelines (59). Since the burden of RSV bronchiolitis is high, research must aim for the development of an anti-RSV vaccine, as well as new antiviral agents.

Vaccination against measles, mumps and rubella (MMR) versus autism. Autism is a severe neurodevelopmental disorder affecting the paediatric population (60). Autism spectrum disorders (ASD) include disorders, such as psychomotor regression, language impairment and behavioural social withdrawal, placing patients with ASD in permanent need for healthcare and social support (61). Earlier reports have associated vaccination against MMR with the occurrence of ASD in children (62), thus leading in particularly low vaccination coverage. As a result, outbreaks regarding the vaccine preventable strains have reappeared throughout Europe (63-65), Asia (66,67) and the United States (68,69). Extensive research around the issue

has emerged, soundly dissociating MMR vaccination from any ASD occurrence, even in high-risk populations (70-72). However, the loss of credibility of the MMR vaccine remains a concern. This can be partially explained by failure on behalf of the scientific community to effectively communicate: i) the limitations and bias of the original study of Wakefield *et al* (62) in 1998, ii) the mounting evidence supporting the lack of a causal relationship between MMR vaccine receipt and autism onset, as proven by large epidemiological studies (70-72) and iii) adverse effects of vaccination in the general setting of coincidental, rather than causal associations. Another contributing factor must be attributed to a powerful influence by the public media, such as television, newspapers and internet, regarding MMR vaccination, ultimately leading to a subsequent negative public health response. In the future, more effective communication strategies are required to reassure parents of vaccine safety and importance.

Ocular viral infections in neonates and children. The ocular manifestations of viral infections in neonates and children vary greatly and can range from innocuous to vision threatening (73). The majority of viral conjunctivitis in children are caused by adenovirus, a DNA virus, which can cause a range of human diseases, including upper respiratory tract infection. Viral conjunctivitis is associated with epidemic keratoconjunctivitis, pharyngoconjunctival fever and acute haemorrhagic conjunctivitis (74). Signs include eyelid oedema and tender pre-auricular lymphadenopathy, prominent conjunctival hyperaemia, follicles and punctate epithelial keratitis. In viral infections in children, the involvement of the anterior segment is mild and self-limited; spontaneous resolution usually occurs within 2-3 weeks, except in cases of congenital infection, which are often associated with significant alterations in ocular structures.

Neonatal conjunctivitis (also known as ophthalmia neonatorum) is defined as conjunctival inflammation developing within the first month of life. It is the most common type of infection in neonates, occurring in up to 10% of neonates. It is often identified as a specific entity distinct from conjunctivitis in older infants as it is often the result of infection transmitted from the mother to the infant during delivery (74). *Molluscum contagiosum* ocular infection in children is caused by a specific double-stranded DNA poxvirus, which typically affects otherwise healthy children with a peak incidence between the ages of two and four. Transmission occurs through contact, with subsequent autoinoculation. Presentation is with chronic unilateral ocular irritation and mild discharge, while lesions are usually self-limiting. Primary infection with herpes simplex virus (HSV) is usually associated with eyelid and periorbital vesicles, papillary conjunctivitis, discharge and lid swelling. Dendritic corneal ulcers can also be present, particularly in patients with atopic infection can lead to eczema herpeticum, which can be very severe (75-77). Varicella-zoster virus (VZV) is a serious, but rare, viral infection in children, in which prolonged inflammation may lead to corneal thinning or perforation, glaucoma and cataract formation (74).

Involvement of the posterior structures mostly related to HSV and VZV is potentially sight-threatening. Retinal or optic nerve involvement should be suspected in any child, who complains of an acute onset of blurred vision in the absence of anterior segment inflammation or opacities in the ocular media.

Optic neuropathy may occur as an isolated sign, although it is more often associated with a more generalised involvement of the central nervous system (77,78). While specific therapy is not always available, the early diagnosis of ocular viral disease in children should aid in the amelioration of acute symptoms and in the prevention of long-term complications.

Otorhinolaryngologists versus HPV-associated lesions. HPV is responsible for many benign lesions of the airway tract and the genital area in the adult population, as well as for cancer of the larynx and oral cavity, particularly subtypes 16 and 18 (79,80). A recent study (81) also revealed an increased frequency of HPV infections in neonates and children. Otorhinolaryngologists are the specialists, who treat children with HPV-related lesions localised in the oral cavity, the oropharynx and larynx. These lesions are mostly benign. There are four types of HPV-related lesions concerning the upper airway track: i) squamous papilloma, ii) verruca vulgaris, iii) focal epithelial hyperplasia and iv) condyloma acuminatum.

In children, the most common clinical expression of HPV is recurrent respiratory papillomatosis (RRP). It causes hoarseness of the voice and sometimes the lesions can cause obstruction of the upper airway track. In adults, the clinical behaviour differs, as the disease requires fewer surgical excisions than in children. In children, the lesions caused by HPV often need many surgical procedures before they become extinct and quiescent. Inverted papilloma, which is a type of squamous papilloma, is strongly associated with HPV subtypes 6 and 1 and its incidence in children is twice as high compared to adults (82). Fortunately, the majority of these lesions can be surgically removed and provide the young patient with a good prognosis. Microsurgery, transoral laser microsurgery (TLM) and endoscopic endonasal approach (EEA) are some of the most frequent surgical methods of excision. A review of recent studies dealing with HPV lesions in children revealed only a few cases, which have been treated surgically. The most common approach of surgical treatment is using TLM. However, laser treatment can cause several complications, such as stenosis, burns of the airway tract and scars. An alternative to TLM are microdebriders (83). Microdebriders provide a more accurate excision, removing only the affected tissue and preserving the healthy tissue. The preservation of healthy epithelium is very useful, when repeated interventions are needed, particularly in children. When the lesion causes obstruction of the airway tract, a tracheotomy is necessary to keep the airway open. However, it should be avoided and performed only when it is an emergency because of the danger of spreading the disease to the respiratory tract (84). In the future, the association between HPV-related lesions in children and cancerous lesions in adults needs to be considered carefully, revealing the importance of vaccination in children against HPV (85).

Immunology of infectious mononucleosis (IM). IM is the main clinical manifestation of Epstein Barr virus (EBV) infection (86). Other agents, such as CMV, toxoplasma and adenovirus, produce a similar illness. The incubation period ranges from 33 to 49 days (87). Clinical presentation is usually prolonged (average 16 days) and ranges from a non-specific flu-like illness to the more distinctive triad 'fever, pharyngitis, lymphadenopathy-splenomegaly'. Other clinical manifesta-

tions include fatigue, hepatitis and eyelid oedema. Possible complications are meningoencephalitis, haemolytic anaemia, thrombocytopenia, rash, conjunctivitis, haemophagocytic syndrome, myocarditis, neurologic diseases, pancreatitis, parotitis, pericarditis, pneumonitis, psychological disorders and splenic rupture. Laboratory findings include the elevation of liver enzymes and lymphocytosis with a marked increase in the number of atypical lymphocytes in the peripheral blood (87). Additionally, immunophenotypic alterations of lymphocytes have been described in the various phases of EBV infection (88). More specifically, a reduction of B-lymphocytes and an increase in the number of CD3⁺CD8⁺, T-lymphocytes, with a subsequent decrease in the CD3⁺CD4⁺/CD3⁺CD8⁺ ratio is noted (89).

In the study by Panagopoulou *et al* (86), which was presented at the Workshop, researchers aimed to examine whether there is an association between the immunophenotypic alterations and the variability of the clinical presentation of IM. Although several studies (89-91) have examined the immunophenotype of lymphocytes in EBV infection, very few (89) have correlated these with the clinical course. The presented study (86) showed that the immunophenotypic analysis of cytotoxic T cells provides important information on the physiology of the immune response to EBV infection. Additionally, it may potentially play a predicting role, providing information on the expected clinical course, potential complications and the time to recovery from EBV infection.

Merkel cell polyomavirus (MCPyV): A novel emerging virus of childhood. MCPyV is a newly-discovered small, human DNA virus, which causes a widespread, previously unrecognised, human infection in adulthood and childhood (92,93). It is classified in the family *Polyomaviridae*, a group of non-enveloped, double-stranded DNA viruses with icosahedral symmetry, which can infect a variety of vertebrates, including humans and can cause malignant tumours upon their inoculation into heterologous hosts (94). First described in January 2008, the prototype sequence of MCPyV has a 5,387 base pair genome and contains the early region, which encodes the large tumor (LT) antigen and the small tumor (sT) antigen and the alternative tumor antigen open reading frame (ALTO), the late region, which encodes VP 1, VP 2 and VP 3 and a non-coding regulatory region. Of note, the genome of MCPyV has been detected in approximately 80% of Merkel cell carcinoma (MCC) cases (95). Although MCC is a relatively rare, highly aggressive, human skin cancer of neuroendocrine origin, its worldwide incidence has increased over the past twenty years from 500 to 1,500 cases per year. In the majority of MCC cases, MCPyV is integrated into the host genome in a monoclonal manner and the viral T antigen has truncating mutations, which render the T antigen unable to initiate the DNA replication required to propagate the virus (94).

Recent serological data using enzyme-linked immunosorbent assay (ELISA) techniques have suggested that MCPyV infection is common in childhood and occurs during early childhood, after the disappearance of specific maternal antibodies against MCPyV (93). MCPyV DNA has been detected in nasopharyngeal aspirate samples collected from children, indicating the presence of MCPyV in the upper respiratory tract of children (96,97). MCPyV is acquired in childhood through

close contact involving saliva and the skin (93). As to date, the mode of MCPyV transmission has not been fully elucidated, the precise role of the respiratory secretions in MCPyV transmission in childhood requires further investigation. The respiratory tract system is involved as a unique reservoir of MCPyV in children and respiratory secretions seem to play a significant role in MCPyV transmission in childhood. Moreover, future studies are required in order to fully elucidate the potential implications of MCPyV infection in neoplasms in children.

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