7th World Congress of the World Society for Paediatric Infectious Diseases

Conference Review™

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In this review:

Welcome to our review of WSPID 2011, the 7th World Congress of the World Society for Paediatric Infectious Diseases.

WSPID provides an opportunity for clinicians to share the latest knowledge and receive updates on treatment and prevention of paediatric infectious diseases. Dr Tony Walls attended WSPID 2011 and considered the following presentations to be of particular interest. The scientific programme for WSPID is available at http://www2.kenes.com/wspid/Scientific/Pages/Scientific_Program.aspx

We hope you find this review of WSPID 2011 interesting and useful in your current practice.

Kind regards,

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Symposia presentations

Effectiveness of pediatrics vaccination programme: Canadian experience

Presenter: Dr Mark Loeb, McMaster University, Canada

Summary: This was presented at a symposium sponsored by Sanofi Pasteur "New evidence in pediatric influenza: a high global burden efficiently reduced through expanded vaccination". Dr Loeb reported findings from his recently completed cluster randomised trial that immunised children in the unique Hutterite community against influenza in order to reduce transmission in Hutterite colonies.

Comment: Previous studies have suggested that vaccinating children against influenza may provide indirect protection to other members of the community. However, none have been of sufficient quality to demonstrate this convincingly, or large enough to quantify the effect. This study (Loeb et al. JAMA 2010;303(10):943-950) was unique in that it was conducted in small, relatively isolated Hutterite communities. The communities were randomised to receive either the inactivated seasonal influenza vaccine recommended for 2008–9 or Hepatitis A vaccine, and the primary outcomes were laboratory confirmed influenza A or B in people who had not received the vaccine. PCR was used for diagnosis with serological confirmation. On average 83% of children in the communities were vaccinated, and the estimated protective effectiveness of the vaccine for non-vaccinated community members was 59%.

Vaccinating children and adolescents seems to have a significant effect on rates of influenza infection in adults. Such high coverage rates would be very difficult to achieve in New Zealand – influenza vaccine was free to children in Canterbury during the 2011 influenza season and the estimated coverage only just reached 20%.

Perspectives on the cause, management and control of resistant *S. pneumoniae*

Presenter: Professor Keith Klugman, Emory University, USA

Summary: This was presented at a GSK-sponsored symposium "Prevention of paediatric pneumococcal invasive disease, pneumonia and acute otitis media: recent data and implications for clinical practice". Prof Klugman discussed risk factors for penicillin-resistant and levofloxacin-resistant pneumococcal infections, and drivers of multiple resistance. He outlined the impact the introduction of PCV7 has had on drug-resistant *S. pneumoniae*, particularly serotype 19A invasive pneumococcal disease. To date, there are no reports of bacteriologically confirmed failure of intravenous penicillin therapy for pneumonia. Professor Klugman concluded that multiple risks exist for antibiotic resistance, most of which can be directly linked to antibiotic exposure. Pharmacodynamics suggest IV penicillin or ceftriaxone have good activity for pneumonia, but penicillin is ineffective for meningitis.

Comment: The key message of this presentation was that increasing rates of resistant pneumococcal disease in communities are mostly driven by increased antibiotic usage. While the rates of invasive pneumococcal disease (IPD) in children in the USA have fallen significantly since the introduction of PCV7 in 2000, the proportions of infections due to non-vaccine serotypes have increased. Particularly worrying has been the increase in serotype 19A disease, where a high proportion of isolates have penicillin resistance.

A recently published study (Hicks et al. Clin Infect Dis 2011;53(7):631-639) looked at rates of IPD between 1996 and 2003 and compared these to prescribing rates in primary care during this time period. It was pleasing to see that overall the rates of antibiotic prescribing had reduced in 7 different surveillance sites. However sites with high rates of antibiotic prescribing had higher proportions of IPD non-susceptibility than low prescribing sites. Cephalosporin and macrolide prescribing in the community were associated with multidrug non-susceptibility and serotype 19A IPD.

Effectiveness of PHiD-CV vaccination on IPD: the Quebec experience

Presenter: Professor Phillipe De Wals, Quebec, Canada

Summary: This was presented at the GSK-sponsored symposium "Prevention of paediatric pneumococcal invasive disease, pneumonia and acute otitis media: recent data and implications for clinical practice". Professor De Wals discussed data from Quebec where Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) has been used in universal vaccination and has been shown to be highly effective in preventing invasive pneumococcal disease.

Comment: The New Zealand infant immunisation schedule recently changed its pneumococcal vaccine from using PCV7 (Prevenar) to PHiD-CV (Synflorix) to provide coverage for an additional 3 pneumococcal serotypes. Many other countries have changed to using PCV13 (Prevenar13) which provides coverage for 6 additional serotypes when compared to PCV7, including serotype 19A. Canada made the same switch in 2009 and this presentation looked at the immediate impact it had on IPD in Quebec, where they had 97% vaccine coverage. A year after the introduction of PHiD-CV the rates of IPD in children <1 year of age had fallen from 41.2/100,000 to 28.5/100,000, and in children 1–2 years from 43.4/100,000 to 34.8/100,000. Interestingly there was an apparent drop in the rates of IPD due to serotype 19A, a serotype not included in the PHiD-CV vaccine.

However, we know that the rates of IPD and the proportions due to various serotypes in regions fluctuate from year to year. The time frame of this study was too short to draw any firm conclusions about the effect of PHiD-CV vaccine on pneumococcal serotypes in Quebec. It is somewhat reassuring that the introduction led to a reduction in the overall rates of IPD but we cannot conclude that a similar pattern is likely to occur in New Zealand. Equally it is difficult to conclude that the pattern of serotype changes that occurred between 2009 and 2010 in Quebec would continue. Unfortunately we will never know as Canada replaced the PHiD-CV vaccine with PCV13 in December 2010.

RSV infection: current and future prevention and treatment

Presenter: Professor Jan LL Kimpen, University Medical Center, Utrecht, The Netherlands

Summary: This was presented at the "Viral Infections in Children – Evidence Based Management" ESPID Society symposium. Professor Kimpen began by discussing ERS recommendations for the treatment of RSV bronchiolitis, followed by the American Academy of Pediatrics' recommendations for the use of palivizumab for prevention of RSV bronchiolitis. Innovative treatments for RSV infection were discussed, including vitamin D, CPAP, leukotriene inhibitors, RNA-based therapy, fusion inhibitors and Nanobodies®. Challenges for the development of RSV vaccines for paediatrics include vaccination timing, the failure of natural infection to induce immunity that prevents reinfection, the legacy of vaccine-enhanced illness, and efficacy and safety concerns. Professor Kimpen also looked at the R&D pipeline for treatment of RSV infection.

Comment: This presentation began with a statement that there are no new treatments for RSV infection in children – something we get used to hearing in Paediatrics. This is an infection that has a high burden of disease in young children and something we would dearly love to be able to prevent, or have an effective treatment for. Three new treatment strategies in the early stages of development were presented. The first, RNA interference, has been shown to prevent RSV infection in experimentally infected adults and reduce symptom scores (DeVincenzo et al. PNAS 2010;107:8800-8805), and the incidence of new or progressive bronchiolitis obliterans in adult lung-transplant recipients (Zamora et al. AM J Respir Crit Care Med 2011;183:531-538). The other two, a small molecule RSV fusion inhibitor and Nanobodies specific for RSV fusion protein both showed promising reductions in viral loads and inflammation in mouse models of RSV infection. They both seem to be promising new developments but more work is needed before either could be used therapeutically.

Antibiotic prophylaxis for paediatric UTI

Presenter: Professor Jonathan Craig, University of Sydney, Australia

Summary: This was presented at the "Pediatric UTI – Management and Prevention in 2011" consensus symposium. Professor Craig first discussed the outcomes of symptomatic UTI in children. Recurrence is common (occurring in 1–30% of children) and pyelonephritis occurs in 40%. However, ESKD and hypertension are unlikely. NICE guidelines (2007) are out of date and AAP guidelines are fatally flawed. Trial data suggest the following: cotrimoxazole prevents UTI by about 6% over 1 year; NNT is 16; the treatment effect is consistent across different patient groups; any renal benefit is likely to be very small and unimportant; cotrimoxazole is safe and may reduce need for antibiotics for other indications; nitrofurantoin may be more effective. Professor Craig commented that no one should receive antibiotic prophylaxis although high risk groups such as those with a high risk of recurrence and infants with severe index infection could be considered.

Comment: Antibiotic prophylaxis following UTI is only really of benefit in preventing further symptomatic UTI and should only be considered in a select group of patients. The effect on preventing further UTIs is only modest, and any effect on long-term renal complications is probably negligible. The results of the PRIVENT trial (Craig et al NEJM 2009;361:1748) and other trials was presented along with an appraisal of the recent guidelines. I think we should be resisting the temptation to put children with recurrent symptomatic UTI on long term prophylaxis as the benefits seem small and the risk of development of antibiotic resistance seems anecdotally to be significant.

***Independent commentary by Tony Walls**, who is a Senior Lecturer in the Department of Paediatrics, University of Otago, Christchurch and a Paediatric Infectious Diseases Specialist. He has an ongoing interest in childhood vaccinations, and his current research includes a study on the aetiology and impact of pneumococcal vaccination on otitis media with effusion in New Zealand children.*

Infectious encephalitis

Presenter: Cheryl Jones

Comment: Managing encephalitis in children provides many challenges for Paediatricians. Most of the information we have on the aetiology of encephalitis comes from predominantly adult studies such as the Californian Encephalitis Project, and the Aetiology of Encephalitis Study Group in the UK. Even in carefully designed studies where extensive investigations are performed, a very high proportion of encephalitis cases have no clear aetiology identified. One of the few studies conducted in the southern hemisphere to date was unable to find a cause for encephalitis in 70% of cases (Huppatz et al. Emerg Infec Dis 2009;15:1359). With this in mind, the PAEDS surveillance network in Australia are about to begin active surveillance of cases of encephalitis in children presenting to tertiary paediatric hospitals, which will include extensive molecular diagnostic testing on CSF samples for a wide variety of potential pathogens.

Herpes simplex virus continues to be the most commonly identified cause of encephalitis. A study from Sweden using structured interviews with parents found that 53% of infants with HSV encephalitis still had persistent symptoms at age 12 months (Fowler et al. Pediatrics 2010;126:e828). Many of these were cognitive problems and personality changes. Even some children who were considered to be fully recovered at discharge reported persisting symptoms at follow-up evaluations. We may be underestimating the long-term effects of HSV encephalitis and lengthy follow-up may be appropriate for these children. This presentation also discussed the recently published trial of 6 months of acyclovir suppression therapy in infants with HSV encephalitis (Kimberlin et al. NEJM 2011;365:14). Children randomised to acyclovir suppression had significantly higher mean Bayley mental-developmental scores at 12 months than infants randomised to placebo. Reliably assessing developmental progress in children 12 months of age is very difficult and these children need long term follow-up to determine the real significance of this result.

Group A streptococcal vaccines

Presenter: J Dale

Summary: This was presented at the "Group A Streptococcal Infections" symposium.

Comment: The heavy burden of disease in children due to Group A streptococcal (GAS) infections is well known and was highlighted in this symposium. This presentation went through the steps that have led to a phase I trial of a new GAS vaccine, including the trials and tribulations of developing a new vaccine along with commercial partners. At least 15 different potential vaccine antigens have been identified for GAS and most of the antibodies to these have been shown to be protective in mouse models. However the M protein is the only one to be evaluated in trials, and there is some evidence that M protein antibodies provide protection against infection. Due to the many different serotypes, initial development focussed on a 26-valent M protein based vaccine. This was shown to be immunogenic, safe and well tolerated yet this has not proceeded to further development. Professor Dale's group has now developed a 30-valent vaccine that could potentially cover 98% of GAS types causing disease in the USA. Trials of this new vaccine are due to get underway shortly in Canada and results will be eagerly anticipated.

Management of KD and its complications: what works?

Presenter: J Burns

Comment: This presentation focussed on what to do when children with Kawasaki disease don't respond to first line therapy with intravenous immunoglobulin (IVIG). Between 15 and 20% of KD cases will be IVIG resistant. These children generally have higher levels of inflammation at presentation and have higher rates of coronary artery aneurysms. Most experts would recommend using a second dose of IVIG if there is no initial response and about 50-80% of patients will respond to this. Other options include use of very high dose steroids (30 mg/kg/day) given in short courses, or long courses of steroids (2 mg/kg/day). There is very little evidence for any of these treatment approaches. Infliximab (a monoclonal antibody against TNF-α) has been tried in IVIG-resistant KD because TNF-α levels are known to be very high in the most severely affected children. In a Phase I trial in the USA 12 children with IVIG-resistant disease received infliximab and 11 responded (Burns et al. J Pediatr 2008;153:833). In a retrospective study comparing IVIG to infliximab for IVIG-resistant disease, patients who had received infliximab had fewer days of fever and were discharged from hospital sooner (Son et al. J Pediatr 2011;158:644). There was no difference in coronary artery outcomes or adverse events although the study was not large enough to detect these.

Unraveling the pathogenesis and etiology of pneumonia with pneumococcal conjugate vaccines

Presenter: Shabir A Madhi, University of Witwatersrand, South Africa

Summary: Dr Madhi discussed the use of pneumococcal conjugate vaccines (PCVs) as probes for understanding the interaction between pneumococcus and other pathogens associated with pneumonia hospitalisation. He summarised the efficacy and effectiveness of PCVs against pneumonia, and commented that vaccine efficacy trials probably underestimate the contribution of pneumococcus as cause of pneumonia in hospitalised children. He also noted that higher vaccine effectiveness against clinical or lobar pneumonia is likely to be due in part to an indirect effect. *S. pneumoniae* may play a lesser role in the aetiology of non-severe, outpatient pneumonia.

Comment: Most cases of pneumococcal pneumonia in children are not confirmed microbiologically. For this reason estimating the impact of pneumococcal vaccination on paediatric pneumonia is challenging. This presentation highlighted the clinical impact of conjugate pneumococcal vaccines on all-cause pneumonia and radiologicaly confirmed pneumonia from a wide variety of sources. It appears that the vaccine effectiveness in preventing hospitalisation with pneumonia may be even greater than suggested in early RCTs. The introduction of PCV7 appears to have been associated not only with reductions in admissions due to pneumococcal pneumonias in children, but with reductions in admissions for RSV and influenza associated pneumonia as well (Simonsen et al 2011 mBio;2:e00309-10).

Poster presentations

Persistence of the immune response to an investigational multicomponent meningococcal serogroup B (4CMenB) vaccine following priming in infants or toddlers

Authors: Kimura A et al for the V72P13 Meningococcal B Vaccine study group

Summary: This study investigated the persistence of the immune response to an investigational, multicomponent meningococcal serogroup B (4CMenB) vaccine in infants. 300 children who were immunised against 4CMenB as infants in a 4-dose series (2, 4, 6 and 12/13 months) and 86 children who were immunised as toddlers with 2 doses (12 and 14 or 13 and 15 months), were assessed 12 months after their last dose. 112 vaccine-naive children aged 24–26 months served as controls. Seroprotection rates (% hSBA titers ≥5) were similar after the infant and toddler series, and persisted for 12 months. Seroprotection rates over the 12-month period were high against Neisserial Adhesin A (NadA), and to a lesser extent against factor H binding protein (fHbp), but declined quickly against outer membrane vesicles from New Zealand outbreak strain (OMV). All hSBA levels were higher than those of controls, who displayed little activity. In conclusion, protective immune responses to 4CMenB persisted for 12 months after vaccination, with high levels against 2 of 3 tested vaccine antigens.

Comment: The development of an effective vaccine against serogroup B meningococcal disease has been challenging vaccine manufacturers for a long time now. New Zealand is one of the few countries in the world to have used an OMV vaccine to target a specific subtype of Group B Neisseria meningitidis during an epidemic. This vaccine only provides protection for the P1.4 subtype and therefore is unlikely to be effective in most other countries. Group B is still the most common serotype causing invasive disease in New Zealand, with the most common subtype being the P1.4 epidemic strain.

This new 4-component vaccine covers a range of meningococcal Group B subtypes and has shown much promise in early trials looking at immunogenicity. There were good serological responses in infants as well as toddlers to several of the components of the vaccine, suggesting the potential to be very efficacious. It is estimated the vaccine would cover 76% of Meningococcal Group B strains in Australia. However, it is a little disappointing to see that antibodies against the OMV for the NZ outbreak strain declined markedly soon after vaccination. This is similar to the rapid decline in antibodies seen with the MeNZB vaccine when given to infants (Jackson et al. Arch Dis Child 2011;96:744), and raises questions about how effective this vaccine would be in preventing group B disease in New Zealand.

Pertussis vaccination in infancy lowers the incidence of pertussis disease and the rate of hospitalisation after one and two doses

Authors: Gustafsson L et al

Summary: This Swedish study analysed the age-specific incidences of pertussis disease and the rates of hospitalisation for children who received 0, 1 or 2 doses of an acellular pertussis vaccine prior to pertussis disease. Data for approximately 1 million children were reviewed. In children aged 3–<5 months, the incidences of pertussis disease with at least 14 days of cough were 264/100,000 children with no prior pertussis dose and 155/100,000 children with 1 dose prior to onset of disease. In children aged 5-<12 months, incidences of pertussis disease were 526, 95, and 24/100,000 for infants with 0, 1 and 2 doses, respectively. The hospitalisation rate for infants with 1 dose was significantly lower than that for unvaccinated children of the same age. In conclusion, pertussis vaccination has a significant impact on pertussis disease and hospitalisation rates after the first dose.

Comment: While New Zealand successfully reached a target of having 90% of children fully vaccinated by 24 months this year, many infants still have delays in receiving their immunisations. A case control study from Auckland 1995-1997 showed that delayed immunisations were a risk factor for being hospitalised with pertussis. The Gustafsson study took a population based approach, using the Swedish national database for pertussis and matching it to immunisation data on coverage and timeliness. The results show that children who had received one dose of vaccine (first given at 3 months in Sweden) had a significantly lower rate of pertussis, and that a second dose provided substantial additional protection. Those with delayed or no immunisation had significantly higher rates of hospitalisation when compared to age-matched controls who had been vaccinated. Improving the timeliness of infant immunisations is crucial for preventing pertussis in children and is the next big challenge for immunisation practice in New Zealand.

Impact of the national rotavirus immunisation program in Australia

Authors: Dey A et al

Summary: This study investigated the impact of the national rotavirus immunisation programme in Australia. Hospitalisation rates for rotavirus and non-rotavirus gastroenteritis in young children before and after the vaccine was introduced in July 2007 were calculated from National Hospital Morbidity data (AIHW) and population data. The rate of rotavirus hospitalisations in children aged <5 years declined by 70.8%, from 261.2/100,000 in July 2001–June 2006 to 76.4/100,000 in July 2008–June 2009. During the same time period, the rate of non-rotavirus hospitalisations in children aged <5 years fell by 33.9%, from 1419.2/100,000 to 937.5/100,000. A reduction was also seen in children and adolescents aged 5–19 years, indicating herd immunity. In conclusion, hospitalisations for severe rotavirus disease and all-cause acute gastroenteritis in children aged <5 years have declined substantially since the introduction of rotavirus vaccination in 2007.

Comment: This was one of several presentations on the impact of rotavirus immunisation in Australia. It nicely demonstrates both the direct and indirect effects of vaccination on hospital admissions. Hospital admission data just represent the worst cases of rotavirus and the real impact of these vaccines will be in the reduction of mild to moderate cases that are cared for at home. We could expect significant reductions in hospital admissions due to gastroenteritis if rotavirus vaccine were to be introduced into the New Zealand immunisation schedule.