European Society for Paediatric Infectious Diseases
Conference Review

Making Education Easy

May 28 – Jun 1 2013, Milan, Italy

In this review:

Welcome to our review of the 31st Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID), held in Milan in late May.

The ESPID meeting comprised keynote lectures, symposia, educational workshops and meet-the-expert sessions, encompassing the entire field of paediatric infection-related diseases. Participation of a large number of internationally renowned experts ensured a rich environment for discussion. Stewart Reid and Lesley Voss attended ESPID 2013 and considered the following presentations to be particularly interesting. For further information on ESPID 2013, see online at http://www2.kenes.com/espid2013/Pages/Home.aspx.

We hope you find the conference review interesting and useful in your clinical practice.

Kind regards,

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Safety issues related to the use of adjuvants

Speaker: T Vesikari

Summary and comment (SR): Timo Vesikari presented the story about narcolepsy following an AS03 adjuvanted flu vaccine. This adjuvant was used to improve the immunogenicity of H5N1 vaccine (necessary for an adequate immune response in children for that vaccine) and was included in the H1N1 vaccine of GSK (Pandemrix®). Surveillance data showed there was a significant increase in narcolepsy, but the early data from Finland had great difficulty being published, being rejected by both NEJM and Lancet. The increase in narcolepsy observed from Finland was 17 times the background rate but it only occurred in individuals with a specific HLA tissue type. Professor Vesikari presented data from Ireland, UK and Sweden showing a similar magnitude of increase in narcolepsy.

M59, a strong adjuvant, contains squalene. AS03 in addition to squalene contains DL-alpha-tocopherol and it is probable that its inclusion was overkill. H1N1 vaccine does not require much adjuvant but H5N1 and H7N1 vaccines do require significant adjuvants. AS03 adjuvanted seasonal vaccine should not be used, but what about already stockpiled H5N1 adjuvanted vaccine containing AS03?

Another related issue is that there is AS04 adjuvant in the 2 component HPV vaccine. AS04 is completely different from AS03 and contains 3-O-desacryl-4'-monophosphoryl lipid A and aluminium hydroxide. Prof Vesikari, in response to a question, stated that the effect of this adjuvant has been carefully studied in Finland and no increase in narcolepsy has been detected.

Session: ESPID Symposium 4. Advances in vaccinology

Independent commentary by Dr Stewart Reid.

Stewart Reid has been a Lower Hutt GP for more than 35 years. From 1980–2011 he was involved in the committee advising the Government on immunisation and he chaired it for about 50% of that time. Dr Reid has been involved in the writing of all 5 editions of the NZ immunisation handbook and was awarded the MNZM for services to Health in the 2013 New Year Honours list.

Independent commentary by Dr Lesley Voss.

Lesley Voss is a Paediatric Infectious Disease Consultant based at the Starship Children's Hospital, Auckland. In this job she provides care and advice for children with complex infectious diseases, including TB and HIV. Dr Voss trained at Otago University and completed her infectious disease training at Mayo Clinic, USA. She has been practicing at the Starship Children's Hospital since 1993. She has participated in a number of national advisory groups and is the current Chair of the NZ-ASID subcommittee.

MENINGOCOCCAL C VACCINATION

Is a single dose of MenC in the first year of life enough?

Speaker: H Findlow

Summary: Clinical trials that investigated a reduced infant meningococcal serogroup C conjugate (MCC) schedule showed that a single-dose priming vaccination in infancy can be considered. The UK Joint Committee on Vaccination and Immunisation has recommended the use of a single priming dose at 3 months with the move of the second infant dose to adolescence.

Session: Satellite Symposium organised by Baxter

A randomised controlled study to evaluate induction of immune memory following infant vaccination with conjugate serogroup C *Neisseria meningitidis* vaccines

Speaker: A Khatami

Summary: Serogroup C meningococcal (MenC)-specific memory B-cell responses following different MenC conjugate vaccine schedules in infancy were presented. 1-dose MenC conjugate vaccine priming was found to be as efficient as the current 2-dose primary schedule in eliciting a memory B-cell response. MenC-TT priming induced more memory B-cells than MenC-CRM, which may explain improved persistence of bactericidal antibody documented with this vaccine.

Session: Oral session 4. Vaccinations in special circumstances

Comment (SR): These two related presentations support the 1 + 1 + 1 schedule change for the UK: in particular a single dose of MenC vaccine at two months of age. The percentage of subjects attaining a titre ≥8 was 50% with Menigitec®, 80% with Menjugate® (both CRM conjugates) and 96% with NeisVac-C® (a tetanus toxoid [TT] conjugate). Two doses of any of the vaccines gave an excellent response. The GMT had fallen substantially prior to the booster dose at 13 months but in response to a TT conjugate (Hib MenC TT conjugate) a substantial anamnestic response was seen whether primary vaccination was with NeisVac-C® or Menjugate®. It was higher when the infant dose was with NeisVac-C®. In the second study data support that priming with a single dose of MenC conjugate is efficient and acceptable and that an excellent anamnestic response is seen to a second dose administered in the 2nd year of life. When boosting with TT conjugate more memory cells were generated if the individual was primed with TT conjugate than if primed with one or two doses of CRM conjugate. There was no difference in response seen between one and two priming doses of CRM conjugate vaccine. One month after boosting with TT conjugate there was no difference between unprimed children and those who received CRM priming, but those who received priming and boosting with TT conjugate generated more memory B cells than those primed with CRM conjugate. However, no data were presenting covering priming and boosting with CRM conjugate. It is therefore not known whether the TT booster response is because the TT conjugate is more immunogenic or because priming and boosting occurred with the same conjugate. One of the strategies that NZ could adopt to create a space for a MenC vaccine dose in the first year of life would be a 2 + 1 pneumococcal vaccine schedule. A key point made, indicating that vaccine protection wanes and circulating antibody is required for protection, is that the immune response following infection in previously vaccinated individuals is greater than that in individuals infected who had not been vaccinated. It seems that although the anamnestic response occurs, it is too late to prevent disease. For sustained protection however, doses in the second year of life and adolescence are required.

Cohort study for 30 years: persistence of measles, mumps and rubella antibodies induced by 2-dose MMR vaccination

Speaker: I Davidkin

Summary: A cohort study was started in Finland in 1982 at the same time the 2-dose MMR nationwide vaccination programme was introduced. Over time, the persistence of MMR vaccine-induced antibody levels in the cohort has been studied. This follow-up study showed a remarkable decline of measles, mumps and rubella antibody levels in the 30 years after vaccination.

Comment (SR): Data were presented from Finnish cohort study concerning 30-year immunity following MMR vaccine with the first dose in 1982 and second dose in 1987, with high coverage for both doses. This longitudinal study started with a cohort of 350 individuals and just over 160 individuals were available for this analysis. In this cohort, the data show that rubella immunity is stable with close to 100% remaining seropositive, for measles 90% remain seropositive and for mumps immunity had declined more significantly to around 80% seropositivity. The GMT declined against all three antigens but immunity depends on antibodies and cellular immunity. In summary, there have been some cases of measles in vaccinated individuals, in mumps outbreaks approximately 50% of cases have occurred in vaccinated individuals but protection against rubella is secure. These data do raise the possibility that adult booster doses of MMR vaccine may be required; disease surveillance with known vaccination status will determine whether such doses are required.

Session: Oral session 4. Vaccinations in special circumstances

Influence of vaccination against influenza A (H1N1) during pregnancy on pregnancy outcomes in The Netherlands: a cross sectional linkage study

Speaker: N van der Maas

Summary: The safety of influenza A (H1N1) vaccination with Focetria® during the second or third trimester of pregnancy was presented. Follow-up safety data for 1357 vaccinated women were compared with data for 669 unvaccinated women. Multivariate logistic regression analysis adjusted for confounding variables found no association between H1N1-vaccination and small-for-date babies, preterm delivery, or the need for assisted delivery.

Comment (SR): Influenza vaccine is now recommended during pregnancy, because influenza occurring in pregnancy can be very severe. Vaccination of mothers also reduces influenza in infants. The study had more than 2000 subjects, two-thirds of whom were vaccinated and one-third were not. There was no difference in pregnancy outcomes, including small for dates babies, prematurity etc, including assisted delivery. These data are as expected and very reassuring.

Session: Oral session 4. Vaccinations in special circumstances

The relationship between specific antibody titres at birth and response to primary immunisation

Speaker: L Pollock

Summary: The relationship between specific antibody titres to pertussis, Haemophilus Influenzae type b (Hib), tetanus and pneumococcus in mother-infant pairs at birth and following infant primary immunisation was evaluated. 99 healthy mother-infant pairs were recruited from a UK maternity unit; 61 completed follow-up. Maternal and infant antibody levels at birth to pertussis and Hib were low: 33% and 43% of infants had protective titres to pertussis and Hib, respectively. Change in infant antibody level post-immunisation was inversely correlated with antibody level at birth, but most infants still developed protective antibody levels post-vaccination (Hib 66%; pertussis 90%; tetanus 96%).

Comment (SR): Data on a possible effect of maternal immunisation, in particular pertussis, were presented to address the question of whether the maternal antibody levels attained may impair the immune response in infants who are subsequently vaccinated. A comparison was done between (unvaccinated) mothers with low and high titres 72 hours postpartum against the target disease and the response in their infants one month following their three infant doses. There was no significant difference for pertussis and the minor differences seen in tetanus and pneumococcal titres are probably not clinically significant with the majority of infants achieving protective titres. No data were presented on the effect of maternal immunisation as yet; this paper was an attempt to predict what the effect might be.

Session: Poster discussion 1. Vaccines 1

Improvement in hospital quality of care after the introduction of rotavirus vaccination: a pilot study in Belgium

Speaker: A Alwan

Summary: This Belgian report determined whether hospital quality of care during winter epidemic seasons was improved after the introduction of rotavirus vaccination. Using data from a paediatric ward in a Belgian hospital, nine variables were selected: hospitalisation, bed-day occupancy, bed turnover, nosocomial infection, deaths, unplanned readmission, full-time equivalent, sick leaves, and overtime work. Two factors, hospital pattern and personnel management, were extracted for analysis. A significant reduction in both factors was seen in the post-vaccination period; score analysis per factor and per day allowed for identification of stress periods (mainly seen in the pre-vaccination period). These changes indicate an improvement in quality of care after introduction of rotavirus vaccination.

Comment (SR): This paper describes the improvement in the quality of hospital care pre and post introduction of rotavirus vaccine suggesting that there was a particular impact on staff. The methodology presented may be applicable in other settings. This was a theme in other presentations and it is an important issue. The possibility that rotavirus vaccination could reduce the hospital burden when it is at its highest merits careful consideration.

Session: Poster discussion 1. Vaccines 1

The neonatal exposure to thimerosal containing vaccines has no influence on children's cognitive development

Speaker: D Mrozek-Budzyn

Summary: This study determined the relationship between neonatal exposure to thiomersal-containing vaccines and cognitive development of children during the first 7 years of life. The cohort was recruited prenatally in Krakow, Poland, and included 310 children vaccinated as neonates against hepatitis B using vaccines with or without thiomersal. Results of cognitive developmental tests did not differ between children exposed and not exposed to thiomersal-containing vaccines as neonates.

Comment (SR): All studied children were a sample from a cohort study on the susceptibility of fetus and child to environmental factors who were followed in Krakow by a team from Columbia University. In this study, data were presented on the possible effect on cognitive development of neonatal exposure to thiomersal-containing vaccines. This was a very comprehensive study looking at cognitive development and intellectual impairment and included multiple tests over seven years. There was a very reassuring finding; thiomersal containing vaccines had no harmful influence on children's cognitive development. NB: Thiomersal-containing vaccines have not been used in NZ since around 2000.

Session: Poster discussion 12. Vaccines 2

Antibody persistence one year after vaccination with four doses of the investigational meningococcal serogroup B vaccine, 4CMenB

Speaker: T Vesikari

Summary: This study assessed antibody persistence 1 year after the last immunisation in children who received 4 doses of 4CMenB at 2, 4, 6, and 12/13 months. 305 vaccinated children and 116 vaccine-naive controls were compared. One month after their 4th dose, 94–100% of vaccinated children had protective hSBA levels (titre ≥5) against the 4 antigens. One year later antibody titres had waned, but 62% still had titres ≥5 against fHbp, 97% against NadA, 36% against NHBA and 17% against NZOMV. The equivalent proportions in the age-matched, vaccine-naive subjects were 3%, 1%, 26% and 0%, respectively.

Comment (SR): Prof Vesikari presented 1-year persistence data on the 4-valent MenB vaccine (Bexsero®), demonstrating persistence of antibody at age two years following the 2, 4, 6 and 12 month schedule. Two of the antigens, NadA and fHbp, persisted well, but the OMP and NHBA did not persist well, with titres falling close to baseline. He suggested that the vaccine should probably be reformulated, leaving out the New Zealand Por A OMV. He suggested this change may not have much impact on immunogenicity and there would be a probable reduction in reactogenicity. This vaccine was also the subject of an industry-sponsored symposium at ESPID (see the following report).

Session: Poster discussion 12. Vaccines 2

A new vaccine for the prevention of meningococcal serogroup B disease: clinical and safety data

Speaker: M O'Ryan

Summary and comment (SR): Data covering the immunogenicity and safety of the 4-component group B vaccine Bexsero® were presented. The vaccine includes the New Zealand PorA P1.4, and three genomic proteins designed to give broad coverage: factor H binding protein (fHbp), neisseria heparin binding antigen (NHBA) and neisserial adhesion A (NadA). It has been studied in 7,800 subjects, 6,000 infants, 250 children and 1700 adolescents. The serological correlate of protection used was attaining an SBA titre >1 in 4, the suggestion being that this is an established correlate of protection (NB: in NZ a 4-fold rise in SBA titre was used as the correlate). It was also stated that because Group B meningococcal disease is relatively rare it is impossible to do an efficacy study.

The vaccine was given in a 2, 4, 6, 12 schedule or a 2, 3, 4, 12 schedule. There is a substantial drop in the PorA titre prior to the booster at 12 months. However fHbp dropped to 80%, NadA to 99% and NHBA to 61% of subjects attaining bactericidal titre >1:4. An excellent response was seen in adolescents to all 4 antigens whether the spacing between doses for the two dose schedule was 1, 2 or 6 months. There is variable persistence of bactericidal antibodies when measured in infants 28 months after the 4th dose, 42–76% inclusive of all antigens. Most have persistence against 1 antigen and 50% against 2 antigens. There is a robust anamnestic response with further boosting. Bexsero® can be administered concomitantly, with no interference demonstrated for the routine vaccines.

Tolerability is very similar to MeNZB, i.e. it causes injection site reactions and pyrexia; the pyrexia comes on after 6 hours and is generally settled by 24 and certainly by 48 hours. One crucial point is that the safety of Bexsero® has not been established in infants less than 8 weeks of age and the European data sheet states "it should not be used under 8 weeks". This restriction could create considerable problems were this vaccine to be introduced into NZ and may require a study starting at 6 weeks of age. It remains to be seen if the immune response will translate into protection against clinical disease and how long such protection will last.

Session: Satellite Symposium organised by Novartis Vaccines and Diagnostics

QuantiFERON to diagnose infection by mycobacterial tuberculosis: performance in infants and older children

Speaker: A de Lauzanne

Summary and comment (LV): This is a further paper on the use of QuantiFERON in children. Once again low sensitivity of approximately 40–50% in children under 1 year of age was found. When IGRAs were first introduced, there was great excitement that they would enable us to move away from Mantoux tests (with all their difficulties including both interpretation and needing a visit for reading of the result at 72 hours), and have a simple blood test with a clear result. Unfortunately many studies have confirmed this poor sensitivity and specificity in young infants and there has been widespread consensus that its use in young children remains problematic. However, as IGRAs have been more widely used in adults, the expertise at placing Mantoux tests is declining and this may result in an inadequate test being used in a vulnerable group of infants.

Session: Poster discussion 2. Bacterial infections

Paediatric parapneumonic empyema (PPE) in children in Germany - results on therapeutic management from a nationwide surveillance study

Speaker: F Segerer

Summary and comment (LV): Empyema in children can be a significant complication of pneumonia, often resulting in prolonged hospitalisation and antibiotic use, occasionally with the need for surgical intervention. This study evaluated outcomes after different therapeutic interventions. It found that early VATS procedures resulted in a shorter duration of hospital stay, but these children tended to be older which may also influence hospital stay. Although there were 400 children with PPE in the initial group, these were broken down into groups by interventions, so the numbers for evaluation were quite small in some intervention groups. Despite introduction of pneumococcal vaccine, we continue to see cases of significant empyema, frequently with no organism found. Studies are needed in NZ to evaluate the size of the problem, the aetiology, and the most appropriate interventions to minimise both short and long term morbidity.

Session: Poster discussion 2. Bacterial infections

GBS meningitis in babies <90 days of age: a UK and Republic of Ireland prospective study

Speaker: I Okike

Summary and comment (LV): This comprehensive prospective study found that Group B streptococcal (GBS) remains the leading cause of meningitis in the UK with an incidence of 0.16/1000 live births similar to the incidence from 2000–2001 of 0.15/1000 live births. The majority of cases were late onset and presenting with symptoms in the community. It was interesting to note that only 55% had fever at presentation making this a poor marker of sepsis in these young infants. Although the overall mortality had decreased from 12% to 5% there was an increase in babies surviving with complications. The incidence for early onset disease was 0.05/1000 live births which is less than the rate found in a study conducted through the NZPSU of 0.23/1000 live births with a 9.7% mortality rate. This incidence had halved since a previous study in 1998–9 but remains higher than that from this UK study. Unfortunately there are very limited NZ data on the rate of LOS GBS and without this information it is difficult to determine if there has been an overall change in the incidence of GBS in NZ. Consideration should be given for a broader epidemiological study on neonatal infection, both early and late-onset, in New Zealand. Currently, New Zealand is reviewing the national GBS policy which at this time is a risk-based intrapartum antibiotic policy, similar to that used in the UK and Ireland although there is very limited information on how well this is implemented. GBS vaccines to prevent this disease need to be given a high priority.

Session: Poster discussion 2. Bacterial infections

RSV and recurrent wheeze: the clinical evidence

Speaker: L Bont

Summary and comment (LV): Respiratory syncytial virus (RSV) bronchiolitis remains a major cause of hospital admissions in young infants and can result in long term morbidity with episodes of recurrent wheezing. Recurrent wheeze post-RSV is probably multifactorial in aetiology, including factors associated with innate immunity, environment, airway dysfunction and pre-existing susceptibility. Palivizumab was introduced as a prophylactic agent to reduce episodes of RSV infection in the very vulnerable infant. Dr Bont presented findings from the MAKI trial of palivizumab use in infants born at 32–34 weeks' gestation. This randomised controlled trial found a significant reduction in wheezing days as well as a lower incidence of RSV-related hospitalisations, and of medically attended nonhospitalised RSV infection. Unfortunately, despite these findings the current expense of palivizumab will continue to limit its use. Cost-benefit studies are an essential requirement for further evaluation to enable increased use of this drug in New Zealand and this study suggests they should include cost savings from decrease in use of both hospital and community medical costs.

Session: Satellite Symposium organised by AbbVie

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15 years prospective surveillance for neonatal HSV in Australia indicates declining mortality, increasing HSV1 disease and over representation of young mothers

Speaker: C Jones

Summary and comment (LV): Neonatal herpes simplex virus (HSV) remains a devastating disease with significant morbidity and mortality despite aciclovir use. This study using data from the Australian paediatric surveillance unit (APSU) found little change in total incidence of neonatal HSV over this 15-year time period but did show a rise in HSV1 disease. It is possible that this accounts for the slight decrease in mortality although it still remains high at 18.6%. Interestingly there was an unexplained overrepresentation of young mothers, with a median age of 27 years. One important finding was a normal CSF white cell count in 12/96 infants which were found to be HSV PCR positive, indicating that despite normal CSF parameters the PCR is required to rule out meningitis/encephalitis. A third of these children were born after caesarean section and in only 52% of the total did the mother have a history of genital herpes, reinforcing the need to have a high level of suspicion for herpes disease in neonates presenting with sepsis-like illness.

Session: Oral session 3. Recurrent respiratory tract infections

Impact of a quadrivalent conjugate (MenACWY-CRM) or a serogroupB (4CMenB) meningococcal vaccine on meningococcal carriage in English university students

Speaker: R Read

Summary and comment (LV): Herd immunity through reduction in nasopharyngeal carriage of organisms has been an important component of disease control with previous conjugate vaccines, including Hib and pneumococcal vaccination programmes. Previous monovalent meningococcal C vaccine studies have also found reduction in oropharyngeal carriage. This study evaluated the impact on carriage of 2 new meningococcal vaccines – a quadrivalent vaccine and monovalent meningococcal B vaccine. Unfortunately the primary analysis did not find any impact of either vaccine on carriage. The question of any herd immunity effect from these vaccines will require large studies or implementation programmes to ascertain the effect of these vaccines on herd immunity and cannot be factored into cost-benefit studies at this time. Currently there are no meningococcal vaccines on the New Zealand schedule but issues around herd immunity will be important to develop ideal schedules to provide maximum protection to those most at risk.

Session: ESPID Symposium 3. Complications of common infections

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