

## Allergy, immunity, and infection

### G192 EPIDEMIOLOGY OF CHILDHOOD ALLERGY AND ANAPHYLAXIS AND EPINEPHRINE PRESCRIPTIONS IN WALES: 1994-1999

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**Background:** There has been variable increase in the incidence of anaphylaxis throughout the world. However the mortality from anaphylaxis has remained unchanged. Few data exist about prescription habits of self-injectable epinephrine by General Practitioners.

**Objectives:** To describe the epidemiology of:

1. anaphylaxis and allergic reactions in children less than 15 years and

2. EpiPen and EpiPen junior prescriptions by General Practitioners in Wales from 1994-99.

**Methods:** This was a retrospective population based study. The incidence of anaphylactic reactions was obtained by International Classification of Diseases coding from Health Solution Wales. Health Solution Wales records prospective data on the incidence of all diseases and NHS prescriptions in Wales. All children with anaphylaxis and allergic reactions were included. Those with reactions due to iatrogenic causes were excluded.

EpiPen and EpiPen junior prescription rates in primary care throughout Wales were obtained from Health Solution Wales. The population estimates and social class distribution for various regions in Wales were obtained from the Government Statistical Service.

**Results:** See figure below.

Comparison of the socio-economic status between different regions in Wales and EpiPen prescriptions revealed a positive correlation between EpiPen prescription and higher socio-economic class (Correlation coefficient = 0.28).

**Discussion:** The 4 fold increase in allergy and anaphylaxis has produced a 20 fold rise in EpiPen prescriptions

The association between EpiPen prescriptions and regions of higher socio-economic class is intriguing.

### G193 DOUBLE BLIND PLACEBO CONTROLLED FOOD CHALLENGE TO LOW DOSE PEANUT PROTEIN IN CHILDREN WITH PEANUT ALLERGY

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**Background and Objective:** Total avoidance of peanut is difficult for children with peanut allergy. Many foods may contain traces of nut or are labelled as such. This study assessed clinical reaction to low doses of peanut protein, in children known to have reacted to peanut, by Double Blind Placebo Controlled Food Challenge (DBPCFC).

**Methods:** 25 children with a clinical history of moderate to severe reactions to peanut underwent DBPCFC, following informed consent. The dose of peanut received was gradually increased to a maximum of 120 mg peanut protein. Skin tests were performed prior to the test, and serum tryptase levels, specific and total IgE and taken before and after the test. Previous specific IgE results were also analysed.

**Results:** 14 of 23 children receiving up to 120 mg peanut protein had objective clinical reactions, of whom 10 required treatment. 11 reactors had subjective sensations at lower doses and only one 'reacted' to placebo. There was a significant difference in specific IgE between reactors and non reactors ( $p < 0.01$ ) and specific IgE  $> 15$  had an overall positive predictive value (PPV) for a reaction of 0.9 (95% CI 0.56-0.99). Skin tests showed no significant difference ( $p = 0.26$ ). Mean difference in tryptase levels pre and post challenge, in reactors approached significance ( $p = 0.06$ ), compared to non reactors.

**Conclusions:** DBPCFC was successfully completed in a group considered to be 'high risk'. 78% of children with objective reactions exhibited warning sensations at very low doses. Specific IgE may be a better predictor of those with a clinical reaction than skin testing. 40% of those tested did not react to low dose peanut protein and could be challenged at higher doses.

### G194 PROTEIN BASED DIAGNOSIS OF X-LINKED LYMPHOPROLIFERATIVE DISEASE (XLP) IN MALES WITH BONE MARROW APLASIA

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The major clinical manifestations of XLP are fulminant infectious mononucleosis (58%), lymphoma (30%) and hypogammaglobulinaemia (31%). Other rare clinical manifestations include aplastic anaemia, lymphoid granulomatosis and vasculitis (3% each). The gene defective in XLP (SH2D1A) encodes a protein (SAP) which is involved in the regulation of lymphocyte activation. We have previously demonstrated that immunoblotting for SAP in peripheral blood mononuclear cell preparations can be used as a rapid and cost effective diagnostic test for XLP.

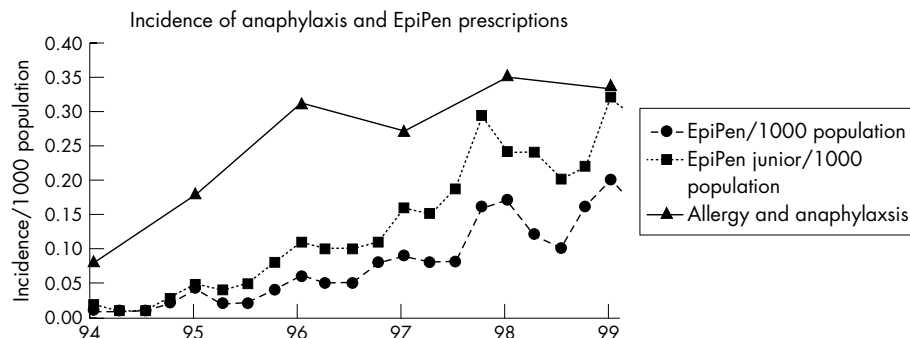
We have documented absent SAP expression in a number of patients with bone marrow aplasia. Two boys were shown to both lack SAP expression and to have mutations in SH2D1A, resulting in a definitive diagnosis of XLP. The first, previously well, boy presented with aplastic anaemia aged 8 years. The second had been diagnosed with hypogammaglobulinaemia in early childhood, and developed an ultimately fatal pancytopenia in his early teens. We will also describe a child with absent SAP expression but no identified mutation who presented with pancytopenia and dysgammaglobulinaemia aged 12 years. This is consistent with published data where only two thirds of males with classical XLP have a mutation in SH2D1A. However, false negative protein results can occur in T-lymphopaenia and further analysis is being undertaken.

XLP is a condition with a high mortality, but which can be treated with bone marrow transplantation. As individuals may be asymptomatic for many years, accurate diagnosis of index cases is critical for early diagnosis and optimum management of the patients and their siblings. These boys highlight the incidence of aplastic anaemia in this syndrome and emphasize the utility of protein expression as a diagnostic tool.

### G195 MINI UNRELATED DONOR TRANSPLANTS FOR CONGENITAL IMMUNODEFICIENCIES

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We report our results on 22 consecutive unrelated donor (UD) bone marrow transplants for congenital immunodeficiency using non-myeloablative (mini) conditioning. The transplants were performed



Abstract G192 Figure.

between October 1998 and May 2001. Of these, 15 were fully matched and 8 were mismatched at one or more loci. 6 children had Severe Combined Immunodeficiency (SCID) and 16 had non SCID immunodeficiencies (CID 7, CD40 ligand deficiency 4, Wiskott 4, other 1) The mean age at transplant was 8.3 years (range 1–21 years). The majority of children had significant organ dysfunction prior to transplant. The patients were conditioned using Fludarabine/ Melphalan and ATG(13) or Campath 1H(9). One child died due to RSV pneumonitis on day 10.7 children had viral reactivation (CMV and/or EBV) and 3 children had EBV disease. One child had acute GVHD > grade 2 and one child has chronic GVHD. The median period of follow up is 19 months (range 3–37 months). 21/22 children survive (95%) which compares to 60% survival in 20 previous patients receiving UD BMT with ablative conditioning. All children have achieved T-cell engraftment and 17/21(80%) > 20% myeloid engraftment. We conclude that in comparison to ablative transplants using unrelated donors; mini transplants improve survival and reduce transplant related morbidity and mortality while achieving comparable engraftment and immune reconstitution. There maybe a potential for reduced late effects.

### 196 ADENOVIRUS INFECTIONS DURING BONE MARROW TRANSPLANTATION

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The aims of this study were to establish the prevalence of adenovirus in a paediatric population during bone marrow transplantation (BMT), and to establish the efficacy of early intervention with anti adenoviral agents.

The cohort of patients consisted of 130 patients who had a BMT in our unit between January 1999 to July 2001. Case records of all patients were retrospectively analysed. All patients were monitored weekly, for the presence of adenovirus DNA, in blood by PCR, and in stools by electron microscopy. NPAs were sent if respiratory signs developed. When the virus was detected in blood or at two or more sites (i.e. disseminated disease), intravenous ribavirin was used as first line agent, cidofovir, as second line, and donor lymphocyte infusion (DLI) as third line.

The efficacy of treatment was determined by regular monitoring. A total of 48 patients were adenovirus positive (37%). The virus was found in 24% of the haematology/oncology patients, and 58% of immune deficient children. 18% of children became viraemic, 30% excreted the virus in the stools, 7% in NPA and 19% developed disseminated disease. Factors associated with viraemia were; T cell depleted grafts (odds ratio OR 2.66), graft versus host disease (OR 6.15), mismatched unrelated grafts (OR 3.81), steroids (OR 3.98), allografts (OR 6.36) and fludarabine (OR 2.67). Of the 25 patients with disseminated disease, 23 were treated with intravenous ribavirin. Nine patients also received cidofovir, and one patient received third line therapy with DLI. Three patients died, (a mortality rate of 12% amongst disseminated cases) all from adenovirus subgenus C hepatitis and multiorgan failure. Two of these three patients lacked T cells at the time of infection, and had had haploypre grafts.

This mortality rate is much lower than that reported in other series. We conclude that adenovirus is a significant cause of morbidity and mortality in this population and that weekly blood PCR is an effective strategy, allowing early treatment. arly treatment with anti adenoviral agents, leads to reduced mortality.

### G197 DUODENAL T CELL INFILTRATION WITH CRYPT HYPERPROLIFERATION AND COLOCALISATION OF IGG AND C1Q ON ENTEROCYTE BASOLATERAL MEMBRANES IN REGRESSIVE AUTISM

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**Background:** Immunohistochemistry has demonstrated a novel form of lymphocytic colitis in children with regressive autism<sup>1</sup>. Following reports of duodenitis in an American cohort<sup>2</sup>, we have employed similar techniques to study duodenal inflammation in 25 children with regressive autism in comparison to 18 histologically normal age-matched controls, 11 children with coeliac disease and 5 with cerebral palsy and mental retardation (CP).

**Methods:** Duodenal biopsies were taken endoscopically and snap-frozen. Immunohistochemistry (IHC) was performed for lymphocyte

and epithelial lineage and functional markers, as well as immunoglobulins G, A and M and complement C1q. We quantified the density of intraepithelial and lamina propria lymphocyte populations, crypt cell proliferation rates using Ki67 monoclonal, and localised immunoglobulin and complement C1q within the mucosa. Colocalisation was determined by double fluorescence and confocal microscopy.

**Results:** Routine histopathology showed normal architecture but increased enterocyte density and Paneth cell numbers in the autistic children. IHC showed significantly increased lymphocyte infiltration in both epithelium and lamina propria, with highly upregulated crypt cell proliferation, compared to normal and CP controls. Compared to coeliac disease, CD8 IEL and lamina propria plasma cell densities were lower, but all lamina propria T cell population densities were higher and crypt proliferation similar. Most strikingly, IgG deposition was seen on the basolateral epithelial surface in 23/25 autistic children, co-localising with complement C1q. This was not seen in the other conditions.

**Conclusions:** These findings demonstrate a novel form of enteropathy in autistic children, in which increase in mucosal lymphocyte density and crypt cell hyperproliferation occur with epithelial IgG deposition. The features are suggestive of an autoimmune lesion.

1. Furlano R, et al. *J Pediatr* 2001;138:366–72.

2. Horvath K, et al. *J Pediatr* 1999;135:559–63.

### G198 TREATMENT INTERRUPTIONS OF HAART IN PAEDIATRIC HIV: EFFECT ON CD4 COUNT

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**Aims:** Highly Active AntiRetroviral Therapy (HAART) has dramatically reduced morbidity and mortality in HIV. However, with increasing concerns about toxicity and adherence, structured treatment interruption (STI) trials are starting in adults. The rate of CD4 cell decline off HAART has not been determined in children. We analysed changes in CD4 during interruptions of HAART in order to assist in the design of a paediatric trial.

**Methods:** Data on clinical events, T cell subsets, HIV RNA viral load and HAART history were collected in the CHIPS study on 285 children on 3 or 4-drug HAART during 2000 from 12 centres in UK and Ireland. Of these, 33 (median age 6.8 year) had 37 interruptions for median 13.9 (range 4.9–87.3) weeks. The slope of decline of CD4 cell count and CD4% per month off HAART was calculated, adjusting for age and CD4 before starting HAART.

**Results:** Reasons for interruption included 'request of parents' (n=10) and poor adherence (n=7). Only 11 children had HIV RNA <10 000 copies/ml (of whom 3 <400 copies/ml) prior to interruption. The same HAART was restarted after 11 interruptions, was changed after 18, and 8 children remained off HAART. During 22 interruptions with sufficient data, the average CD4 decline was 18 cells/mm<sup>3</sup>/month (95% CI -38 to +4, p=0.08); CD4% declined by 0.65%/month (95% CI -0.92 to -0.38, p<0.001). The decline was 30 cells/mm<sup>3</sup>/month in children with CD4% <15%, compared to 14 in those with CD4% >15% at initiation of HAART. In 4 children restarting the same HAART, CD4 declined further in 2 (both poor adherers), and increased in 2 (with fall in HIV RNA (both 'parent request')). 3 children developed AIDS while off HAART (2 lymphoma).

**Conclusions:** CD4 cell decline rate varied considerably following interruption of HAART. An approach to paediatric STI trials may be to base the length of STI on the rate of CD4 decline rather than having fixed STI periods.

### G199 CONVALESCENT SERUM RESPONSES FOLLOWING INVASIVE HAEMOPHILUS INFLUENZAE TYPE B (HIB) DISEASE IN VACCINATED AND UNVACCINATED CHILDREN: WHAT IS THE ROLE OF IMMUNOLOGICAL MEMORY?

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**Aims:** To investigate the attributable contribution of conjugate vaccines, through priming for immunological memory, to the prevention of invasive Hib disease.

**Methods:** Serum was collected from 93 British children, who had been fully immunised with Hib conjugate vaccine, following recovery from Hib meningitis or epiglottitis between 1992 and 2001. Convalescent serum antibody concentrations specific for the type b capsule were compared with those of an historical cohort of 92 unvaccinated Australian children who had experienced invasive Hib disease, recruited between 1988 and 1990. Confounding factors contributing to the convalescent antibody response were identified using regression analysis.

**Results:** Significantly higher ( $p < 0.0001$ ) concentrations of Hib antibodies following meningitis were observed in vaccinated [GMC 8.32 ig/ml (95% CI 4.47, 15.46)] than in unvaccinated children [0.11 ig/ml (0.05, 0.27)]. When corrected for the confounding variables of age at presentation of meningitis and timing of serum collection, this difference remained significant ( $p = 0.003$ ). In children recovering from epiglottitis, no such effect of immunisation on adjusted convalescent responses was observed ( $p = 0.26$ ) [vaccinated 2.96 ig/ml (1.51, 5.80); unvaccinated 5.01 ig/ml (2.77, 9.09)]. This may reflect priming through carriage in unvaccinated children with epiglottitis, who were older and had higher antibody responses to disease than those with meningitis. In immunised children, a history of premature delivery was significantly associated with lower antibody concentrations following invasive Hib infection.

**Conclusions:** These results indicate that priming for a memory response is not always sufficient to protect against invasive Hib infection. Thus, although a majority of children in the UK are now protected from Hib disease by immunisation, the relative roles of immunological memory and other immune mechanisms in conferring protection remain unclear.

## G200 IMMUNOGENICITY OF MENINGOCOCCAL C CONJUGATE VACCINE IN PRETERM INFANTS

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**Background:** The recently introduced meningococcal C conjugate vaccines (MenC) are recommended for term and preterm infants from 2 months of age. Preterm infants have previously been found to have lower antibody concentrations than term babies in response to some vaccines, including Hib conjugate vaccines.

**Aims:** To establish whether vaccination according to the UK immunisation schedule elicits adequate serological immune responses against MenC in preterm infants.

**Methods:** Infants were recruited at two neonatal units and vaccinated at the chronological age of 2, 3 and 4 months in accordance with current UK immunisation recommendations (Hib-DTwP, OPV and MenC), using a CRM197-conjugated meningococcal polysaccharide vaccine (Meningitec®, Wyeth). Blood samples were taken at 2 and 5 months of age and serum analysed for antibodies to MenC (SBA and IgG (ELISA)).

**Results:** Among 22 infants with a mean gestational age of 34 weeks (range 29–37 weeks) and a mean birth weight of 1963g, all infants achieved SBA responses  $\geq 1:8$  (CI 85%–100%) after 3 doses of MenC. All had a  $\geq 4$ -fold rise in SBA (CI 85%–100%). The mean IgG concentration increased from 0.6µg/ml (CI 0.23–0.98) pre-vaccination to 28.6µg/ml postvaccination (CI 20.6–36.5) and SBA from  $< 1:4$  to 1:992 (GMT).

**Conclusions:** These results indicate that, using the recommended UK schedule, preterm infants of more than 29 weeks gestational age can be expected to derive excellent short term protection against MenC disease. Long term protection in this cohort will be assessed by the rate of decline in antibody levels and the presence of immunological memory at 12 months of age.

## G201 THE IMPACT OF SEROTYPE REPLACEMENT ON INVASIVE PNEUMOCOCCAL DISEASE POST IMPLEMENTATION OF PNEUMOCOCCAL CONJUGATE VACCINES: THE IMPORTANCE OF EVALUATING ATTACK RATES AND VIRULENCE OF NON-VACCINE SEROTYPES

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**Aims and Methods:** Two longitudinal pneumococcal [Spn] carriage studies have been conducted in conjunction with an ongoing active

surveillance of invasive pneumococcal disease [IPD] in the same area in the UK. The results of these carriage studies were pooled and analysed in conjunction with the IPD surveillance to determine, for each serotype [ST], the likelihood of causing disease.

**Results:** The incidence of acquisition was significantly associated with the incidence of IPD by ST,  $p < 0.001$ . This association is mostly determined by a limited number of STs that cause a significant proportion of IPD (6B, 6A, 19F, 14, 18C, 23F, 9V, and 19A). With the exception of STs 6A and 19A, these STs are in the 7-valent vaccine. When the vaccine STs are removed from the analysis Spn STs fall into groups: 1) STs that are frequently acquired with a high incidence of IPD (19A, 3); 2) STs that are not frequently acquired with a high incidence of IPD (12F, 1, 7F, 8); 3) STs that are frequently acquired with a low incidence of IPD (10A, 11A, 15B, 23A, 21); and 4) STs that are not frequently acquired with a low incidence of IPD (38, 9A, 5, 9N, 16F, 20, 31, 35F, 15A, 17F, 33F, 22F, 24F, 13, 27, 37, 31, 23B, 18B).

**Conclusions:** Spn STs fall into distinct groups based on attack rates and frequency of acquisition. Some studies have demonstrated that ST replacement occurs post introduction of the Spn-conjugate vaccines and there is a concern that this may compromise vaccine efficacy. It seems probable that those STs that have a high likelihood of causing disease once acquired (groups 1 and 2) may compromise vaccine efficacy if replaced by these STs occurs. On the other hand it seems likely that groups 3 and 4 will not compromise vaccine efficacy unless they acquire new virulence genes. Seven and 11-valent Spn-conjugate vaccines include STs 1, 5, 3 and 7F. Two STs, 12F and 8, are not in any conjugate vaccine formulation undergoing clinical trials, and have a high likelihood of causing IPD once acquired. Rigorous surveillance of these STs is required to determine how the Spn population will re-structure post vaccination.

## G202 INFLUENZA AND MENINGOCOCCAL DISEASE IN ADOLESCENTS

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**Background:** There is a second peak of meningococcal disease (MD) in older teenagers although the reasons for this are unclear. Preceding illness is a recognized risk factor for MD and viruses including influenza have previously been implicated.

**Aims:** To determine if preceding influenza infection and/or other preceding upper respiratory tract illnesses are risk factors for MD in 15–19 year olds.

**Methods:** We undertook a prospective population-based case-control study undertaken in 6 regions of England. Cases were matched to GP-identified controls of the same age and sex. Questionnaire data and blood samples were obtained concurrently in convalescence. ELISAs for influenza types A (H3N2 and H1N1) and type B were performed. A history of a respiratory "viral" illness in the 2 weeks prior to MD (or 2 weeks prior to interview in controls) but distinct from the MD prodrome was noted.

**Results:** Multivariate logistic regression analysis controlling for the potential confounding effects of seasonality and behaviour (eg. smoking, kissing) suggests that preceding illness is a risk factor for MD (OR=2.3; 95% CI: 1.3–4.3;  $p = 0.005$ ). Such illnesses were clearly separate in time and nature from the MD prodrome. Multivariate analysis of variance did not detect significant differences in influenza serology between cases and controls ( $p = 0.66$ ).

**Conclusion:** A preceding viral-like respiratory illness predisposes to MD in teenagers. This preceding illness is distinct from an MD prodrome. Influenza is not a common risk factor for MD in older adolescents.

## 203 MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS C VIRUS

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**Aims:** To quantify the risk of mother-to-child transmission of hepatitis C virus (HCV) allowing for risk factors and to clarify the natural history of vertically acquired infection using prospectively collected data.

**Methods:** Within the European Paediatric HCV Network prospective study HCV infected women are enrolled during pregnancy and detailed information collected according to a standard protocol. Children are followed up with clinical and laboratory information

collected at each visit. HCV infection in the child is defined by two or more positive PCR tests on separate occasions and/or anti-HCV antibody positivity beyond 18 months of age.

**Results:** At data analysis, 354 mother-child pairs had been enrolled at 16 centres. 20 infants were infected, 224 uninfected and 110 were of indeterminate infection status (< 18 months old). Excluding these 110, 11 (21.6%) of 51 children born to HCV/HIV co-infected women were infected compared to 8 (4.3%) of 188 children born to women with only HCV infection (odds ratio=6.2, 95%CI 2.3–17.0). Elective caesarean section delivery was associated with a lower vertical transmission risk than other deliveries among HCV/HIV co-infected women (odds ratio=0.10, 95%CI 0.01–0.62) but not among women with only HCV infection (odds ratio=0.90, 95%CI 0.18–4.65). Neonatal anti-retroviral prophylaxis was also associated with a lower risk of HCV infection. Viraemia patterns varied in the 20 infected children. 6 were PCR positive every time; 11 were both positive and negative and 3 were PCR negative each time. 4 children had hepatomegaly, 2 also splenomegaly, but the other 16 children were asymptomatic.

**Conclusions:** Although HCV/HIV co-infected women are at substantial risk of transmitting both HIV and HCV, in women with only HCV infection the risk of vertical transmission is low and there are currently no prophylactic interventions. Infected children are usually asymptomatic in the first years of life. The significance of different viraemia patterns for progression of disease remains to be clarified.

### G204 PAEDIATRIC TUBERCULOSIS IN EAST LONDON

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**Objectives:** To assess BCG immunization status, demographic and clinical features, and notifications of children <15 years age with tuberculosis in East London.

**Methods:** Paediatric TB cases in Tower Hamlets and Hackney were identified retrospectively between 1995–2000 using health authority notifications and positive *M. tuberculosis* laboratory isolates.

**Results:** Of 121 possible paediatric TB cases, 80 (66%) were true cases, 9 (8%) atypical mycobacterial infection, 17 (14%) chemoprophylaxis and 15 (12%) entry errors. The age distribution was bimodal, with peak incidence between 3–5 years and 12–15 years. Forty-six cases (56%) were UK born, while the remainder were born in either South Asia or Sub-Saharan Africa. Fifty-three cases (66%) had pulmonary disease and 27 (34%) had extrapulmonary disease, including 8 cases (10%) with invasive TB (military and meningeal TB). Forty-nine (60%) were immunised with BCG including 4 of 8 children with invasive TB (military and meningeal). Twenty cases (69%) of TB occurred within 5 years of receiving BCG vaccination. Using the screening method, vaccine efficacy is estimated at 50%.

**Conclusions:** TB notifications may be inaccurate in representing the true incidence of TB in children. Over two thirds of children with TB were born in the UK and were BCG immunised. We found an unusually high rate of invasive disease (military and meningeal TB) of which half had received BCG vaccine. These findings question the role of BCG vaccination in preventing TB, particularly severe forms, in a high prevalence area in the UK.

### G205 THE AETIOLOGY OF COMMUNITY ACQUIRED PNEUMONIA IN SOUTH AFRICAN CHILDREN WHO FAIL TO IMPROVE ON WHO RECOMMENDED THERAPY

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**Aims:** To determine the response rates of paediatric community acquired pneumonia to standard anti-microbial therapy in an area with a high prevalence of HIV.

To determine the aetiology of pneumonia in those who fail therapy in order to design rational second line antibiotic protocols.

**Methods:** Children aged 1 month to 5 years are admitted to the study if they fulfil the WHO criteria for severe or very severe pneumonia and informed consent is obtained. Admission investigations include linked anonymous HIV viral load. They are commenced on intravenous benzylpenicillin and gentamicin, with the addition of high dose co-trimoxazole in those under one year. Children who fail to respond to antimicrobial therapy are investigated further by either

ultrasound guided lung aspiration or non-bronchoscopic bronchoalveolar lavage (NBAL).

**Results:** Interim results are presented. There is a case fatality rate of 15%, which is age dependent. 70% of the children are infected with HIV (confirmed on pcr). The overall response rate to first line therapy is 69%. As the HIV results are still unlinked it is not possible to determine the differences in response rates to children who are and are not infected with HIV. A definitive diagnosis has been made in 82.6% of children who failed first line therapy. At least two pathogens have been isolated in 37% of these cases. 10 % of the admitted children had proven PCP pneumonia. All of these children were aged between 2 and 4 months of age. Thirteen of the fifteen organisms isolated in non-responders are gram-negative organisms, *Klebsiella pneumoniae* being the single most commonly isolated organism after PCP.

**Conclusions:** These are the highest rates of HIV in children with community acquired pneumonia yet published. However the majority of children still responded to simple first line therapy.

### G206 BACTERAEMIA DUE TO STAPHYLOCOCCUS AUREUS IN CHILDREN

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Bacteraemia due to *Staphylococcus aureus* is common in children, but not well-reported. Between January 1995 and December 2000, we identified 97 significant episodes of *S. aureus* bacteraemia in children admitted to Kilifi District Hospital, accounting for 10% of all positive blood cultures. Their median age was 17 months (range: 1 day–12 years), 46 were male and 10 were considered to be nosocomially-acquired. A focus that was clinically consistent with staphylococcal infection was identified in 52/97 (54%) cases—of these, 88% had multiple foci. Children with a focus were likely to be older, present later and have a longer duration of hospital stay. Most children in this group (90%) received intravenous cloxacillin on admission in contrast to none of those without a focus. In the former group, mortality was only 6% compared to 47% among those without a focus ( $p < 0.0001$ ). In particular, 10/13 (77%) neonates without a staphylococcal focus died compared to none of the 11 neonates presenting with a focus ( $p = 0.0001$ ). Eight of the 10 neonates in the former group died within 48 hours of admission, before empirical antibiotics could be changed to include cloxacillin. In a multivariable regression model, absence of a focus (OR: 16.8; 95% CI: 3.23–86.4) and younger age (OR: 3.7; 95% CI: 1.3–10.9) remained significantly associated with mortality. Thus, children most at risk of death associated with *S. aureus* bacteraemia are least likely to have clinical features traditionally associated with this infection. This study questions whether anti-staphylococcal antibiotics should be included as part of empirical treatment in children, particularly neonates, with septicaemia.

### G207 ABSTRACT WITHDRAWN

### G208 BEHAVIOURAL SEQUELAE POST ACUTE KAWASAKI DISEASE

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**Aims:** To measure a number of behavioural and social parameters within a cohort of Kawasaki disease patients.

**Methods:** Parents of children with past diagnosis of Kawasaki disease were recruited to complete several behavioural screening questionnaires. These included the Child Behaviour Check List, Strengths and Difficulties Questionnaire and the Parenting Stress Index. Sixty five sets of questionnaires relating to the patient cohort received were eligible for inclusion (KD group). Two control groups were used, a hospital (HC) control and a sibling control (SC) group.

**Results:** 40% of the KD group showed elevated internalising scores in the clinical or borderline-clinical range. This compared with 18% of hospital controls and 13% of sibling controls ( $P = 0.04$ ). Higher behavioural scores were attained by the KD group within the internalising sub-categories of somatic problems (KD 61, SC 54;  $P = 0.02$ ) and withdrawn traits (KD 56, SC 51;  $P = 0.02$ ) compared with sibling controls. The KD group were also shown to be experiencing more thought problems (KD 57, SC 50;  $P = 0.03$ ) compared with sibling controls. Further difficulties within conduct (KD 3.3, HC 1.4;  $P = 0.04$ ) and prosocial (KD 6.7, HC 8.3;  $P = 0.04$ ) categories are also highlighted for the KD group when compared with the hospital controls. Additionally, the KD group were also shown to be experiencing significantly

greater overall total difficulties when compared with the hospital control group (KD13.7, HC 8.6;  $P=0.02$ ). PET scans were performed on nine patients to investigate severe behavioural problems. Three patients showed minor changes, possibly a resolving cerebral vasculopathy.

**Conclusions:** The results demonstrate that Kawasaki disease can be associated with significant behavioural sequelae in the longer term. Referral to a clinical psychologist where necessary could form an important added dimension in the long term management of Kawasaki Disease.

### G209 THE NATURAL HISTORY, DEVELOPMENT AND PROGRESSION OF PEANUT AND MULTIPLE NUT ALLERGY: FINDINGS IN 746 NUT-ALLERGIC CHILDREN.

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**Introduction:** Peanut allergy is common and increasing in prevalence, however the natural history, development and progression of multiple nut allergies throughout childhood are not well characterised. We provide the first information on a large number of children on the features, severity, and development of both peanut and tree nut allergy.

**Methods:** An observational study of 746 children interviewed, with a typical history of an allergic reaction to at least one nut. Severity of reactions (graded) or tolerance, to up to 5 nuts was obtained and SPT/CAP performed for all patients.

**Results:** Of 746 children; M:F=1.3:1; 87% had at least one other allergic disease (asthma-55%, eczema-67%, rhinitis-34%). Median age at first peanut or nut reaction was 2y(0.4–16y), 68% of first reactions occurred by 4 years of age. Peanut caused the most severe reaction in 67%, then Brazil nut (12%), hazelnut (5%), walnut and almond (2%). The most severe reactions in 42% involved skin only (erythema and/or urticaria and/or angioedema), skin and gastro-intestinal symptoms only in 20%, wheeze and/or laryngeal oedema in 31% and severe dyspnoea and/or collapse in 7%. Patients seen for the first time in the allergy clinic in the first year of life were more likely to be sensitised (i.e. have nut-specific IgE on testing) to only one type of nut than those who presented later (47% v 18%). Sensitisation to two or more nuts was increasingly common with increasing age at presentation (54% at 3y, 85% at 6y). Clinical allergy to multiple nuts was more common in patients seen for the first time after 6 years of age (33% v 13%).

**Conclusions:** This is the largest study to describe the features and development of peanut and nut allergy in children. Peanut and nut allergy is an important and common cause of severe allergic reactions in children, with 283 (38%) reactions in this series involving the respiratory or cardiovascular system. We show for the first time that very young nut-allergic children are more likely to be sensitised (positive specific IgE) to only one type of nut and that multiple nut sensitisation develops with age. This is reflected in the higher proportion of children allergic to multiple nuts from the age of six years on. This suggests that early institution of complete peanut and nut avoidance is necessary to prevent the development of multiple nut allergies, which are usually severe and long-lived.

### G210 EFFECTS OF ANTIRETROVIRAL THERAPY (ART) ON MORBIDITY AND MORTALITY OF UK AND IRISH HIV INFECTED CHILDREN

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**Aims:** To analyse changes in mortality, hospital admission rates and receipt of antiretroviral therapy (ART) in HIV infected children in UK and Ireland.

**Methods:** Data on clinical events, T-cell subsets, HIV-RNA viral load and ART history were collected on a standard form on all children in follow-up since 1996 at 12 centres in UK and Ireland participating in the Collaborative HIV Paediatric Surveillance (CHIPS) study. For mortality analyses, data on 75 additional children at these centres who died before 1996 were available from the National Study of HIV in Pregnancy and Childhood (NSHPC).

**Results:** Among 586 children (median age 7.2 years, 66% black African; 35% born abroad; 85% cared for in London), the proportion of those on ART on 3 or 4 drugs increased from 9% in 1996 to 90%

in 2000. Of these, proportions on PI; NNRTI; PI+NNRTI and 3 NRTI based regimens are currently 41, 45, 7 and 8% respectively. Recent HIV RNA values are <400 in 42% children (<50 copies/ml in 20%) and mean CD4% increased by 9% at 24 weeks after start of ART, with no significant differences between centres. Hospital admission rate fell from 1.37 per year at risk in 1996 to 0.57 in 2000 (total admissions 354 in 1996, 261 in 2000). Length of hospital stay also decreased by 57%. Admission rates were higher in infected children born to mothers not diagnosed in pregnancy compared with those born to mothers diagnosed antenatally (0.65 v 0.30 per year-at-risk in 2000,  $p<0.001$ ) and were higher in the 6 months after HIV diagnosis than later (3.09 v 0.4,  $p<0.001$ ). Mortality decreased significantly after 1998 (e.g. there were 24 deaths out of 291 children in follow-up in 1996 compared with 4 of 501 in 2000). Deaths from PCP still occur in babies born to undiagnosed women.

**Conclusions:** Mortality has decreased significantly with use of HAART and improved rates of antenatal HIV diagnosis. Hospital admission rates have fallen by 26% since 1996, but as the number of HIV children in follow-up continues to rise, the need for paediatric HIV services continues to increase.

### G211 ONE DOSE OF MENC-T CONJUGATE VACCINE IN INFANCY PRODUCES HIGHER MUCOSAL IGG AND IGA RESPONSES THAN 2 OR 3 DOSES AND OPTIMAL POLYSACCHARIDE VACCINE AT 13 MONTHS

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Three meningococcal group C conjugate vaccines have been used in the UK programme which commenced in late 1999, two diphtheria toxin- and one tetanus toxoid- conjugates (MenC-T, Baxter). It is not yet known what effects these vaccines will have on nasopharyngeal carriage. We have previously shown that the former 2 vaccines induce IgG but not IgA responses in saliva at 5 months (m) after 3 doses. We collected saliva from 90 infants at 2m of age immediately prior to commencing primary immunisation with MenC-T and one month after their primary course. 30 received only one dose (2m only—group (Gp)1), 30 received 2 doses (2 and 4m, Gp 2), 30 received 3 doses (2,3 and 4m—Gp 3). Samples were snap frozen on dry ice immediately after collection and held at  $-70^{\circ}\text{C}$  until analysis by immunoassay for anti-MenC IgG and IgA. There were modest but significant ( $p<0.05$ ) increases in salivary IgG after priming in groups 2 and 3 (pre 4.5, post 10.0, 12.5 ng/ml respectively) but significantly higher post-priming concentrations in group 1 who had had only one dose (29.8ng/ml) ( $p<0.05$ ). There were no significant rises in salivary IgA post priming in groups 2 and 3 (pre 2.0, post 2.7 and 2.6 ng/ml) but, again, significant rises in group 1 (12.3 ng/ml). Following a booster dose of unconjugated MenC polysaccharide at 13 months all 3 groups showed a clear rise in salivary IgG at 14 months—group 1 having the highest concentrations (35.0, 19.2, 27.0 ng/ml, respectively). IgA levels at the same time point also rose but once again less in group 2 (8.9, 3.4, 7.5 ng/ml). These surprising data suggest that one dose of this vaccine may induce better mucosal immune responses in infancy than either two doses or three and may also prime better for mucosal memory immune responses to a polysaccharide challenge. Although serum responses—indicating protection against invasive disease—will also be important in predicting optimal future primary schedules, these results suggest it may be possible (and maybe even preferable) to give only one dose of this vaccine to infants in the future. Further studies with this and the other MenC conjugate vaccines will demonstrate how to induce optimal protective mucosal immunity.

### G212 DEVELOPMENT OF A LIPOPOLYSACCHARIDE BASED VACCINE AGAINST INVASIVE NEISSERIA MENINGITIDIS SEROGROUP B DISEASE

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There is currently no effective vaccine for *Neisseria meningitidis* serogroup B (NmB) disease. Our aim is to develop a conjugate vaccine based on defined lipopolysaccharide (LPS) glycoforms. A set of monoclonal antibodies (mAbs) has defined inner core epitopes in a 100% of invasive NmB strains. One of these mAbs, B5, recognises a conserved and antibody accessible inner core LPS epitope found in 76% of a representative global collection of 65 hypervirulent NmB

strains. Phosphoethanolamine (attached to 3-position of beta-chain heptose of NmB LPS) is critical for mab B5 reactivity. Mab B5 is opsonic and variably bactericidal against NmB strains. In passive protection studies of infant rats (n=27) following i.p. challenge with NmB strains 8047, M986, 2996 >20µg mab B5 per rat was completely protective (no detectable bacteremia). In contrast, 19 controls had a geometric mean bacteremia (GMB) of  $229 \times 10^3$  CFU/ml,  $3.09 \times 10^3$  CFU/ml and  $118 \times 10^3$  CFU/ml against strains 8047, M986 and 2996 respectively. 5µg of anticapsular B mab per rat was not able to protect against 8047, M986 and 2996 (n=15) and resulted in GMB of  $0.16 \times 10^3$  CFU/ml,  $5.13 \times 10^3$  CFU/ml and  $1.6 \times 10^3$  CFU/ml respectively. In contrast, 1µg antioporin P1.2 mab was able to protect infant rats against all strains (n=17) with no detectable bacteremia. Thus an inner core LPS epitope of encapsulated NmB strains can be a target for protective immunity *in vivo*. Taken together, we have shown that inner core LPS glycoforms are relatively conserved, antibody accessible and capable of inducing protective antibodies against NmB. Our data therefore encourage further investigation of inner core glycoforms as candidate vaccines for the prevention of NmB invasive disease.

### **G213** ANTIMICROBIAL PRESCRIBING PRACTICES IN A PAEDIATRIC TERTIARY REFERRAL HOSPITAL

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Antimicrobial resistance is an increasing problem and is now considered a major threat to public health. One method of controlling antimicrobial resistance in hospitals is through the prudent use of antimicrobials. This can be achieved via the use of in-house evidence-based Guidelines which ideally would be reviewed on a regular basis. A Department of Health report emphasises the importance of monitoring anti-microbial use and optimising prescribing. To look at prescribing practices and adherence to in-house antimicrobial Guidelines, a serial point prevalence study was carried out in a large Paediatric Tertiary referral centre. Ward pharmacists collected information on a specified day for all inpatients. The drug, dosage, route, duration and indication were recorded. Forty one percent of inpatients were prescribed at least one antimicrobial on that day. Sixty five percent of prescriptions were for indications covered by the Trust antibiotic Guidelines, and of those, 85% were prescribed according to the Guidelines. Prescribing for the treatment of cytomegalovirus and chest infections showed the greatest disparity from the Guidelines with 40% and 47% of prescriptions respectively. Post-operative antimicrobials were continued beyond the recommended 48 hours in 15% of prescriptions for surgical prophylaxis. On the whole, there was good concordance with the existing Guidelines. The study highlighted areas of prescribing aberration, where new policies need to be developed, and was a starting point for review of the current Trust Antibiotic Guidelines. The study will be repeated at 6 monthly intervals to look at trends in prescribing. Serial point prevalence studies are simple, reproducible and provide detailed prescribing information that can be used to monitor antimicrobial use and guide decision-making.