

Final abstract number: 1.001

Session: Genetics of Innate Immunity (invited)

Date/time: Friday, 20 June, 2008, 09:00-09:45 hrs

Room: Conference Hall 1-3

Genetics of Innate Immunity

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The general sensing apparatus used by the mammalian innate immune system was first revealed by a classical mutation, affecting the so-called *Lps* locus of mice. Positional cloning disclosed that *Lps* mutants, which were unable to sense bacterial lipopolysaccharides (LPS), had defects in Toll-like receptor 4, which thus emerged as the key transducing component of the LPS receptor. It is now known that awareness of microbes depends upon a small collection of germline-encoded receptors that are rather flexible in their recognition specificity and collectively discriminate between self and non-self. Mammals depend upon the TLRs to such an extent that mice lacking TLRs are quickly overwhelmed by a wide variety of infections. We have applied a classical genetic approach (mutagenesis and positional cloning) to analyze innate immunity in mice. Among the phenomena probed are Toll-like receptor signal transduction and resistance to infection by mouse cytomegalovirus (MCMV), a herpesvirus that has unusually sharp dose-lethality characteristics in the host species. Where TLR signaling is concerned, total of 22 mutations affecting 18 genes have been identified by screening approximately 30,000 mice. These mutations delineate much of what we know about how the mouse becomes aware of infection and begins to mount a response. With regard to the MCMV resistance screen, 46 phenovariants have been collected from among 22,000 mice screened to date. These affect genes in five functional categories, classed as 'sensing', 'signaling', 'effector', 'homeostatic', and 'developmental'. Through positional cloning, we have identified approximately half of these mutations. We estimate that a minimum of 300 genes and perhaps more than 1000 genes make non-redundant contributions to defense against MCMV. We hope to identify all of these genes and determine how they operate together to protect the host.

Final abstract number: 2.001

Session: Influenza in Animals and People (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

The Ongoing Epidemic of Highly Pathogenic Avian Influenza

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There are very few diseases that have spread as fast and wide among its hosts as the Eurasian strain H5N1 of avian influenza virus. Currently over 60 countries have reported H5N1 HPAI introduction since it first emerged as a transboundary animal disease crisis in late 2003. The misguided panic of an imminent human pandemic led government, regional and international organisations, financial and donor institutions to stress preparedness planning including accumulation of anti-virals and vaccines forgetting that the origin of the malady was - and remains - a poultry problem. Notwithstanding the important efforts for preparedness for a human pandemic, the veterinary national and international efforts to prevent, detect, and control the H5N1 highly pathogenic avian influenza strain emphasised "tackling the disease at source", but funding interests lagged and the country's national veterinary services were unable to mount sufficient border and regulatory controls to keep the disease in South East Asia. Notable risks were trade - some of it legal - poor hygienic conditions in an under-regulated poultry production systems and associated marketing practices, migratory bird risks, and movement of people with their prized possessions: gifts in the form of poultry or prize fighting cocks. Maintenance of the virus in chicken production systems seems to overlap areas where rice production and duck husbandry coincide. Early in February 2004 FAO offered a series of technical projects to assist countries and regions establish networks of epidemiology units and veterinary diagnostic laboratories, and feed information into the WHO/Ministry of Health systems. The success was further emulated in Eastern Europe, Middle East, Africa and the Americas through FAO's own funds and attracting vast support from multiple donors. The success of an intervention measure is taken at the local level to curb a poultry disease that affects people's livelihoods and avoid a single human fatality from H5N1; but success also extends to the recognition of the veterinary services as a Public Good and requires the political and financial resources for its rational development and ever-increasing professionalism.

Final abstract number: 2.002

Session: Influenza in Animals and People (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

Present Situation and Clinical Features of A/H5N1 Human Infection

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Human infection with Influenza A/H5N1 had been recognized since a decade ago. It can be regarded as one of newly emerging infectious diseases. To date the disease has affected many countries worldwide. Hundreds of cases had been reported to WHO with 50-60% fatalities. In Indonesia as of March 2008, 129 cases had been reported since 2005 with inevitably high fatality rate (81,4%). Some preliminary reports suggested that the high fatality rate may correlate with the virulence of the virus strain circulating in the country, high viral load and the dissemination of the virus into important organs outside the lung such as blood, brain and the gastro-intestinal tract. New cases is still taking place in the country due to many factors: geographic and demographic, poultry farming structure, vaccine availability, poultry movement, geopolitical (decentralization impact) and migratory birds may plays some roles.

The demographic characteristic showed that all age groups may be affected with slight predominance in young adult group. There is no significant different between male and female in term of prevalence. A proportion of the cases (about 50%) had history of direct contact with sick, healthy or died poultry, 30% had history of indirect contact with poultry in the environment either sick or healthy. In about 20% of the cases the history of contact to source of infection could not be concluded.

Fever, cough and breathlessness are the most frequent encountered clinical feature. For the purpose of screening some criterias for suspect are used: ILI, ARI or pneumonia with history of contact with AI source of infection, rapid progressive pneumonia leading to ARDS or fatality, unresponsive pneumonia treated adequately with antibiotics, clustering, or when viral infection is likely (leucopenia, lymphopenia). Antibiotics are used as initial treatment of CAP empiricly and when there is evidence of secondary bacterial infection. Antiviral treatment with oseltamivir has limited clinical benefit especially when given earlier .

Final abstract number: 2.003

Session: Influenza in Animals and People (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

Progress on Global Preparedness for Influenza Pandemic, WHO

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WHO and international experts believe that the world is now closer to another influenza pandemic than at any time since 1968. Since the re-emergence of the highly pathogenic H5N1 avian influenza virus in Southeast Asia in 2003, the virus has rapidly spread to parts of Eurasia, Middle-East and Africa and entrenched in some countries. Consequently, sporadic or clusters of human infection with the virus has been continuously reported with high case fatality proportion. WHO has published various technical guidelines and planning guidance for Member States to better respond to outbreaks and better prepared. The areas of work include global surveillance, outbreak investigation, diagnosis, vaccine development, infection control, pharmacological and clinical management of patients, stockpile development and research coordination. There is an ongoing process to revise and update the WHO influenza pandemic preparedness plan based on increased scientific knowledge and consensus reached during the series of international consultations.

The other major activity is to develop a protocol on the rapid operations to contain the initial emergence of pandemic influenza. The attempt is to stop the emergence of an influenza pandemic at its source which is an extraordinary operation that requires international support that is unprecedented in history.

Now more than 100 Member States have developed national influenza preparedness plans and it is now the time for testing the plans. WHO is working closely with partners and conducted some pilot exercises in high-risk countries. The experience gained through these exercises, statistical analysis of past pandemics and modelling studies have identified some key public health actions. Influenza vaccine development evolved rapidly than ever before, shedding lights on better preparedness. The use of inter-pandemic vaccines and the global stockpile strategies are being discussed among technical experts and representatives of national health authorities worldwide. The first recommendations were made by the Strategic Advisory Group of Experts in November 2007.

Final abstract number: 2.004

Session: Influenza in Animals and People (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

Progress on Pre-pandemic/Pandemic Influenza Vaccine

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As pandemic influenza is a matter of global crisis management, WHO has urged to increase international production and supply of pandemic vaccines. For this, each country should establish influenza vaccination policy depending on annual health burden and economical situation. In Asia, while only Japan and China produce seasonal influenza vaccines, several countries including India, Indonesia, Singapore, South Korea, Taiwan, Thailand, and Vietnam, are planning to establish local production of pandemic vaccines. However, pandemic vaccine policy should be based on sustained annual vaccine measures. WHO started to support these countries to implement their local vaccine production of pandemic vaccines. Technical transfer to these facilities by vaccine manufactures in developed countries is essential, but it is conflicting with business and profits of the manufactures.

To develop human H5N1 influenza vaccine, Japan experienced a low immunogenic property in humans of split-type vaccines derived from A/Hong Kong/156/97(H5N1). The Japanese project of H5N1 vaccine development aimed to develop a pandemic vaccine with highly immunogenic and to spare antigens to provide larger population with the vaccines in a short period of time. The WHO prototype vaccine strain, NIBRG-14, propagated in eggs was fixed with formalin. Based on animal experiments, alum-adjuvanted, inactivated whole virus vaccines were prepared. Phase 1 clinical studies followed by Phase 2+3 studies were conducted with 1.75, 5, and 15 mcg HA/dose in one or two doses, and subcutaneously or intramuscularly. Results of the clinical studies showed that the vaccine with 15 mcg HA was tolerable and did not cause severe adverse event. Serum antibody responses were induced efficiently by one or two shots with the high (15) or medium dose (5), respectively, of the vaccines, meeting all of the three EMEA criteria. There results indicated that the inactivated whole virus vaccine conjugated with alum adjuvant is a practically suitable formulation of H5N1 pandemic vaccines. The serum antibody induced by the Clade 1 vaccine cross-reacted significantly with three subclades of Clade 2 viruses.

Based on the data, the Government has introduced national stockpile policy of prepandemic vaccines, now with 20 million courses. Stockpile is to scale-up annually. Before expiration of each batch, vaccination to volunteers of the prioritized groups and then general population is under discussion.

Final abstract number: 3.001

Session: Synergy of Bacterial Flora in the Nasopharynx: Impact on Prevention Strategies (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: Plenary Theatre

Clinical Implications of Nasopharyngeal Bacterial Colonization

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During childhood, the nasopharynx is colonised by a variety of bacteria including *Streptococcus pneumoniae*, *Haemophilus influenzae* (mainly non-typable strains - NTHi) and *Moraxella catarrhalis* [1]. Generally, nasopharyngeal carriage of these bacteria is asymptomatic. However, under certain circumstances, bacteria in the nasopharynx may cause systemic or localised disease. *S. pneumoniae* is a leading cause of invasive pneumococcal disease (IPD) [1]. Elimination of nasopharyngeal pneumococcal colonisation, e.g. by pneumococcal conjugate vaccines, is strongly associated with a reduction in IPD and pneumonia [2].

The relationship between nasopharyngeal colonisation and otitis media (OM) is more complex. The pathogenesis of OM involves migration of *S. pneumoniae*, NTHi or *M. catarrhalis* from the nasopharynx to the middle ear. There is a direct relationship between colonisation by pathogens and the first occurrence of acute OM, and colonisation early in life by any of the three pathogens is associated with recurrent OM [3, 4].

S. pneumoniae, NTHi and *M. catarrhalis* are exclusively human pathogens and occupy the same niche, the nasopharynx, along with ~700 different microbial species. Several mechanisms are involved in establishing and maintaining colonisation and in determining the outcome of competition among strains and species. *S. pneumoniae* and NTHi interact synergistically and antagonistically via mechanisms that include mediators of innate immunity including Toll-like receptors, bacteriocins, hydrogen peroxide production, cell-mediated immunity and complement-dependent phagocytosis [5,6,7]. A vaccine comprising pneumococcal capsular polysaccharide conjugated to an NTHi surface protein has efficacy in preventing OM caused by both *S. pneumoniae* and NTHi [8], which provides proof of principle of the feasibility of preventing OM caused by both bacteria. As vaccines are developed and tested, surveillance of nasopharyngeal colonisation will be important because of the critical role it plays in the pathogenesis of OM, pneumonia and other respiratory tract infections.

1. Garcia-Rodriguez, et al. J Antimicrob Chemother, 2002; 2. Overturf, et al. Pediatrics, 2000; 3. Smith-Vaughan, et al. Int J Pediatr Otorhinolaryngol, 2008; 4. Faden, et al. J Infect Dis, 1997; 5. Pericone, et al. Infect Immun, 2000; 6. Lysenko, et al. LoS Pathog, 2005; 7. Ratner, et al. Proc Natl Acad Sci U S A, 2005; 8. Prymula, et al. Lancet, 2006.

Final Abstract Number: 3.002

Session: Synergy of Bacterial Flora in the Nasopharynx: Impact on Prevention Strategies

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: Plenary Theatre

Antibody Responses Following Administration of 10-Valent Pneumococcal Non-Typeable *Haemophilus influenzae* Protein D-Conjugate Vaccine (PHiD-CV) in Filipino Infants

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Background: This double-blind, controlled study (107007/NCT00344318) evaluated the immune responses of the candidate vaccine, PHiD-CV (GlaxoSmithKline Biologicals), designed to protect infants against pneumococcal and non-typeable *Haemophilus influenzae* diseases, following co-administration with DTPw-HBV/Hib + OPV at 6-10-14 weeks of age (EPI schedule) in the Philippines.

Methods: 400 healthy Filipino infants 6 to 12 weeks of age were randomized (3:1) to receive either PHiD-CV or licensed 7vCRM vaccine (*PrevenarTM/PrevnarTM*) co-administered with DTPw-HBV/Hib + OPV. Vaccine immune responses were assessed one month post-dose III (22F-inhibition ELISA, ELISA, micro-neutralization assays).

Results: For each of the pneumococcal serotypes common between both vaccines, observed percentages of infants with antibody concentration $\geq 0.2\mu\text{g/mL}$ were within the same range for both groups (PHiD-CV group: $\geq 91.2\%$; 7vCRM group: $\geq 86.3\%$). At least 99.6% of PHiD-CV vaccinees had antibody concentrations $\geq 0.2\mu\text{g/mL}$ against pneumococcal serotypes 1, 5 and 7F. Anti-pneumococcal geometric mean antibody concentrations were within the same range for both vaccines except for serotypes 18C and 19F for which higher immune responses were observed in the PHiD-CV group. Moreover, immune responses of all co-administered vaccines were in line with previous observations, with the exception of responses against polio virus types 1 and 3 which seemed lower in the 7vCRM group. Based on these immunogenicity results, PHiD-CV could potentially prevent 79% of IPD in Filipino infants compared to 62% for 7vCRM (abstract# 3.003), reflecting the importance of the additional serotypes (especially 1 and 5) for IPD in the Philippines.

Conclusion: PHiD-CV elicited high immune responses for each of the 10 pneumococcal vaccine serotypes in infants vaccinated according to the 6-10-14 week's schedule. No evidence of negative immunological interference between PHiD-CV and co-administered vaccines was observed.

Final Abstract Number: 3.003

Session: Synergy of Bacterial Flora in the Nasopharynx: Impact on Prevention Strategies

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: Plenary Theatre

Impact Estimate of the 10-Valent Pneumococcal Non-Typeable *Haemophilus influenzae* Protein D-Conjugate Vaccine (PHiD-CV) on Invasive Pneumococcal Disease (IPD) in Middle East and Asian Countries

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Background: The candidate PHiD-CV vaccine (GlaxoSmithKline Biologicals), contains 3 additional serotypes (1,5,7F) in comparison to the licensed 7vCRM vaccine (*Prevenar*TM/*Prevnar*TM).

Methods: Public health impact of PHiD-CV was estimated based on serotype-specific vaccine effectiveness (SSVE) values for 7vCRM¹, country-specific IPD serotype distribution and serotype-specific immunological differences between PHiD-CV and 7vCRM when co-administered at 6-10-14 weeks of age with DTPw-HBV/Hib and OPV vaccines in the Philippines (abstract# 3.002). SSVE's for PHiD-CV (each serotype in common with 7vCRM and 6A) were obtained by multiplying 7vCRM SSVE's by the ratio of the percentages of PHiD-CV- versus 7vCRM-vaccinated children reaching a predefined immunogenicity threshold one month after 3 primary doses. SSVE's for 19A (both vaccines) and for 1,5,7F (PHiD-CV) were set essentially equivalent to the % children achieving the threshold for each serotype. The overall impact of each vaccine in country-j ($IPD-IE_{overallj}$) is shown in equation 1 below.

Results: Using the 0.2µg/mL threshold (22F-ELISA) as basis of comparison and applying the IPD-IE to IPD serotype data from several countries, PHiD-CV is estimated to prevent approximately 59-85% of IPD while 7vCRM would prevent 38-75% as shown in table below. Similar results were obtained using ELISA 0.35µg/mL or OPA 1:8 as immunological thresholds for comparison. Since countries might be using different immunization schedules or DTPa-based co-administered vaccines, IPD-IEs were also computed using immunogenicity data from a European study in which PHiD-CV or 7vCRM were co-administered with DTPa-HBV-IPV + Hib-MenC at 2-4-6 months of age. Calculated IPD-IEs (PHiD-CV: 57-80%; 7vCRM: 36-74%) were within the same range as those mentioned above.

Conclusion: PHiD-CV would be predicted to prevent 59-85% of IPD in children depending on the relative importance of serotypes 1, 5, 7F in the above noted Middle East and Asian countries.

¹WhitneyCG Lancet 2006 368:1495-502.

Final abstract number: 3.004

Session: Synergy of Bacterial Flora in the Nasopharynx: Impact on Prevention Strategies (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: Plenary Theatre

Otitis Media: Why Is it so Difficult to Treat or Prevent?

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Otitis media (OM), one of the most common childhood diseases, is a polymicrobial disease encompassing a spectrum of ear conditions that can lead to complications such as mastoiditis, invasive disease and hearing loss. *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae* (NTHi) account for up to 80% of cases of bacterial acute OM (AOM) worldwide. There is a direct relationship between early nasopharyngeal colonisation by *S. pneumoniae* and NTHi and early first episodes of AOM, and failure to eradicate these pathogens (particularly NTHi) completely from the middle ear is associated with treatment failure [1]. Furthermore, over 50% of *H. influenzae* isolates from patients with recurrent and refractory OM produce b-lactamase and are intrinsically resistant to ampicillin and amoxicillin, the mainstays of treatment.

Accurate diagnosis of OM aetiology in young children is often difficult, so AOM is usually treated empirically with antibiotics without identifying the causative pathogen. Such non-targeted therapy contributes to treatment failure and increasing antibiotic resistance. Despite treatment guidelines that call for watchful waiting, AOM is the leading indication for antibiotic prescription in many developed countries [2].

Preventing the first episode of AOM is probably the optimal approach to reducing the burden of OM. The pneumococcal conjugate vaccine (PCV)-7 has had modest success against all-cause OM [3], possibly because it targets only *S. pneumoniae*. Post-PCV-7, an increase in the proportion of AOM cases attributable to NTHi has been observed [4, 5]. The Pneumococcal Otitis Efficacy Trial (POET) showed that the 11-valent pneumococcal *H. influenzae* protein D - conjugate vaccine candidate reduced 35.3% of NTHi-attributable and 57.6% of *S. pneumoniae*-attributable AOM cases, resulting in a clinically relevant 33.6% prevention of overall AOM episodes [6]. Taking into account the dynamics of nasopharyngeal colonisation by *S. pneumoniae* and NTHi, a dual pathogen vaccine like the protein D conjugate vaccine, coupled with judicious antibiotic treatment, could substantially reduce the burden of AOM.

1. Bryce, et al. Lancet, 2005; 2. Obonyo, et al. Eur J Microbiol Infect Dis, 2006; 3. Lucero, et al. Cochrane Database Syst Rev; 4. Grijalva et al. Lancet, 2007; 5. Whitney, et al. N Engl J Med, 2003

Final abstract number: 3.005

Session: Synergy of Bacterial Flora in the Nasopharynx: Impact on Prevention Strategies (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: Plenary Theatre

Preventing Pneumonia: Lessons and Future Implications

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Pneumonia is the leading killer of children worldwide [1]. *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) are the leading causes of bacterial pneumonia in young children, with *S. pneumoniae* being the most common cause. The role of other bacteria such as non-typable *H. influenzae* (NTHi) in childhood pneumonia is not clear.

Hib conjugate vaccines almost eliminated Hib disease in regions where they were introduced into the national immunisation programme, and they demonstrated protective efficacy against Hib bacteraemic pneumonia [69% (3-90%; 95% CI)] [2]. Seven- and nine-valent pneumococcal conjugate vaccines (PCVs) reduced the incidence of (and hospitalisation caused by) vaccine-serotype pneumonia in children aged less than 2 years [3]. Additionally, the PCVs reduced all-cause pneumonia in vaccinees and their contacts (herd immunity) [4]. The PCVs also reduced rates of disease caused by antibiotic-resistant *S. pneumoniae* [5].

The characteristics of Hib and pneumococcal conjugate vaccines thought to be associated with protection against pneumonia are multi-factorial. Vaccine induction of functional protective immunity is critical for adequate protection against pneumonia, as is the induction of immunological memory. For a new conjugate vaccine, a similar immunogenicity profile to existing vaccines that are effective against pneumonia may suggest similar efficacy. A vaccine class effect could therefore be envisaged providing several criteria are met, such as adequate opsonophagocytic titres and anti-pneumococcal IgG concentrations, and boostability. Under a vaccine class effect, notwithstanding the caveats pertaining to it, a new candidate PCV such as the Pneumococcal *Haemophilus influenzae* Protein D - Conjugate Vaccine (PHiD-CV) might also be expected to offer protection against pneumonia.

1. Bryce, et al. Lancet, 2005; 2. Obonyo, et al. Eur J Microbiol Infect Dis, 2006; 3. Lucero, et al. Cochrane Database Syst Rev, 2004; 4. Grijalva et al. Lancet, 2007; 5. Whitney, et al. N Engl J Med, 2003.

Final abstract number: 5.001

Session: Infectious Diarrhea and Enteric Fever (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: 304/305

Close Encounters of the ETEC-type

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Enterotoxigenic *Escherichia coli* (ETEC) is a multivalent pathogenic organism that has been sub-classified into different phenotypic groups based on the type of exoproteins it produces. These include enterotoxins and colonization factors apart from other antigens like the lipopolysaccharide (LPS), which are part of the 'O' antigen. Over 100 types of 'O' groups have been detected in ETEC strains in combination with different flagellar (H) antigens, that together make the serotype (O:H) of the bacteria. Although extensive efforts have been made to determine the prevalence of the toxins and colonization factors in ETEC strains isolated in different regions of the world, relatively little is known about the serotype of the bacteria circulating in different countries, especially those that are prevalent at this time.

Recent epidemiological studies have shown that ETEC strains from different regions differ in their phenotypic characteristics. These findings are important to determine which vaccines would be suitable for use in one region but not in another as a measure of protection against ETEC infections. ETEC isolated from two geographically different locations, Mexico and Bangladesh, have been characterized for their 'O' and 'H' antigens as well as for their enterotoxin types and colonization factor production. Overall a variety of ETEC phenotypes were found to be present in both settings. Twelve serotypes were common in both settings. A few serogroups were only present in isolates from Bangladesh (O20, O115, O126, O128, O114), while others were present only in strains isolated in Mexico (O103, O170, O22). The predominant colonization factors in both settings were CFA/I, CS5+CS6, CS6 as well as CS1+CS2/CS3. Colonization factors were produced by strains belonging to a few 'O' serogroups, CFA/I (O126 and O128), CS5+CS6 (O115 and O167), CS6 (O169), CS1+CS2/CS3 (O6). Based on these results, formulation of an effective multivalent ETEC vaccine will have to include not only the major colonization factors and LT toxin but also the LPS of important serogroups. An inactivated killed ETEC vaccine that has undergone extensive testing includes strains of serogroups O6, O25, O78 and O167. Based on the present data this vaccine would in addition need the incorporation of strains belonging to serogroups O115 and O126 to be more effective in the protection against the most common cause of bacterial diarrhea in early childhood and the second most predominant cause of diarrhea in adults in endemic countries, including tourists travelling to these areas.

Final abstract number: 5.002

Session: Infectious Diarrhea and Enteric Fever (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: 304/305

Typhoid Vaccines as Routine Public Health Tools for Developing Countries: An Idea Whose Time Has Come

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Despite the availability of two internationally licensed, newer generation typhoid vaccines that are safe and effective and despite an annual global typhoid mortality burden estimated at over 200,000 deaths, typhoid vaccines are not routinely used as public health interventions in developing countries with high typhoid burdens. Although there are multiple reasons for the failure to introduce these vaccines into public health programs for the poor, a gap in evidence to inform vaccine policy is a major factor. To address this gap in evidence, the International Vaccine Institute, with the support of the Bill and Melinda Gates Foundation, has coordinated a multi-country, multidisciplinary program of research, called the Diseases of the Most Impoverished (DOMI) Program, to inform policy about typhoid vaccine introduction in Asia. This research program, which has been undertaken in Bangladesh, China, India, Indonesia, Pakistan, and Vietnam, has demonstrated the burden of typhoid fever to be high, but geographically heterogeneous. The research has also demonstrated a high financial cost associated with typhoid fever, and a modest cost of purchasing and delivering one of the two currently available, internationally licensed typhoid vaccines (Vi polysaccharide). Demonstration projects with Vi vaccine have shown that the vaccine is feasibly delivered in mass immunization campaigns in both school and community settings, and when delivered in these campaigns the vaccine confers both direct and herd protection. As well, there is a high population demand for a vaccine with the cost and characteristics of Vi polysaccharide, and even a willingness on the part of developing country populations to pay for this vaccine, particularly for vaccination of children. In aggregate, these findings have helped to motivate a recently published, strengthened WHO recommendation for routine typhoid vaccination in settings with high typhoid disease burdens.

Final abstract number: 5.003

Session: Infectious Diarrhea and Enteric Fever (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: 304/305

The New Emerging Strain of Cholera: One Step Ahead of Genomics

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A remarkable event in recent years has been the emergence of strains of *Vibrio cholerae* O1 that possess traits of both the classical and El Tor biotypes. These strains were first encountered from sporadic cases of cholera isolated from 1992 onwards in Matlab, Bangladesh. Phenotypic and genotypic traits failed to categorize these strains into classical or El Tor biotype and were designated as the Matlab variants. The Matlab variants assumed greater significance when strains of *V. cholerae* O1 isolated from Beira, Mozambique in 2005 displayed typical traits of the El Tor biotype but carried the classical CTX prophage. A more recent analysis of *V. cholerae* O1 strains isolated in Bangladesh during the past four and a half decades revealed that from 2001 onwards all strains associated with cholera belonged to the El Tor biotype but produced classical cholera toxin (CT) which was different from the prototype El Tor biotype that produced El Tor CT. This new variant of the El Tor biotype is now dominant in several other countries. At this time, it is not certain whether the change in CT subtype in the El Tor strains will enhance their epidemic potential. Given that there are differences between the classical and El Tor biotypes, the selection of the El Tor biotype which produces classical CT would seem to indicate an evolutionary optimization of the El Tor biotype and represents a new more efficient emerging form of the El Tor biotype. Under the cholera surveillance program of the International Centre for Diarrheal Disease Research in Bangladesh, an increasing trend in the number of cholera patients as well as in the severity of the disease has been observed. Globally, also there has been a substantial increase in the incidence of cholera and in the number of outbreaks of cholera.

Final abstract number: 5.004

Session: Infectious Diarrhea and Enteric Fever (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: 304/305

Rotavirus and Rotavirus Vaccines: Are We There Yet?

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Rotavirus vaccines currently licensed in more than 90 countries hold the promise of preventing more than 600,000 diarrhea deaths and many hospitalizations and doctor visits worldwide. The positive impact of vaccination programs is just becoming evident in US and middle income countries of Latin America and as yet, no major danger signs such as intussusception have clouded the horizon. At the same time, the efficacy of these new rotavirus vaccines has not been demonstrated in poor developing countries and some ominous signs are appearing that are cause for concern. The immune response to the GSK vaccine in infants in S. Africa and Bangladesh has been substantially less than that measured in studies in Latin America, the US and Finland and this difference may be reflected in lower efficacy. Trials now ongoing should determine the efficacy in two populations in Sub-Saharan Africa. The reasons for this impaired immune response are numerous - high titers of maternal antibody, breast feeding practices, and interfering gut flora, micronutrient deficiency- to name a few and ways to address these issues will be key to either improving these vaccines or to rejecting them should the results of ongoing field trials prove disappointing. To date, no serious discussion has been given to the level of efficacy that the international community would deem acceptable for rotavirus vaccines to receive a global recommendation from WHO. Research is needed today to identify the cause of the low immune responses and to identify strategies to improve this problem. Insurance policies to consider new vaccines should be considered as well so that alternative vaccine candidates are in the wings should they be needed.

Final abstract number: 6.001

Session: Beyond Cardiovascular Disease: Statins and Cholesterol in Infectious Diseases
(invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: 302/303

Statins and Sepsis: Multiple Modifications at Multiple Levels

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Mortality from sepsis is a leading cause of death worldwide. Clinical observational studies of the effect of statins in reducing the morbidity and mortality of sepsis suggest a prevention, and possible treatment, effect. Effects at the transcriptional level lead to the reduced expression of various inflammatory mediators by leukocytes and endothelial cells. Heme oxygenase induction has anti-oxidant, anti-inflammatory, and cytoprotective effects. Direct blockade alters leukocyte-endothelial cell interaction, while reduced expression of MHC-II affects T-cell function. That statins do not target individual inflammatory mediators, but possibly reduce the overall magnitude of the systemic response, may prove an important distinguishing feature modulating the host response to septic insults.

Final abstract number: 6.002

Session: Beyond Cardiovascular Disease: Statins and Cholesterol in Infectious Diseases
(invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: 302/303

Statins in Animal Models of Infection

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Statins, are effective lipid lowering agents used extensively in medical practice. Recent statin studies have extended statin therapy to the acute manifestations of cardiovascular disease and have suggested cholesterol independent therapeutic benefits, termed "pleiotropic" effects, which have added a wide scope of potential targets for statin therapy. Since the approval for clinical use in humans of lovastatin as the first statin several statins have become commercially available including pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin (withdrawn in 2001), pitavastatin and rosuvastatin. While all these statins share HMG-CoA reductase inhibition as common mechanism of action, they differ in absorption, affinity, binding, solubility and excretion. Apart from causing variations in efficacy of cholesterol lowering between the agents, differences in these pharmacologic properties might also be relevant with respect to so called "pleiotropic" effects of statins. These "pleiotropic" effects include anti-inflammatory and antioxidative properties, improvement of endothelial function and increased nitric oxide bioavailability and thus might contribute to the benefit observed with statin therapy. Notably, these important immunomodulatory effects of statins have been demonstrated to be independent of lipid lowering and appear to be mediated via interference with the synthesis of mevalonate metabolites (nonsteroidal isoprenoid products). In addition, mechanisms for anti-inflammatory actions of statins have been revealed that are not related to the isoprenoid metabolism. For instance, it has been identified that some statins act as direct antagonists of LFA-1 due to their capacity to bind to the regulatory site in the LFA-1 i-domain. Several animal models of infection ranging from bacterial, and fungal to viral causative agents have been studied toward potential beneficial application of statins. The present talk will give an overview of animal models of infection with respect to effects of statin treatment.

Final abstract number: 6.003

Session: Beyond Cardiovascular Disease: Statins and Cholesterol in Infectious Diseases
(invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: 302/303

Observational Studies of Statins in Bacteremia

P. Kruger

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Statins have become the most widely used drugs for lowering cholesterol with at least 15% of patients requiring admission to hospital on established statin therapy, and this number is growing each year. However, statins have been postulated to have beneficial effects independent of their lipid lowering including anti-inflammatory and immunomodulatory roles. Evidence is emerging from observational studies and basic science research that HMG Co A Reductase inhibitors (statins) might be associated with a reduced mortality in sepsis.

A number of observational studies have suggested that patients on statins for heart disease are less likely to develop infections and that their infections are less likely to be severe or result in death. Not all studies support a benefit associated with statin therapy for patients with sepsis. Other studies have suggested that stopping statins in patients that present with infections (as suggested by current guidelines), may worsen outcomes.

The desire to incorporate the ever expanding potential of these agents into routine clinical practice for patients with sepsis must be tempered by the potential for adverse effects. There is a significant body of evidence that the side effects of statins may be more frequent and serious in the critically ill. A variety of less well known toxicities are being reported as these agents gain more widespread use.

This is a rapidly growing field of fascinating experimental biology that suggests an urgent need for the investigation of the pharmacology and a reappraisal of the therapeutic indications of these drugs in patients with sepsis. This may provide new insights to the role of lipids and the endothelium in the response to infection. The potential for statins as an adjuvant therapy in sepsis is a simple, inexpensive intervention that warrants further prospective investigation.

Final abstract number: 6.004

Session: Beyond Cardiovascular Disease: Statins and Cholesterol in Infectious Diseases (invited)

Date/time: Friday, 20 June, 2008, 10:15-12:15 hrs

Room: 302/303

Parasites as host cholesterol consumers: The special case of *Toxoplasma gondii*

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Background: All protozoan parasites pathogenic for humans are cholesterol auxotrophs and must acquire cholesterol from the host. Defining the acquisition process provides insights into pathogenesis and avenues for therapeutic intervention.

Results: The obligate intracellular protozoan parasite *Toxoplasma gondii* actively invades all nucleated mammalian cells and resides within a parasitophorous vacuole (PV), surrounded by a specialized membrane (PVM). From that location, parasites acquire host cell cholesterol endocytosed by the host cell LDL receptor pathway. The parasite actively recruits host microtubules, resulting in selective attraction of host endolysosomes to the PV. Microtubule-based invaginations of the PVM serve as conduits for delivery of host endolysosomes within the PV, where they are sequestered by a tubular coat. Blocking cholesterol exit from the endolysosomes inhibits parasite growth. Cholesterol transits the parasite plasma membrane in a protein-dependent fashion, then accumulates in the parasite interior, in a process augmented by the parasite Rab5. Neither statins nor disruption of the host cell endoplasmic reticulum or Golgi functions impair cholesterol delivery to *Toxoplasma*. With excess host fatty acids and LDL, cholesterol is rapidly esterified by a parasite acyl-cholesterol acyltransferase (ACAT), and accumulates in parasite lipid bodies. This process can be inhibited by selected ACAT inhibitors, that induce parasite plasma membrane destabilization and rupture. By contrast, malaria parasites residing in a PV within hepatocytes acquire needed cholesterol from both host plasma LDL and the host endogenous biosynthetic pathway. Pharmacological interference with the host mevalonate pathway reduces *Plasmodium* development in hepatocytes.

Conclusions: In combination, these results show how a series of unique parasite adaptations selectively drive parasite acquisition of cholesterol from the host cell. Depending upon the parasite and host cell, manipulations which impair cholesterol transport to the PV, cholesterol storage within the parasite, or host cell cholesterol synthesis, block parasite growth.

Final abstract number: 8.001

Session: Models of Tools for Optimizing Public Health Preparedness: The Case of Pandemic Influenza (invited)

Date/time: Friday, 20 June, 2008, 14:30-15:15 hrs

Room: Conference Hall 1-3

Planning for Pandemics: Epidemiological Analysis in the Formulation of Public Health Policy

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Many new quantitative epidemiological tools have been developed in recent years to aid in the formulation of public health policy and to delineate optimal control interventions for epidemics of directly transmitted respiratory tract infections such as influenza A. The presentation will describe the range of methods that can be applied and their strengths and weaknesses for different situations. Specific applications will focus on SARS and influenza A. The current situation with H5N1 will be examined and various control interventions used alone or in combination will be analysed using simulation approaches. Novel methods to meld economic considerations of cost and benefit with those of transmission dynamics will be introduced and used to assess current country based pandemic plans. The paper will end with a discussion of the adequacy of currently published country wide and international plans for pandemic control with a focus on the presence or absence of detail in these plans and the importance of speed of implementation and logistics.

Final abstract number: 9.002

Session: The Challenge of Multiple- Resistant Gram-Negative Bacteria (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

Epidemiology of Multiple-Resistant Gram-Negative Bacteria in Europe and North America

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Background: Recent reports of multidrug resistant (MDR) gram-negative rods (GNR) are concerning; however, it is not clear how extensive this problem is nationally. The National Healthcare Safety Network (NHSN) collects information on select hospital-associated infections (HAI) from about 600 hospitals throughout the U.S. and is a system that may be used to evaluate this problem.

Objectives: To describe the prevalence of MDR among *K. pneumoniae*, *P. aeruginosa* or *A. baumannii* HAIs reported to NHSN.

Methods: HAIs due to the aforementioned pathogens reported to the NHSN device or procedure modules from January 1, 2006 to September 15, 2007 were evaluated. Isolates were included if they had susceptibility results for at least 1 agent in each of 4 classes of antimicrobials: aminoglycosides, quinolones, beta-lactams (penicillins and cephalosporins), and carbapenems. Isolates were classified as MDR if reported as resistant or intermediate to all drugs tested in all 4 classes. Other potentially important resistance phenotypes were also evaluated. Pooled mean (%) MDR were determined by pathogen and HAI type. To better characterize the national prevalence, results were stratified to control for facilities that reported large numbers of MDR-GNR (outlier facilities).

Results: Overall, 313 hospitals in 42 states reported 4,790 hospital-associated infections with selected GNR: 2,432 *P. aeruginosa* (bloodstream infection [BSI] 327, ventilator associated pneumonia [VAP] 889, urinary tract infection [UTI] 866, surgical site infection [SSI] 350); 1,740 *K. pneumoniae* (BSI 490, VAP 417, UTI 650, SSI 183); and 791 *A. baumannii* (BSI 221, VAP 439, UTI 92, SSI 39). Among *P. aeruginosa*, 3% of isolates were MDR and 6% were non-susceptible (NS) to both quinolones and aminoglycosides, agents often added to beta-lactams to treat *Pseudomonas*. Among *K. pneumoniae*, 8% of isolates were MDR and 10% were NS to carbapenems. Among *A. baumannii*, 26% were MDR. MDR isolates were reported from 68 (30%) facilities in 21 states and were more commonly reported from larger hospitals (>500 beds, $p < 0.001$). The percent isolates that were MDR varied slightly by type of HAI (table). Pooled mean (%) MDR varied when states with outlier facilities were excluded (table).

Conclusions: As defined, MDR among GNR is not rare in US hospitals reporting data to NHSN. MDR-GNR were not confined to one geographic region and are more common, but not limited to, larger hospitals. The paucity of novel antimicrobial agents in development to treat these organism places increasing emphasis on infection control efforts.

Final abstract number: 9.003

Session: The Challenge of Multiple- Resistant Gram-Negative Bacteria (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

Burden and Future Gram-Negative Resistance in Asia/Australia

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Resistance of Gram negative bacilli to commonly used antibiotics is commonplace in the Asia-Pacific region. In general, rates of resistance are highest in India and some parts of China and lowest in Australia and New Zealand. Extended-spectrum beta-lactamase (ESBL) producing *Klebsiella pneumoniae* and *Enterobacter cloacae* are significant nosocomial pathogens in the region. Rates of ESBL production in some species is as high as 80% in some institutions. Community-onset ESBL producing *Escherichia coli* is becoming evident in certain geographic regions such as Thailand, India and some parts of Australia. CTX-M-15 has been described in this scenario in India. There are reports of KPC-producing organisms in China, but thus far this resistance mechanism has not been described elsewhere in Asia/Pacific. Metallo-beta-lactamase producing *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacteriaceae* are well described in the Asia-Pacific region. Carbapenem resistant *A. baumannii* is a particularly problematic pathogen in some ICUs. Significant issues with regards to the high prevalence of antibiotic resistant Gram negative bacteria in the region include over the counter availability of antibiotics in some countries, agricultural use of antibiotics and suboptimal infection control. Attention to these issues is essential to forestall the onset and spread of polymyxin resistance in the region.

Final abstract number: 9.004

Session: The Challenge of Multiple- Resistant Gram-Negative Bacteria (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

How to Prevent the Spread of Multiple-Resistant Gram-Negative Bacteria in the Hospital Setting

S. Harbarth

Geneva University Hospitals, Geneva, Switzerland

Infections caused by multi-resistant Gram-negative bacteria are thought to cause increased morbidity, longer length of hospital stay, and higher treatment costs when compared to infections caused by susceptible strains. Successful control of healthcare-associated, multi-resistant Gram-negative bacteria is relying on several complementary control strategies. Clearly, there is no level of antibiotic resistance where control measures are not warranted any more. First, early detection of resistance carriage may allow rapid contact isolation of identified carriers and improve the adequacy of antibiotic prophylaxis and treatment, especially in critically ill patients. Several recent outbreak reports have shown the importance of surveillance and screening cultures in order to prevent transmission and infection by multi-resistant Gram-negative bacteria in the critical care setting. Although the most efficient screening strategy depends on the local situation and type of resistance and is therefore still a matter of debate, most affected acute care hospitals should install a screening policy for patient groups at high risk of carriage of pan-resistant *Acinetobacter* spp or carbapenem-resistant *Klebsiella* spp (e.g. roommates of newly identified carriers) and apply specific preventive measures (contact isolation) applied to identified carriers, especially in the critical care setting. Second, eradicating carriage of multi-resistant bacteria may reduce the rates of infection. However, no controlled studies are available indicating that this approach may work. Third, strict compliance with standard precautions and hand hygiene could prevent most cases of cross-transmission, even without the need for recognition of individual carriers of resistant microorganisms. Unfortunately, many studies have shown that compliance of healthcare workers with hand hygiene recommendations remains low. Implementing alcohol-based hand rinses can improve compliance and decrease cross-infection. Finally, antibiotic selection pressure contributes to the increase in prevalence of multi-resistant Gram-negative bacteria. Data from several recently published studies suggest that restriction of certain classes of antibiotics may decrease rates of multi-resistant Gram-negative bacteria in the hospital setting. Other well-designed investigations are needed to confirm that reduction in antimicrobial overuse has a favorable effect on infection rates caused by multi-resistant Gram-negative bacteria.

Final abstract number: 10.001

Session: Overcoming the Challenges of Pertussis Control (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Plenary Theatre

Burden of Pertussis Worldwide: Strategies to Reinforce Pertussis Control in Children, Adolescents, and Adults

K. Forsyth

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Pertussis disease is a significant cause of morbidity and mortality amongst the unimmunised or insufficiently immunised. Data on pertussis disease trends will be presented. As for solutions, in spite of immunisation campaigns targeted at parents of infants and children, there are still major problems with. Strategies to reduce the burden of pertussis disease include; universal adult immunisation, selective immunisation of mothers and close family contacts of newborns, selective immunisation of health care workers, selective immunisation of child care workers, universal immunisation of adolescents, pre-school boosters at 4-6 years of. No single strategy is likely to be appropriate for all. Data on pertussis disease and discussion around these public health policy issues for the prevention of pertussis will be discussed.

Final abstract number: 10.002

Session: Overcoming the Challenges of Pertussis Control (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Plenary Theatre

Pertussis Control in Infants and Children

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In the prevaccine era, pertussis was one of the most common childhood bacterial infections with more than half of children becoming infected before school age. The disease was one of the leading causes of infant death in the 19th century.

The introduction of whole-cell pertussis vaccine in the 1940s and its subsequent widespread use globally has resulted in a reduction in the incidence, morbidity and mortality of this disease. The whole-cell pertussis vaccine was nevertheless associated with frequent local and systemic adverse reactions, occasionally some that were more severe such as febrile seizures or hypotonic-hyporesponsive episodes. The shift, in the 1990s, from whole-cell pertussis vaccine to less reactogenic acellular pertussis vaccine was associated with significantly reduced rates of vaccine-associated adverse events. In recent years, acellular pertussis vaccine has been incorporated into the immunization schedules of many developed countries, gradually replacing whole-cell pertussis vaccine. Dosing schedules vary between countries. As it has become apparent that the epidemiology of pertussis is gradually shifting to the adolescent and adult age groups, many countries are augmenting their program of immunization by having introduced, or are planning to introduce, an acellular pertussis vaccine booster dose for use in children 6 years of age or in the adolescent age group.

The use of combination vaccines with inclusion of acellular pertussis vaccine in many countries has been proven to be efficacious and prevents children from undergoing an excessive number of injections. The individual components included in these combination vaccines can be adjusted according to differences in the burden of disease in different countries.

Final abstract number: 10.003

Session: Overcoming the Challenges of Pertussis Control (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Plenary Theatre

The Role of Pertussis Booster Vaccinations in Adolescents and Adults

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In most developed countries, long-standing vaccination programs for infants and young children have led to substantial decreases in pertussis disease since their introduction in the 1940s. More recently, however, there has been a resurgence of pertussis case reports, most notably among adolescents and adults. Immunity from childhood pertussis vaccinations wanes after several years, but natural boosting through repeated subclinical infection is now uncommon; most adolescents and adults are again susceptible to pertussis. Manifestations of pertussis in these age groups are highly variable, ranging from mild symptoms unlikely to prompt medical care through typical whooping cough. Complications are common and include sleep deprivation, school and work disruptions, rib fractures, and pneumonia.

Adolescents and adults not only experience substantial morbidity and complications from pertussis, they play an important role in transmission of *Bordetella pertussis* to children. Multiple studies have documented that parents and other family members are the main source of pertussis infection in infants. Of particular concern are very young infants, who are at greatest risk for hospitalization and mortality from pertussis, and who are either incompletely vaccinated or unvaccinated.

To address these concerns, adolescent/adult-formulation tetanus-diphtheria-acellular pertussis (Tdap) vaccines, sometimes combined with injectable polio vaccine, have been developed. These Tdap vaccines have been shown in clinical trials to be safe and at least as immunogenic against pertussis as their analogous pediatric vaccines. In Canada and the US, Tdap vaccination is recommended for all adolescents and adults < 64 years of age. Emphasis is placed on vaccinating young adolescents and on vaccinating adults (eg, new parents, child-care workers, and certain healthcare-personnel) who have close contact with infants. Canadian experience suggests that Tdap vaccine usage has contributed to further decreases in pertussis. Full control of this disease, however, may require decennial boosting with Tdap vaccine, which is currently under study.

Final abstract number: 11.001

Session: New Perspectives on Vaccine-preventable Diseases in Adults: Pneumococcal Disease and Herpes Zoster (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Opening Remarks - Adult Immunisation: Some Thoughts

J. Hanna

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Adult immunisation can be categorised in several ways:- immunisation for travel - immunisation for certain occupations (eg. health-care and child-care workers)- immunisation for those with certain medical conditions (eg. asplenia), - immunisation for the elderly.

Immunisation for the elderly, in particular, is gaining greater recognition and greater credibility. Ageing populations, the increasing prevalence of certain medical conditions in the aged, and a desire to keep the aged in optimal health, all have contributed to this recognition of the need for vaccines for, and for the delivery of these vaccines to, the aged.

However, this greater recognition of the need has not yet been matched by greater uptake of vaccines by the elderly, even in affluent industrialised countries. For example, uptake of the annual influenza vaccine in those aged ≥ 65 years in the United States increased from 33% to 66% in the 1990s, but has not increased since. Other countries do not even have mechanisms in place to determine the coverage of vaccines in the elderly; in Australia, for example, although influenza and pneumococcal polysaccharide vaccines are provided free to those aged ≥ 65 years, there is not yet a mechanism to determine uptake of these vaccines.

Perhaps the main reasons for this disconnection between intent and outcome are that "adult immunisation is not yet an essential element within the culture of adult medicine nor is it a health care priority in the minds of the public". This suggests that increasing demand for adult immunisation by improving professional and public awareness should be given greater priority; indeed this need for greater awareness has been given priority in a recent policy statement on adult immunisation from the Infectious Diseases Society of America.

Final abstract number: 11.003

Session: New Perspectives on Vaccine-preventable Diseases in Adults: Pneumococcal Disease and Herpes Zoster (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

A Vaccine for the Prevention of Herpes Zoster and Its Complications

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Varicella (chickenpox) is associated with a viremia that results in a life-long association of the varicella-zoster virus (VZV) with neurons in sensory ganglia. VZV remains in a clinically inapparent (latent) form in these neurons because of the presence of VZV-specific immune responses that appear at the time of the childhood varicella infection. However, when these responses decline, as occurs with immune suppression, the latent VZV reactivates and causes herpes zoster (HZ). These same protective responses also decline naturally as part of the aging process. This explains why HZ occurs in approximately one-quarter of all people in their lifetime; 20 % of cases occur in those who are 50-59 years old and 60% occur in older people (incidence is 1/100 persons per year for those ≥ 60 years). Not only does the incidence of HZ increase with aging, but the duration and severity of this painful disease increases with aging, as does its main complication - prolonged pain (post-herpetic neuralgia; PHN). Since HZ is the consequence of declining VZV-specific immunity, it was suggested that boosting this immunity in older people would prevent HZ and/or lessen its severity. A double-blinded, placebo-controlled, trial of a live, attenuated, HZ vaccine has proven this hypothesis to be correct. The HZ vaccine reduced the frequency of HZ (by 50%) and it reduced the pain and suffering (including PHN) by ~65%, and as a consequence, is recommended in the United States for routine use in people ≥ 60 years of age. The details of the clinical trial and potential issues raised by its use will be discussed.

Final abstract number: 11.004

Session: New Perspectives on Vaccine-preventable Diseases in Adults: Pneumococcal Disease and Herpes Zoster (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Herpes Zoster and Post Herpetic Neuralgia (PHN) - The Taiwan Perspective

C.C. Yang

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The objective of this study is to estimate the incidence of HZ among the Taiwanese population, and investigate the disease burden of HZ by analyzing the utilization of health care resources. Data from 2001 to 2003 were collected from the National Health Insurance Research Database (NHIRD), containing health insurance enrollments and claims data from over 97% of the Taiwanese population. Incident HZ cases were identified through HZ diagnosis codes on health care claims. Overall incidence rates were age-and sex-adjusted. The cost of outpatient visits and hospitalizations were obtained. The prescription patterns of antiviral and neuropathic pain medications were examined. The data will be presented in the meeting.

Final abstract number: 11.005

Session: New Perspectives on Vaccine-preventable Diseases in Adults: Pneumococcal Disease and Herpes Zoster (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Herpes Zoster (HZ) and Post-herpetic Neuralgia (PHN): Burden of Illness, Healthcare Utilization, and Costs; the Thai Perspective

P. Pitisuttihum

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Background: Herpes Zoster is characterized by vesicular cutaneous eruption with dermatomal distribution and is mostly associated with debilitating pain and, later, post-herpetic neuralgia, especially among patients aged more than 50 years, despite early treatment with antiviral drugs. This study aimed to measure the burden of disease, assess the impact on quality of life, and determine healthcare resource utilization and costs associated with HZ and PHN in Thailand.

Methods: This was a prospective cohort study of patients presenting with Zoster rash in 7 hospitals in Thailand. The burden of illness and quality of life due to zoster-associated pain were measured using the Zoster Brief Pain Inventory, the Initial Zoster Impact Questionnaire, and the Euro-QoL. Healthcare utilization, costs, and work-time and productivity lost due to both HZ and PHN, were measured by simple questionnaire describing visits to physicians or clinics, hospitalizations, use of other health-related services, prescription medications, over-the-counter medications, as well as diagnostic tests and procedures performed for the current episode. Healthcare costs were estimated from healthcare utilization data. Indirect costs were measured by simple descriptive questionnaire, to determine time off work taken by patients or caretakers, and lost income.

The above parameters were followed at each visit, at days 0, 7, and months 1, 3, and 6.

Results: 180 patients with HZ were enrolled; 138 were elderly (aged >50 years), 34 were HIV-infected, and 8 were cancer patients. 160 and 104 patients completed month 3 and month 6, follow up respectively (April 10, 08). About 54% presented with rashes, primarily affected the thoracic dermatome; 93.8% reported pain. The detailed results for burden of illness, quality of life, and healthcare costs will be presented.

Final abstract number: 12.001

Session: New Directions in the Treatment of Fungal Infections (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: 304/305

The Changing Epidemiology of Fungal Infection: New Pathogens and Problems

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Invasive fungal infection is increasingly recognized as one of the major causes of mortality and morbidity in healthcare. This is due to the increase in susceptible hosts resulting from various factors such as intense antineoplastic and immunosuppressive agents, breakdown of anatomical barriers, prolonged use of the intravascular catheter, parenteral nutrition, aggressive surgical procedures, broad-spectrum antibacterial agents, and HIV infection. *Candida* spp. and *Aspergillus* spp. are the two most frequently pathogens isolated during the past 2 decades. Although both remain commonest pathogens, the changes in species isolated are observed. *Candida* non-albicans is increasing namely *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, and apart from *A. fumigatus*, *A. flavus*, *A. niger*, and *A. terreus* are increasingly isolated. In the era of intensive chemotherapy and radiotherapy followed by the hematopoietic stem cell transplantation, Zygomycetes, *Fusarium* spp. *Scedosporium* spp. emerge as very difficult-to-treat pathogens. This may be explained by the pattern of the use of antifungal agents: fluconazole, itraconazole, and amphotericin B. The selective pressure of these agents in the presence of prolonged neutropenia and/or severe immunosuppression predispose patients with these amphotericinB-resistant fungal infection. In AIDS patients, *Cryptococcus neoformans* is the most common systemic fungal pathogen worldwide. In addition, endemic fungi such as *Histoplasma capsulatum* in USA and *Penicillium marneffeii* in Thailand are common AIDS-related mycoses. Another unique mycosis reported from Thailand is pythiosis, the infection caused by *Pythium insidiosum*. The most recognized form with high morbidity and mortality is arteritis, commonly presented with limb gangrene, aneurysm and ultimately aortic rupture. Almost all patients have hemoglobinopathy-thalassemic syndrome and expose to this organisms in the environment such as rice field. Treatment of this entity is still problematic since it is not a true fungus and the response to the available antifungal agents is unsatisfactory. Considering its habitat, it is likely that pythiosis is underrecognized in the Southeast Asia region, one should be aware of this entity.

Final abstract number: 12.002

Session: New Directions in the Treatment of Fungal Infections (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: 304/305

Pharmacodynamics of Antifungal Drugs: A Strategy to Optimize Efficacy

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, Madison, WI, USA

Pharmacodynamic studies examine the relationship between drug pharmacokinetics and outcome. These investigations help define the optimal drug exposure associated with treatment efficacy. The analyses of data from experimental models with different antifungal drug classes have identified distinct pharmacodynamic characteristics. Results from these models have been useful for defining the relationship between antifungal exposures and efficacy. More recently clinical data has become available allowing similar investigation. These results of these studies have been similar to those from experimental models and have cemented the clinical significance of these pharmacodynamic concepts. The analyses have been shown to be helpful for the design of antifungal dosing intervals, choice of optimal dose levels, therapeutic drug monitoring, and the development of susceptibility breakpoints. Most of these preclinical and clinical studies have targeted therapeutic efficacy against *Candida* species. More recent studies have also considered other fungal pathogens and have begun to investigate the role of antifungal pharmacodynamics and drug resistance development. Although there remain many unanswered questions regarding antifungal pharmacodynamics, available data suggest usefulness in the application of pharmacodynamics to help guide antifungal therapy.

Final abstract number: 12.003

Session: New Directions in the Treatment of Fungal Infections (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: 304/305

New Generation Triazoles: What Do They Offer and When Do We Need Them?

T.C. Sorrell

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Voriconazole and posaconazole are the latest triazole drugs to be marketed. Voriconazole was developed from fluconazole by substituting a fluoropyrimidine ring for one of the azole groups to enhance the spectrum (to include *Candida krusei*, fluconazole-resistant *C. glabrata*, *Aspergillus* spp, some *Fusarium* strains, *Scedosporium apiospermum* and dimorphic fungi such as *Histoplasma capsulatum*) and adding the α -methyl group to provide fungicidal activity against *Aspergillus* spp. in particular. Posaconazole is structurally derived from itraconazole, with fluorine replacing chlorine substituents in the phenyl ring and hydroxylation of the triazolone side chain. These modifications enhance the potency and spectrum of antifungal activity to include the additional species covered by voriconazole with the exception of *Fusarium* and in addition, the zygomycetes.

Randomised controlled clinical trials (RCTs) have identified that voriconazole is the treatment of choice for invasive aspergillosis in the immunosuppressed. Efficacy has been demonstrated in candidiasis (including against small numbers of fluconazole-resistant *Candida* infections), in fusariosis, cryptococcosis and infections where cheaper agents such as fluconazole would be preferred. The major drawbacks to replacing fluconazole with voriconazole are its cost, adverse effects including a small incidence of photosensitivity, significant drug interactions, and pharmacokinetic issues, which may be resolved by therapeutic drug monitoring in some settings. Posaconazole has been subject to RCTs of its use in prophylaxis against fungal infections in recipients of haematopoietic stem cell transplants where, despite some design flaws, it has performed better than the comparator regimen, and in HIV-associated oro-pharyngeal candidiasis. It has been used as salvage therapy in other settings. The main drawbacks to widespread use of posaconazole include cost, the lack of an intravenous formulation, reduced bioavailability in the absence of food and lack of RCTs of its therapeutic use. Confirmation of improved clinical outcomes from the use of either agent in combination therapy is yet to be obtained.

Final abstract number: 12.004

Session: New Directions in the Treatment of Fungal Infections (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: 304/305

Understanding the Similarities and Differences of Existing and Emerging Echinocandins

M.A. Slavin

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The echinocandins, comprising caspofungin, micafungin and anidulafungin, inhibit beta-(1,3)-glucan. Glucan is found in fungal cell walls but not mammalian cells. As large highly protein bound molecules, none are orally bioavailable or achieve levels in the CSF. The spectrum is consistent across all three agents with fungicidal activity against *Candida*, and fungistatic activity against *Aspergillus*. The echinocandins are not active against *Cryptococcus*, *Scedosporium prolificans* or *Zygomycetes*. All are fungicidal against *Candida species* although MIC₉₀s vary slightly between agents with the lowest MIC₉₀s seen with anidulafungin, then micafungin, and caspofungin. However, it is not clear if these differences are clinically relevant. All have higher MIC₉₀s for *C. parapsilosis*, *C. guilliermondii* and *C. lusitaniae* compared to other *Candida spp.*. Although *C. parapsilosis* remains susceptible despite a higher MIC₉₀, resistance has emerged on treatment. All may rarely cause histamine release with pruritis, rash and swelling. The differences between the agents are shown in the table below:

Final Abstract Number: 13.001

Session: Emergence of EV71 in the Asia Pacific in the Last Decade

Date/time: 6/20/2008, 15:45-17:45 hrs

Room: 302/303

Epidemiology of EV71 Outbreaks in the Region in the Past Decade

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HFMD: Current Knowledge and Challenges for Malaysia and the Asia Pacific Region

Background: Hand, foot and mouth disease (HFMD), especially that caused by EV71 is an important re-emerging disease in the Asia Pacific region, with the potential to cause massive outbreaks that can last for many months, and with relatively high complications rates, and deaths.

Methods: A review of the first-hand experiences gained during the control of the four major HFMD outbreaks in Sarawak was carried out. Relevant epidemiologic information from outbreaks in a number of countries in the Asia Pacific region was also abstracted.

Results: From Sarawak, we learned that since 1997, EV71 outbreaks have occurred every 3 years. The shapes of the epidemiological curves are influenced by social factors such as the media and people's movements during big public holidays. EV71 is not the only virus associated with HFMD, but only EV71 causes very large outbreaks and resulting complications. The genogroups of the EV71 isolated during each major outbreak are genetically distinct from each other. The transmission of EV71 in a susceptible cohort is extremely rapid with only 4-6 weeks between first identification of an EV71 case in our sentinel clinics to peaking.

From Singapore we know that HEV71 transmission occurs mainly in places where preschool children congregate, and public health measures to control the spread of this virus should focus on these places. The 1998 Taiwan outbreak showed that HFMD spreads easily through contact leading to mostly symptomatic cases in children and mostly asymptomatic cases in adults. Proper surveillance systems works, showing trends and the current circulating viruses, and predicting coming outbreaks.

Conclusion: We need to identify the reservoirs of EV71 in the inter-epidemic periods, and develop simple rapid diagnostic tests that can be used in the districts to differentiate EV71 from CA16.

Final abstract number: 13.002

Session: Emergence of EV71 in the Asia Pacific in the Last Decade (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: 302/303

Clinical Studies on EV71 Neurological Disease

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Human enterovirus 71 (HEV71, family Picornaviridae, genus Enterovirus) was first described in 1974 after it was isolated from children with neurological infection in California, USA. Following the report, the virus has been linked to a broad spectrum of neurological manifestations including encephalitis, aseptic meningitis and poliomyelitis-like paralysis. The neurotrophic virus is also associated with hand, foot and mouth disease (HFMD), a common febrile rash illness caused by enterovirus, particularly Coxsackievirus A16. Over the last 10 years frequent explosive outbreaks of HEV71 neurological disease have occurred in many parts of Asia with dozens of fatalities. Brief duration of illness, subtle clinical presentation, very late appearance of ominous signs and unexpected fulminant pulmonary oedema and cardiac dysfunction in previously healthy children with HFMD are the hallmarks of fatal cases of neurological HEV71 infection. As a result, HFMD, which is normally considered an innocuous illness, has become a diagnostic and management challenge to many clinicians in Asia. Clinicians are faced with several important clinical questions when they are presented with a child with HFMD:

1. How to distinguish a child with HEV71 infection from CVA16?
2. How to recognize children at risk of neurological infection and fatal pulmonary oedema?
3. What therapeutic measures are best for a critically ill child with HEV71 infection?

The results of a number of clinical studies that attempted to resolve these clinical questions will be reviewed and presented in this talk. We shall also present new data from a prospective study in Sarawak spanning 3 distinct outbreaks of HEV71.

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Session: Emergence of EV71 in the Asia Pacific in the Last Decade (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: 302/303

Mouse and Non-human Primate Models for EV71 Disease

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During the final stage of polio eradication in the Western Pacific Region (WPR) in the late 1990s, there have been large outbreaks of hand, foot and mouth disease (HFMD) due to enterovirus 71 (EV71) associated with severe neurological diseases. However, pathogenesis of EV71 infection is still poorly understood, in part, due to limited animal models to study the neurovirulence of EV71. Immediately after the identification of EV71 as one of most neurotropic enteroviruses, a non-human primate model for EV71 disease had been established in the 1970s. In response to recent EV71-associated HFMD outbreaks in the WPR, we have extended this non-human primate model to study the molecular basis of EV71 neurovirulence by using different genotypes of field EV71 isolates and genetically modified EV71 mutants derived from infectious molecular clones of EV71. By using the non-human primate model, we found that two major recent lineages of EV71 in the WPR, genogroups B and C, are considered to be neurovirulent, and we have analyzed the attenuation determinants and immunogenicity of EV71 for further vaccine development. The non-human primate model may provide more information on EV71 pathogenesis than previous mouse infection models. However, mouse models, using young mice and/or mouse-adapted EV71 variants, have been widely used to study the in vivo phenotypes of EV71 due to the limited availability of non-human primates. Thus, we have recently developed a novel mouse infection model using NOD/SCID mice and a mouse adapted EV71 variant, and confirmed the presence of the same attenuation determinants of EV71 both in non-human primate and mouse models. Although primate and mouse models would be still important to study the pathogenesis of EV71, identification of the cellular receptor and development of transgenic mice susceptible to EV71 may provide new insights into the molecular basis of EV71 infection in the near future.

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Session: Emergence of EV71 in the Asia Pacific in the Last Decade (invited)

Date/time: Friday, 20 June, 2008, 15:45-17:45 hrs

Room: 302/303

Update on the Molecular Epidemiology of Human Enterovirus 71 in Taiwan Since 1998

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Human enteroviruses 71 (EV71) is a major causative pathogen of hand, foot and mouth disease (HFMD). Its infections caused devastating clinical outcomes in children worldwide. Most EV71 isolates belong to either genogroups B or C, which are each further divided into subgenogroups, B1-B5 and C1-C5. In Taiwan, a large EV71 outbreak occurred in 1998, followed by two lesser outbreaks in 2000 and 2001, which claimed 34, 25, and 26 deaths, respectively. After that, Taiwan CDC established a Taiwan Virology Reference Laboratories Network (TVRLN) in 1999 to examine the specimens collected by our sentinel physicians. There were 11, 309, 455, 175, 59, 209, 330, 4, and 16 EV71 strains isolated by TVRLN each year from 1999 to 2007, respectively. Before that period, all Taiwanese isolates, most obtained in 1980 and 1986, belonged to genotype B only, whereas the ones isolated in the 1998 outbreaks turned out to be subgenogroup C2 and B4, followed by subgenogroup B4 from 1999 to 2003, and subgenogroup C4 from 2004 to 2005. In 2006-2007, the major subgenotypes of EV71 circulating in Taiwan changed to C5, and B5. Although, the annual numbers of HFMD/herpangina cases confirmed to be due to EV71 infection dropped dramatically over the last two years, it seems very likely there is a rising trend of EV71 infections from the very beginning of 2008 in Taiwan. As of March 21, as many as 36 EV71 isolates were confirmed. In conclusion, we believe that there is a need for us to monitor them very carefully to see if the said two newly emerging subgenogroups would create a serious impact on Taiwan public health system.

Final abstract number: 26.001

Session: Drug Discovery as a Public Health Intervention: The Ivermectin Story (invited)

Date/time: Saturday, 21 June, 2008, 09:00-9:45 hrs

Room: Conference Hall 1-3

Drug Discovery as a Public Health Intervention: The Ivermectin Story

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Ivermectin is the 22,23-dihydro derivative of avermectin B1, a macrolide produced by an actinomycete, *Streptomyces avermitilis*, which we discovered in 1973 in a soil sample and later renamed *S. avermectinius*.

The drug arose from a pioneering international collaboration between my group at The Kitasato Institute in Japan and the MSD Research Laboratories in the United States. The outcome of this alliance led to an important advance in animal health products, through development of an extremely safe drug with a broad spectrum of antiparasitic activity. After introduction to the market in 1981 as an anthelmintic, ivermectin soon proved to be the most effective antiparasitic drug ever developed and became a 'blockbuster' market leader within two years.

Ivermectin has also provided immeasurable benefits to human health for over 20 years, improving the lives of hundred of millions of the world poorest people in the process. Thanks to a pioneering drug donation initiative, ivermectin is being used, free of charge, in global programmes to eliminate two devastating diseases that mainly affect poor communities in developing countries. Both diseases are caused by filarial worms, onchocerciasis (river blindness) arising from infection with *Onchocerca volvulus* and lymphatic filariasis (elephantiasis), one of the most prevalent tropical diseases, resulting from infection with either *Wuchereria bancrofti* or *Brugia malayi*.

Ivermectin is so safe that tablets can be administered by non-medical individuals from affected communities following one or two days training.

Ivermectin is also now being used to treat strongyloidiasis, an intestinal parasitic disease widely distributed in South-East Asia and the southern Japanese Islands, and to treat scabies, which is estimated to infect more than 300 million people globally each year.

Genetic analysis of avermectin biosynthesis and genome mapping of *S. avermectinius*, and the potential they offer for development of more effective compounds, will also be discussed.

Final abstract number: 27.001

Session: Evidence-Based Infection Control: What is New? (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

CA-MRSA as a Hospital Pathogen

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There are two epidemics of MRSA: 1) The 30 year old hospital associated strains are increasing in prevalence and escaping to the community with discharged patients, and 2) the strains from the 10 year old community-associated epidemic (CA-MRSA) have quickly escalated in recent years and now are entering hospitals. The CA-MRSA isolates are considerably more virulent than the standard health-care associated ones, perhaps by virtue of the associated toxin- PVL- and therefore create a serious worry for the clinicians. In the last decade a number of clusters have been reported in U.S. and European Hospitals of infections with CA-MRSA. The antibiograms are different currently among the strains in the two epidemics, and many challenges await to be addressed:

At what proportion of all *S. aureus* nosocomial infections will perioperative prophylaxis change, will empirical therapy for sepsis or ventilator-associated pneumonia in the ICU change? How will we identify carriers? Will the outcomes be more serious? What options to prevent and treat these CA-MRSA nosocomial infections exist, and what are the adverse effects of the antibiotic options? These are issues that will be addressed in the presentation.

Final abstract number: 27.002

Session: Evidence-Based Infection Control: What is New? (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

Preventing Catheter-Related Bloodstream Infections

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The use of non-tunneled central venous catheters is increasing among patients in all settings including intensive care units as they enhance medical care. However, catheters and their placement provide an opportunity for bacteria to enter the bloodstream causing infection, or a catheter-associated bloodstream infection (CABSI). These infections contribute significantly to patient morbidity and mortality and are costly to healthcare systems. However, they are preventable. While evidence based guidelines to prevent these infections exist, they are complicated and have been difficult to implement in the healthcare setting. The salient elements have not been systematically translated into a format so that 1) healthcare workers know what they need to do, 2) institutions know how to facilitate the behavior with supplies and 3) the outcomes are communicated to the healthcare workers. The science behind a simple "bundle of non-technologic but infection prevention and control interventions" which can be used in resource limited and rich settings includes the use of 1) hand hygiene prior to placing the line, 2) a chlorhexidine based skin preparation prior at the insertion site of the line, 3) the subclavian vein site over other sites for line placement whenever medical feasible, 4) full barrier drapping of the patient during the procedure, and 5) daily attempts to remove the line. In addition, appropriate line care and dressing use once the insertion is completed were taught. In this paper we will use the experience at an institution and in several other settings to demonstrate how to operationalize such an intervention. We will look at the impact on CABSI rates in adult and pediatric settings.

The intervention can be put in context of a behavioral modification model proposed by Rodgers et al. In this model elements of the intervention include factors that enhance knowledge and facilitate behavior and attitude change. We will review enabling factors primarily from the institution that will improve behavior and we will look at techniques to reinforce behavior.

Final abstract number: 27.003

Session: Evidence-Based Infection Control: What is New? (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

Relevant Vaccines for Health Care Workers

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Immunization among HCWs has two purposes, both which allow for better prevention. Immunization's first purpose is to protect HCWs from several infectious diseases they may be exposed to through professional activities. A second purpose is to minimize the odds of infecting the patients they are taking care of. It should be clear that both objectives are extremely important and should be a priority to any health system. Another consideration is the importance of establishing this preventive measure in low-income regions where the shortage of HCWs is aggravated due to infectious diseases (Hepatitis B and C, TB) affecting these professionals. The landscape of public health has plenty of examples of neglected situations. In developing regions the protection of HCWs has been ignored in the most flagrant circumstances. There is a lack of regulations to establish vaccination programs and the protection needed for accidental injuries.

Any health care service or system should establish an employee health program in collaboration with the infection control department that includes a vaccination schedule for HCWs. It is essential that vaccines for Hepatitis B, Influenza (yearly), Measles, Mumps, Rubella, Tetanus and Diphtheria are administered. According to regional epidemiological circumstances other vaccines may be considered, such as BCG, Yellow Fever, Varicella-zoster, Hepatitis A, Cholera and Influenza A H5 N1.

Surprisingly, HCWs are reluctant to accept vaccination programs as is shown by multiple reports for very low rates of acceptance. This is a challenge every program needs to address, and strategies to improve acceptance should be evaluated. Establishing a wide and continuous vaccination program should be a high priority project in any health care system.

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Session: Evidence-Based Infection Control: What is New? (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

Prevention of Surgical Infections

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Surgical site infections (SSIs) are the second most common cause of nosocomial infections resulting in considerable increase in morbidity and mortality. The U.S. Centers for Disease Control and Prevention (CDC) estimate that 500,000 SSIs occur annually in the United States. Patients who develop SSIs are up to 60% more likely to require intensive care, are up to 5 times more likely readmitted for complications, and twice as likely to die as patients without an SSI. In addition, SSIs increase health care costs by \$ 5-10,000 and double mortality after procedures. Dozens of risk factors have been identified that partly predict the incidence of SSIs. They can be basically classified in risk factors by the underlying diseases of the patient, risk factors of the intervention, risk factors by the surgical team and management, and environmental factors. Multiple strategies have been developed to decrease the incidence of SSIs, but many are given by the patient such as age and underlying diseases. The CDC has developed key compounds that increase the risk of SSIs: Surgery exceeding the T-time, level of contamination of surgery (contaminated or dirty) and ASA score >3. In addition, Wenzel RP and colleagues already demonstrated in the seventies that surgical volume is associated with SSIs. Established risk factors are ongoing infections other than the surgical site, insufficient heating of the patient during surgery, failure to give appropriate oxygen supply and failure to give appropriate, timely antimicrobial prophylaxis. The latter is likely the most important, but very difficult to introduce in a busy operating theatre. Common infection control practices that are poorly supported by clinical trials are laminar air flow for implant surgery, hand antisepsis prior to surgery, and disinfection of the surgical site. Last, but not least, surveillance of SSIs is a well-established, well documented approach to lower the incidence of SSIs. Many hospitals still do not follow this recommendation despite its effectiveness. Endoscopy and robotic surgeries are new developments that further help to keep rates of SSIs at the lowest possible level. However, as patients leave the hospital at a very early stage, post-discharge surveillance becomes mandatory. Many studies indicate that about 50% of the SSIs undergo undetected unless postdischarge surveillance is performed. A lot of research has been performed in the last decade: However, many hospital still fail to implement these new knowledge into clinical practice.

Final abstract number: 28.001

Session: New Generation Multivalent Vaccines Designed to Do More (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: Plenary Theatre

Multivalent Protection Against a Severe Pediatric Disease - Rotavirus

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Rotaviruses are the foremost cause of severe gastroenteritis in young children, being responsible for 600,000 deaths, 2 million hospitalizations, 25 million clinic visits, 111 million episodes and 56% of hospitalizations for febrile gastroenteritis worldwide, each year. Every child is infected by age five years. Rotateq™ is an oral, ready-to-use, 3-dose regimen vaccine, containing 5 human-bovine reassortant rotavirus serotypes given at 2, 4, 6 months of age, that is easily integrated into pre-established immunization schedules. The product has been studied in over 70,000 infants from all five continents. Rotateq™ has proven efficacy of 98% against severe gastroenteritis for G1-4 strains, was well tolerated, including with respect to intussusception in prelicensure and postmarketing surveillance, with no increase in fever, irritability, or hematochezia, while it reduced health care contacts for rotaviruses by nearly 100%. Rotateq™ has FDA-approval and is now in use in 70 countries, with application pending in another 75 countries, worldwide. Rotateq™ is now widely available in USA, Canada, Australia, eleven countries in Europe, Latin America, the Caribbean and also in other parts of the world. Rotateq™ is now in the review process for WHO-prequalification. Given the universal nature of rotavirus gastroenteritis, this vaccine is an extremely important public health priority.

Final abstract number: 28.002

Session: New Generation Multivalent Vaccines Designed to Do More (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: Plenary Theatre

Long Term Benefits of the Quadrivalent Human Papillomavirus Vaccine (HPV)

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It is now realised that 99.7% of cervical cancers are caused by oncogenic HPV infection: and worldwide HPV types 16 and 18 consistently account for 70% to 80% of cases. Moreover HPV types 16 and 18 contribute to 50% of high-grade dysplasias, and 25% of low-grade dysplasias. In addition, HPV is the most common viral infection with condylomata accuminata or genital warts (90% caused by HPV 6/11) being the most common viral sexually transmitted disease. Genital warts peak in the mid-20 age group, commonly recur post-treatment, and consequently are a costly burden in sexual health settings, as well as causing significant psychosocial morbidity to those infected.

In phase III clinical trials of the quadrivalent human papillomavirus vaccine (6,11,16,18), vaccine HPV type-related CIN2/3, VIN 2/3 and VaIN 2/3 were used as surrogate endpoints in determining efficacy against cervical, vulvar and vaginal cancers, respectively. Randomized, placebo-controlled, double-blind trials involving more than 25,000 women aged 15 - 26 years have shown up to 100% efficacy against HPV 6, 11, 16 and 18 related CIN2/3, AIS (adenocarcinoma in situ), VIN, VaIN, as well as genital warts. Through 5 years of follow-up, the clinical efficacy was maintained with no breakthrough cases observed in the vaccine group. In mid adult women aged 24 - 45, the efficacy of quadrivalent HPV vaccine in the prevention of HPV6/11/16/18-related CIN or external genital lesions (EGL) was 92.4%, with efficacy against HPV16/18-related CIN or EGL being 87.8%. Efficacy against HPV6/11-related CIN or EGL was 100%.

In all studies, vaccine was generally well-tolerated, with a significant but slightly higher proportion of subjects reporting one or more injection site adverse experiences than the placebo group.

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Session: New Generation Multivalent Vaccines Designed to Do More (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: Plenary Theatre

Value of the Quadrivalent HPV Vaccine

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Ludwig Institute for Cancer Research, Brazil

Vaccines provide long-term protection by inducing immune memory - the ability to rapidly produce high antibody levels on subsequent encounters with pathogens targeted by the vaccine.

Prophylactic administration of a quadrivalent HPV (types 6/11/16/18) L1 VLP vaccine (GARDASIL®, Merck & Co., Inc.) to 16- to 23-year-olds was 96% effective in preventing HPV 6/11/16/18 persistent infection or related disease through 5 years of follow-up (Villa et al., Br J Cancer, 2006). Sustained efficacy against disease was maintained with no breakthrough cases of HPV 6, 11, 16 or 18-related infection or disease. In the same study, at the 5 year mark, an antigen challenge was given that demonstrated that GARDASIL®(formulated on a proprietary aluminum adjuvant) had induced immune memory, a hallmark of vaccines that induce long-lasting protection (Olsson et al., 2007). It is not known what level of antibodies indicates an individual's ability to fend off HPV infection, but the available data do suggest that HPV vaccines would provide a lengthy period of protection, likely to usher a vaccinated individual through the years of highest infection risk and beyond. Additional studies are ongoing to verify these projections. Based on demonstrated clinical efficacy and favorable safety profile, this quadrivalent HPV prophylactic vaccine is being introduced as a cost-effective means for reducing the morbidity and mortality of cervical/anogenital cancers, as well as the emotional and economic burdens of abnormal Pap tests and genital warts. Compared to a vaccine containing VLPs of only HPV types 16 and 18, the reduction of HPV-associated disease burden is anticipated to be significantly higher with the administration of the quadrivalent HPV vaccine, since HPV 6 and 11 are responsible for approximately 90% of all genital warts and 15% of low-grade cervical neoplasias. The quadrivalent HPV vaccine is the first and only to show 100% efficacy against HPV 6, 11, 16 and 18-related external genital lesions including genital warts, vulvar and vaginal cancers. Moreover, the prevention and cost-savings from HPV 6/11 related diseases will begin relatively early in the first years following vaccine introduction making the quadrivalent vaccine particularly attractive to national policy-makers.

Final abstract number: 29.001

Session: Intradermal Route: The Natural Pathway for Improved Influenza Vaccination (invited)

Date/time: Saturday, 21 June, 2008, 10:15 - 12:15 hrs

Room: Banquet Hall

Global Use of Seasonal Influenza Vaccine

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, Sergy Haut, France

For several years, the Macroepidemiology of Influenza Vaccination Study Group (MIVSG) has documented influenza vaccine distribution, recommendations and reimbursement in an increasing number of countries throughout the world. In 2003, 56 MIVSG countries used 275 million (M) doses, 94% of the 292 M doses distributed worldwide. By 2005, the MIVSG had grown to include 73 countries. These countries used approximately 330 M doses of seasonal vaccine. In most countries, levels of vaccine use (doses distributed/1000 total population) showed relatively little change between 2002, the year before the re-emergence of H5N1 influenza, and 2005, although large differences persisted between individual countries. However, six countries (Belgium, El Salvador, Japan, Latvia, Malta and Mexico) showed substantial increases in vaccine use over this period, and Malta's increase from 124 to 657 doses/1000 was remarkable. In a few countries, vaccine use decreased, sometimes due to supply shortages. Some form of public reimbursement for vaccination was provided in approximately 60% of the surveyed countries, and they tended to have higher levels of vaccine use compared with countries with no public reimbursement. Vaccination recommendations for risk groups showed little change compared with earlier years, although the age cut-off levels for vaccinating older adults decreased in several countries. More interesting, by 2005, seven countries had adopted policies for vaccinating children 6-23 months in age. In the US, the upper age limit for children was extended to 5 years in 2006 and to 18 years in 2008.

In 2005, nine vaccine-producing countries used 59% of all doses of seasonal influenza vaccine, but had only 12% of the world's population. Influenza vaccination is gradually increasing in many countries, especially in those with rapidly developing economies. This growth in seasonal vaccine use will lay the foundation for vaccination programs when the next pandemic occurs.

Final abstract number: 29.002

Session: Intradermal Route: The Natural Pathway for Improved Influenza Vaccination (invited)

Date/time: Saturday, 21 June, 2008, 10:15 - 12:15 hrs

Room: Banquet Hall

The Potential Benefits of Intradermal Vaccination

B.J. Ward

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The intradermal (ID) route of immunization has a fair claim to primacy since the smallpox vaccine was administered via the skin for almost 100 years before the next human vaccine was introduced. Despite this early success and long-standing immunological interest in this route, the large majority of current vaccines are administered either via the intramuscular or subcutaneous routes. The accessibility of the skin is obvious and the potential immunological advantages of ID immunization have been known for some time. Animal models of ID vaccination have generally yielded excellent results with a range of microbial antigens and several ID vaccines have been successfully introduced for human infections such as rabies and hepatitis B. The skin is the largest immune 'organ' of the human body and, unlike subcutaneous and muscle tissues, the skin has evolved specifically to limit the penetration of chemical and microorganisms. As a result, the skin is better prepared than most tissues to actively screen for invasive microbes and to mount appropriate innate and adaptive immune responses. The immunologic characteristics and capabilities of the skin have been the subject of considerable research for many years due to this unique 'front line' position. Until recently however, full exploitation of the potential of the ID route for vaccination has been hampered by the lack of simple, reliable and safe injection systems. Recent advances in delivery system technologies have sparked renewed interest in the ID route for both established and new vaccines. This presentation will provide an overview of the potential immunological and practical advantages of ID vaccination as well as a brief review of historical and recent ID vaccination techniques.

Final abstract number: 29.003

Session: Intradermal Route: The Natural Pathway for Improved Influenza Vaccination (invited)

Date/time: Saturday, 21 June, 2008, 10:15 - 12:15 hrs

Room: Banquet Hall

Clinical Development of a Seasonal Influenza Vaccine by Intradermal Micro-injection

M. Saville

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Background: Annual trivalent inactivated influenza vaccines (TIV) provide protection for hundreds of millions of individuals worldwide. Yet there is need to improve vaccine efficacy for the elderly who are most affected by influenza, and to increase vaccine coverage in younger adults. The intradermal route of vaccination provides a direct and potentially more efficient access to the immune system. An ID TIV was developed with a unique, convenient microinjection system, and 2 dosage presentations specifically for elderly and younger adults (respectively 15µg or 9µg hemagglutinin/strain/dose).

Methods: The immunogenicity and safety of the two presentations of ID TIV have been investigated in several large-scale Phase 2 and 3 studies in several European countries, Australia and New Zealand. In each study, a licensed intramuscular TIV, (Vaxigrip®; 15µg hemagglutinin/strain/dose) was used as a control. Safety evaluation included documentation of solicited and unsolicited reactions. Hemagglutination inhibition responses were evaluated on D0 and D21.

Results: Phase 2 studies in more than 2000 subjects aged 18-60 years or >60 years have demonstrated that the 15µg ID intradermal vaccination induces higher immune responses compared with Vaxigrip against all three strains, as assessed by D21 GMTs and seroprotection rates. Among younger adults, the 9µg intradermal vaccine was demonstrated to induce an equivalent immune response to Vaxigrip.

Safety results showed that both ID vaccine presentations were well tolerated. When 18-60 year olds, subjects were vaccinated a second time either ID or IM, one year after their first vaccination, reactogenicity was not enhanced compared with that observed after the first vaccination.

Conclusion: Using microinjection to deliver antigen via the less-invasive intradermal route, ID TIV was shown to elicit superior immune responses to conventional vaccine in elderly adults, and provides an alternative vaccine for adults that may encourage increased vaccine uptake

Final abstract number: 29.004

Session: Intradermal Route: The Natural Pathway for Improved Influenza Vaccination (invited)

Date/time: Saturday, 21 June, 2008, 10:15 - 12:15 hrs

Room: Banquet Hall

From Immunogenicity to Vaccine Efficacy: Insights from Statistical and Causal Models

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Background & Objectives: The identification of immunological surrogate markers of protection against disease plays a key role in the assessment of the efficacy of any vaccine. The sole identification of an appropriate surrogate marker is however not sufficient to provide an accurate prediction of vaccine efficacy. A statistical model providing a reliable estimation of the relationship between this marker and clinical protection is also required. We review analyses and models that explore this relationship in the case of influenza. We then discuss the application of such models to estimate the gain in efficacy provided by a novel seasonal influenza vaccine given by intradermal microinjection.

Methods & Principal findings: Several markers have been used to assess the immunogenicity of influenza vaccines. Anti-haemagglutinin antibodies, measured by the haemagglutination inhibition (HI) assay is however the only one for which attempts have been made to quantify its relationship with protection against clinical influenza. Seminal analyses focused on the identification of an HI titre level that can be associated with either a 50% reduction (1:40) or a 90% reduction (1:92) in the risk of influenza. More recently, a model using published data from 15 studies, confirmed the significant and positive relationship existing between HI titre and clinical protection against influenza and provided an estimate of the level of protection against influenza for any HI titer. When applied to immunogenicity data from clinical trials with an trivalent, inactivate influenza vaccine given by intradermal microinjection, this model predicts a gain in vaccine efficacy of 14% (95% CI: 10-18) compared with conventional non-adjuvanted inactivated influenza vaccines given intramuscularly.

Conclusions: Statistical models estimating the relationship between HI data and level of protection against influenza provide useful information to predict vaccine efficacy, particularly for comparing vaccines based on their immunological profile.

Final abstract number: 30.001

Session: Viral Hepatitis (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: 304/305

Treatment of Hepatitis C: Yesterday, Today, and Tomorrow

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Approximately 170 million people world wide are infected with Hepatitis C virus (HCV). The therapy of hepatitis C has gone through various phases of development. In the early 90s, therapy was empirical and standard interferon was given initially for 6 months and then for 12 months. Then came along ribavirin, a guanosine analog and an oral drug, which administered with interferon improved sustained virologic response rates and this primarily was achieved by decreasing relapse rates. The current standard of care as therapy for Hepatitis C consists of pegylated interferon-alfa and ribavirin. In genotype 1 patients, sustained virologic response rates have been around 40-60 % after 48 weeks of therapy whereas non-1 patients, primarily made up of genotypes 2 and 3, have an approximate 80 % probability of sustained virology response after 24 weeks of therapy. Although treatment duration has traditionally been fixed, there is a paradigm of virologic response guided therapy that has evolved. For rapid virologic responders, characterized as HCV RNA negativity at week 4, reports suggest that 12-16 weeks of therapy for genotype 2 patients and 24 weeks of therapy for genotype 1 patients may be adequate. In contrast, in genotype 1 patients who have a slow response characterized by a loss of HCV RNA at week 24, a prolonged course of 72 weeks is the optimal regimen. Despite these advances, there is an unmet need for better therapies in the non-responders, in those with advanced and decompensated liver disease, in those with a spectrum of special situations such as transplantation etc, and those who do not tolerate interferon and ribavirin. Thus there is a need for novel therapies with enhanced efficacy, tolerability, and greater ease of administration. We now stand at the edge of an exciting phase with the advent of Specifically Targeted Antiviral Therapy for HCV (STAT-C), wherein orally administered small molecules can provide targeted activity at specific points in the viral life cycle. The ability to target specific steps of replication is apparent in the myriad of novel therapies in research, such as protease inhibitors, nucleoside and non-nucleoside polymerase inhibitors, glucosidase inhibitors, inosine monophosphate dehydrogenase (IMPDH) inhibitors, and immune modulators (Interferons and their inducers, toll-like receptor analogues, therapeutic vaccines). Combination therapies with new small molecules and peg-INF with or without ribavirin are currently being evaluated. One of the challenges of STAT-C therapy would be the prevention of the evolution of drug resistance while enhancing tolerability, decreasing treatment duration, and ultimately achieving higher sustained virologic response rates.

Final abstract number: 30.003

Session: Viral Hepatitis (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: 304/305

Treatment of Hepatitis C in the HIV-Infected Subject

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Liver complications have emerged as an important cause of hospitalization and mortality among HIV-infected persons (1). Anti-HCV treatment offers the opportunity to eradicate HCV, reduce the risk of disease progression and reduce liver-related deaths. These benefits are significant and provide the justification for consideration of HCV treatment in every HIV-HCV coinfecting patient. However, since treatment is not uniformly effective and is associated with side effects in the majority of treated patients, the decision to proceed with treatment requires a careful weighing of risk and benefits for each patient.

Patients should be on a stable ART regimen for at least 3 months prior to starting HCV treatment. Didanosine (DDI) is absolutely contraindicated due to high risk of toxicity (2). Stavudine (D4T) and abacavir are relative contraindicated due to interactions with ribavirin. AZT increases the risk of anemia and should be avoided if possible.

The treatment of choice is peginterferon alfa (peg-IFN) and weight-based ribavirin (1000 mg daily if <75 kg and 1200 mg daily if >75 kg) (3). Weight-based ribavirin is recommended for all genotypes, due to the higher rate of relapse in HCV-HIV coinfecting patients compared with HCV mono-infected patients. The dose of peginterferon alfa-2a is 180 ug weekly and of peginterferon alfa-2b is 1.5 ug/kg weekly. The duration of treatment is 24-48 weeks for genotypes 2 and 3 and 48-72 weeks for genotype 1, 4-6, with the time to loss of HCV determining the length of treatment. Early viral kinetics strongly influences duration of therapy. Shorter duration may be a consideration in patients achieving a rapid virologic response (RVR), defined as undetectable HCV RNA at week 4 of treatment. Longer duration therapy (up to 72 weeks) is a strong consideration in "slow responders". The most consistently identified pre-treatment predictors of SVR are HCV viral load and HCV genotype (4-7). Adherence is an important factor in achieving SVR in HCV-mono-infected patients but data in coinfecting patients is more limited.

Patients labeled as non-responders need to be carefully evaluated to identify those that may benefit from retreatment using optimal doses and duration of current therapies. The available data indicate that subjects who failed a prior course of suboptimal therapy may achieve SVR but at rates lower than treatment-naive patients (8). Overall, the chance SVR in previously treated patients is dependent upon the efficacy of the previous tried regimen.

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Final abstract number: 30.004

Session: Viral Hepatitis (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: 304/305

Metabolic Abnormalities in HIV Infection

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HIV infected subjects often have a multitude of metabolic defects. The clinical outcomes associated with these abnormalities include lipodystrophy, insulin resistance, dyslipidemia, nonalcoholic fatty liver disease, accelerated atherosclerosis with both coronary artery disease (CAD) and peripheral vascular disease. The development of these complications reflect a complex interaction between the patient, the HIV virus, other concomitant infections and HAART therapy. The seriousness of these complications is underscored by the rising mortality from non-HIV related causes in infected subjects. This is particularly important in males > 55 yrs of age where CAD is the leading cause of death. Subjects with HIV infection are at increased risk for myocardial infarction and this risk is related to the use of protease inhibitors (PI). It is however important to note that conventional risk factors e.g. smoking are more important determinants of cardiovascular outcomes rather than the nature of antiretroviral therapy. It is proposed that changes in adipocyte biology drive these metabolic abnormalities. PIs inhibit CRABP-1 which is required for PPAR-g an adipocyte differentiation factor. They also cause mitochondrial injury. Changes in adipocyte function have also been noted in the absence of PI usage. These lead to either lipoatrophy or lipohypertrophy or differential expression of these phenotypes in the same subject. Lipoatrophy is associated with leptin deficiency and can be corrected by leptin. Both lipoatrophy and lipohypertrophy are associated with insulin resistance. HIV infected subjects have increased lipolysis secondary to insulin resistance. This is associated with high free fatty acid levels, impaired metabolic clearance of glucose and hyperinsulinemia. These changes lead to the development of nonalcoholic fatty liver disease (NAFLD). NAFLD accelerates progression to cirrhosis in those co-infected with hepatitis C, promotes resistance to anti-HCV therapy, increased cholesterol production and increased predilection for CAD. PIs increased de novo lipogenesis and also increased HMG CoA reductase while decreasing Cyp7A activity which normally converts cholesterol to bile acids. Dyslipidemia results from both increased lipolysis, decreased clearance of triglycerides and increased cholesterol production. The development of insulin resistance also leads to activation of the innate immune system and an acute phase reaction which creates a systemic proinflammatory, profibrotic state and may activate endothelial cells. Endothelial injury and hyperlipidemia lead to atherosclerosis. PIs block metabolism of mature SREBP-1c and increase its half life thereby increasing the levels of its target CD36. CD36 is expressed on macrophages and promotes cholesterol and lipid uptake thereby creating foam cells and promoting atherosclerosis. To protect subjects from these, the cardiovascular risk can be calculated from Framingham and HIV specific scores. The target LDL cholesterol for those with low risk (< 10% over 10 yrs) is 195 mg/dl while that for moderate risk (10-20%) is 155 mg/dl and high risk (> 20%) is 105 mg/dl. This is accomplished by attention to traditional risk factors, diet and exercise as well as careful selection of HAART. NNRTI have the lowest while PI have the highest metabolic impact. In those with dyslipidemia, statins and fibrates are first line therapy. Lovastatin and Simvastatin are contraindicated due to drug-drug interactions with HAART. It is important to maintain viral suppression while modulating HAART for dyslipidemia because failure to keep the virus suppressed increases the risk of mortality.

Final abstract number: 31.001

Session: *Orientia tsutsugamushi*: a Neglected Pathogen (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: 302/303

Genome Analysis

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Scrub typhus is caused by the obligate intracellular rickettsia *Orientia tsutsugamushi* (previously called *Rickettsia tsutsugamushi*). The bacterium is maternally inherited in trombicuid mites and transmitted to humans by feeding larvae. *Orientia* is a member of the Rickettsiales, a genetically diverse group of the alpha-Proteobacteria, include major mammalian pathogens, such as the agents of epidemic typhus, scrub typhus, ehrlichioses and heartwater disease.

Sequenced genomes of this bacterial order have provided exciting insights into reductive genome evolution, antigenic variation and host cell manipulation. The 2,127,051-bp genome of the Boryong strain, which represents the most highly repeated bacterial genome sequenced to date. The repeat density of the scrub typhus pathogen is 200-fold higher than that of its close relative *Rickettsia prowazekii*, the agent of epidemic typhus. A total of 359 tra genes for components of conjugative type IV secretion systems were identified at 79 sites in the genome. Results suggest intragenomic duplications or multiple integrations of a massively proliferating conjugative transfer system. Diversifying selection on host-cell interaction genes along with repeated population bottlenecks may drive rare genome variants to fixation, thereby short-circuiting selection for low complexity in bacterial genomes.

Final abstract number: 31.002

Session: Orientia tsutsugamushi: a Neglected Pathogen (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: 302/303

Genetic Variability of Orientia tsutsugamushi

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Orientia tsutsugamushi, the agent of the reemerging disease scrub typhus, remains a puzzling microorganism. This alpha proteobacterium, vectorized by trombiculid mites, has a complex genome containing an exceptionally high repeat density likely resulting from duplication and genome recombination events. It also exhibits a great antigenic diversity, with more than 30 serotypes currently identified, and a geographical specificity of strain distribution. The genetic diversity of *O. tsutsugamushi*, which is traduced by differences in mortality rates ranging from < 1% to 50%, has been the subject of few studies. Most genetic analyses of the population structure of *O. tsutsugamushi* were based on the study of genes encoding surface-exposed antigens recognized by the immune response of patients. Of these, the 56-kDa protein-encoding gene, unique to *O. tsutsugamushi*, has been the most extensively studied, representing 70% of all gene sequences available in GenBank for this species. Phylogenetic studies based on this gene identified 6 main clusters (Gilliam, Karp, Kato, Kawazaki, Kuroki, Saitama) but it is likely that more clusters will be described as highlighted by recent studies. When applying the taxonomic criteria used for prokaryotes, the 16S rRNA nucleotide divergence within the *O. tsutsugamushi* species, as high as 4%, would justify the classification of its isolates in more than one species. In addition, to date, there is no genotyping method that would allow tracing *O. tsutsugamushi* at the strain level. Such a tool seems essential given the emergence of antibiotic resistant strains. As a consequence, further studies to understand the genetic variability of *O. tsutsugamushi* are needed and may be performed using modern techniques such as multi-spacer typing or DNA microarray.

Final abstract number: 31.003

Session: Orientia tsutsugamushi: a Neglected Pathogen (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: 302/303

The Use of Genomics for the Early Diagnosis of Scrub Typhus and Other Systemic Infectious Diseases

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Genomic tools and approaches have enabled a more detailed description of host-microbe encounters, and shed light on fundamentally important processes, including the cellular responses associated with infection. Genome-wide transcript-abundance profiles, like other comprehensive molecular readouts of host physiological state, provide a detailed blueprint of the host-pathogen dialogue during microbial disease. Studies of cancer based on genome-wide transcript-abundance profiles have led to novel signatures that predict disease outcome and serve as useful clinical classifiers. The highly dynamic and compartmentalized aspects of the host response to pathogens complicates efforts to identify predictive signatures for infectious diseases. Yet, studies of systemic infectious diseases so far suggest the possibility of successfully discriminating between different types (classes) of infection and predicting clinical outcome. We have collected and analyzed genome-wide transcript abundance patterns early in the course of nonspecific acute febrile illness, and found evidence for classification on the basis of microbial diagnosis. Scrub typhus appeared to have a distinct signature in one study, but this finding needs to be validated. Early explorations in host genomic response profiling suggest the possibility of recognizing etiological factor(s) and predicting the course of disease, at early points in the timeline of the process, but also point to important unmet challenges.

Final abstract number: 31.004

Session: Orientia tsutsugamushi: a Neglected Pathogen (invited)

Date/time: Saturday, 21 June, 2008, 10:15-12:15 hrs

Room: 302/303

Vector and Epidemiology

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Tsutsugamushi disease (scrub typhus) has a long history of investigation and is still an important disease as re-emerging infectious disease. Geographic distribution of the disease is recognized as the "Tsutsugamushi triangle" which extends from Far East Asia, to northern Australia, and to West Asia. The causative agent *Orientia tsutsugamushi* (Ot.) has various serotypes and each has specific vector species of trombiculid mites by endemic areas, and also its pathogenecity is very diverse.

The authors summarize the vectorial competence of main mite species in Asia as follows; From Far Eastern Russia to Korea and mainland Japan, *Leptotrombidium pallidum* is very prevalent both in spring and autumn, and possesses JP (Karp) and JG (Gilliam) type Ot. From East Asia (Korea, China and southern half of Japan) to Southeast Asia, *L. scutellare* makes characteristic distributional pattern as a drastic endemic spot that push up outbreaks in autumn, and is affinitive to Kawasaki, Kuroki and Boryong? type of Ot. From southwestern islands of Japan to Southeast Asia, *L. deliense* is commonly found throughout warm seasons and may transmits various oriental types of Ot. It is interesting that a border dissociating the distributions of *L. scutellare* and *L. deliense* may be in Tokara Islands of southernmost Japan as the Watase line between Palearctic and Oriental regions. Additionally *L. arenicola* and *L. fletcheri* are densely distributed within Southeast Asia, and possesses Ot. types like in *L. deliense*.

Although the clinician must bear in mind that the Tsutsugamushi disease is still an un-neglected disease that causes serious results unless carefully attended, the increasing problems of rickettsioses including Japanese Spotted Fever draw more attention as the infectious diseases. Investigations concerning the early diagnostic method, treatment and host-pathogen cytokine regulation mechanism are going on.

In those times that humans and things move fast globally, we propose here to establish the International network system on the view of epidemiology of the rickettsial diseases.

Final abstract number: 33.001

Session: 21st Century Global Health Protection (invited)

Date/time: Saturday, 21 June, 2008, 14:30-15:15 hrs

Room: Conference Hall 1-3

21st Century Global Health Protection

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Our 21st century 'flat world' can enable solutions to global health challenges through technologies, communication tools, and economic opportunities that a decade ago were not even imagined. But the flat world is also a world that faces daunting challenges - wars and ideological conflicts, climate change, and extreme poverty - that threaten our progress. Pandemics, terrorist attacks, and extreme weather are among the most likely urgent threats that pose large-scale consequences to human health, economic prosperity, and national security. Solutions to these challenges require not only innovation, but also global health leadership evolution. Successful global leaders will need "meta-leadership" skills - the ability to lead horizontally across a complex array of organizations through recognition and development of shared strategic goals, as well as culturally competent methods for adapting and executing these strategies. Ultimately, the entire health network will need to be optimized to assure we have the knowledge and tools to protect people around the globe.

Final abstract number: 34.001

Session: The New Face of Clostridium difficile-Associated Disease (CDAD) (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

The spread of hypervirulent *Clostridium difficile* PCR Ribotype 027 in Europe.

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Background: Since 2002, increasing rates of *Clostridium difficile*-associated infections (CDI) with a more severe course, higher mortality and more complications have been reported in Canada, USA and Europe. This increased virulence is assumed to be associated with higher amounts of toxin production by a strain belonging to PCR ribotype 027, toxinotype III (Type 027).

Methods: Following the first cases of *C. difficile* Type 027 in Europe, a network of microbiologists and epidemiologists from national reference centers was established. *Clostridium difficile* strains were sent to National Reference laboratories for further investigations. The Reference laboratory in Leiden confirmed most of the first isolated Type 027 isolates in each country.

Results: As of April 2008, *C. difficile* Type 027 was found in 16 European member states and in Switzerland. Seven countries only reported sporadic cases of Type 027. Of these 7 countries, 2 countries reported on patients with infections acquired abroad in countries known to be affected by Type 027. One country reported an outbreak with the index patient having acquired PCR ribotype 027 during stay in a foreign hospital. England and Wales, Belgium, France, Luxembourg, Finland and The Netherlands reported a high number of hospitals affected by Type 027.

Application of a recently developed Multi-Locus Variable Number of Tandem Repeat Analysis (MLVA) for *C. difficile* on isolates from individual countries revealed specific subtypes in some countries. Type 027 isolates were generally susceptible to clindamycin and resistant to erythromycin, however clindamycin-resistant, erythromycin-resistant, *ErmB* positive Type 027 strains have been found in Switzerland, France and Ireland. In contrast, erythromycin-susceptible, clindamycin-susceptible strains were found in Denmark and Germany. Information on the attributable mortality was available from France (4%) and The Netherlands (4.1%).

Systematic surveillance studies have been developed in all countries affected by Type 027, but they differ considerably in design.

Conclusions: *C. difficile* PCR ribotype 027, toxinotype III has been found in more than 250 hospitals in 17 countries and is rapidly spreading in Europe.

Final abstract number: 34.002

Session: The New Face of *Clostridium difficile*-Associated Disease (CDAD) (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

Diagnosing *Clostridium difficile*-Associated Diseases: The State of the Art

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Clostridium difficile can cause antibiotic-associated diarrhea, colitis and pseudomembranous colitis, known as *C. difficile*-associated diseases (CDAD). It has been reported in the literature since the late 1970s, and outbreaks continue to occur despite breakthroughs in laboratory diagnosis, effective treatments and infection control programs. During recent years the number of outbreaks of CDAD that are severe has risen significantly in many North American and European hospitals.

Three virulence factors have been described in *C. difficile* strains: toxin A (TcdA), toxin B (TcdB) and binary toxin (CDT). Toxin A is a 308-kDa enterotoxin, toxin B is a 270-kDa cytotoxin and binary toxin is an actin-specific ADP-ribosyl transferase. Toxin A and toxin B are encoded on the large chromosomal region PaLoc that encompassed the two toxin genes (*tcdA* and *tcdB*) and three additional genes for regulatory and transport functions (*tcdC*, *tcdD* and *tcdE*). The binary toxin is encoded by the *cdtA* gene (enzymic component) and the *cdtB* gene (binding component). These factors are now identified by molecular methods.

The main laboratory diagnostic procedures for CDAD involve cultivation of stool specimens on selective media and detection of toxin production by cell culture assays. Several alternative tests are now available for diagnosis of CDAD, such as latex agglutination, immunoblotting, enzyme immunoassay and PCR. The introduction of typing methods such as PCR, ribotyping and PFGE to follow outbreaks of CDAD in hospitals and communities has given important epidemiological data. Real-time PCR to detect *tcdA* and *tcdB* genes directly from stool specimens is now available. The emergence and spread of hypervirulent strains such as BI/NAP1/027 *C. difficile* has made it mandatory to improve rapid laboratory diagnosis and investigate antibiotic resistance mechanisms.

Final abstract number: 34.003

Session: The New Face of Clostridium difficile-Associated Disease (CDAD) (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

Preventing New and Recurrent CDAD

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There are three major risk factors: Advanced age, hospitalization or residence in a chronic care facility and exposure to an antibacterial agent. Principles of prevention:

Antibiotic exposure:

- Low risk: Urinary antiseptics, sulfonamides, vancomycin, metronidazole, tetracyclines, narrow spectrum betalactams, macrolides, linezolid, ketolides, TMP-SMX
- "Big 3": Broad spectrum cephalosporins, fluoroquinolones and clindamycin

Infection control: 1) Single room or cohort, 2) barrier precautions, 3) avoid rectal thermometers, 4) chlorine 1000 ppm room cleaning, 5) early detection, 6) BioQuell - experimental and 7) outbreak - control antibiotics and soap for hand hygiene.

Prevention of relapses: Avoid "bad" Abx and antiperistaltics; role of probiotics and gastric pH control - unknown.

Final abstract number: 34.004

Session: The New Face of Clostridium difficile-Associated Disease (CDAD) (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

Managing CDAD: Current and Upcoming Approaches

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The epidemiology, clinical severity and case-fatality ratio of *Clostridium difficile* infection (CDI) changed dramatically with the emergence of a toxin hyperproducing strain (BI/NAP1/027) in North America and Europe since 2000. These changes have stimulated the quest for novel therapeutic approaches, and a re-examination of the comparative efficacy of metronidazole versus oral vancomycin. Unfortunately, tolevamer, the only novel treatment evaluated so far in phase 3 trials, has proven inferior to comparators, and metronidazole and vancomycin remain the two most commonly used drugs. The major advantage of metronidazole is its low price. The major advantage of orally administered vancomycin lies in its more favorable pharmacokinetics. Facilitating vancomycin-resistant enterococci colonization/infection is a potential drawback of both drugs. The randomized controlled trials published so far used intermediate outcomes rather than outcomes that now preoccupy clinicians: the frequency of complications or recurrences. Pending the development of a prospectively validated scoring system, the IDSA/SHEA expert committee will define severe CDI as any patient with a leukocytosis $\geq 15000/\text{mm}^3$ or a creatinine increased by $\geq 50\%$ from baseline. For patients with mild-to moderate CDI (leukocytosis $< 15000/\text{mm}^3$ and creatinine $< 1.5 \times$ baseline), there is no evidence that vancomycin is superior to metronidazole (even for intermediate outcomes), and metronidazole should be preferred. For patients with severe CDI not infected with BI/NAP1/027, there is reasonable evidence that the better pharmacokinetics of vancomycin translate into a lower probability of complications. For those infected with BI/NAP1/027, the superiority of vancomycin remains to be proven. About one fourth of patients treated with either metronidazole or vancomycin will experience at least one recurrence. There is now some evidence that the more common post-metronidazole recurrences documented recently in some centers may have corresponded to re-infections among patients who remained exposed in the hospital environment.

Final abstract number: 35.001

Session: Cervical Cancer Vaccination: The Need for Strong and Sustained Protection (invited)

Date/time: Saturday, 21 June, 2008, 15:45 - 17:45 hrs

Room: Plenary Theatre

HPV Types 16, 18, 45 and 31: The Most Important Oncogenic HPV Types Worldwide

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HPV infections are the most common sexually transmitted infections. HPV types differ in transmission capacity, virulence and in their ability to induce cancer. Over 90% of HPV-attributable cancers in women are cervical cancer. Most cancers of the uterine cervix are squamous cell carcinomas, while adenocarcinoma represents 10-12% of the global cervical cancer burden (in some countries of Europe and North America it amounts to over 20% of all invasive cervical cancer).

On worldwide estimates, HPV-16 is consistently the most common type (60%) in cervical cancer, followed by HPV-18, -45 and -31. These four types combined account for approximately 80% of squamous cell carcinomas and 90% of adenocarcinomas. Some variability in the ranking thereafter has been described.

Infections with HPV-16, -18, or -45 are associated with a higher risk for progression to cancer. The prognosis of HPV-16 and -18 is now being established by cohort studies with 10+ years of follow-up. The probability and time to progression to HSIL among HPV-16 and/or HPV-18 positive women with normal cytology is significantly higher than for any other of the high-risk HPV types, although the estimates for each individual type other than HPV-16 and -18 have not been firmly established.

Adenocarcinoma is not detected effectively by cervical screening and is increasing in incidence in Europe and North America. It is associated with higher recurrence rates and poor outcomes.

HPV-18 and -45 account for more than 40% of adenocarcinomas.

Among other HPV positive cancer cases, HPV-16 is the dominant type. HPV-18 and -45 are the next most common types, although the relative role of the remaining HPV types is still to be determined.

In summary, on a worldwide scale, prevention of cervical and other genital cancers would greatly benefit from vaccination focused on HPV-16 and -18.

Final abstract number: 35.002

Session: Cervical Cancer Vaccination: The Need for Strong and Sustained Protection (invited)

Date/time: Saturday, 21 June, 2008, 15:45 - 17:45 hrs

Room: Plenary Theatre

The Value of New Adjuvant Technology

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The development of safe and efficacious vaccines against pathogens like malaria, HIV and TB and the induction of protective immune responses in populations with impaired immunity such as the elderly remain major challenges. The growing understanding of the role of the innate immune system in the initial triggering of specific, adaptive immune responses has stimulated new vaccine-concepts, especially in the field of adjuvant development.

Over the past two decades GSK Biologicals has developed an Adjuvant Systems (AS) platform. AS families are formulated with selected antigen(s) and are designed to enhance the immune response to the targeted pathogen for the target population. Extensive preclinical and clinical testing has led to the development of AS-based candidate vaccines for malaria (RTS,S), HSV, H5N1 pre-pandemic influenza, and licensed vaccines for HBV and cervical cancer prevention (HPV) formulated with novel adjuvant technology. The GSK proprietary novel Adjuvant System AS04 (aluminium hydroxide combined with the immunostimulatory molecule, 3-O-desacyl-4'-monophosphoryl lipid A) has been combined with HPV 16 and -18 virus-like-particles to tailor the immune response optimally against a virus that typically hides from the immune system.

The immune response induced by the AS04-adjuvanted cervical cancer vaccine has been assessed in pre-clinical and clinical studies. In clinical studies, GSK's both HPV-16 and -18 L1-VLPs when adjuvanted with AS04, induced a stronger and more sustained immune response for at least 4 years after the first dose, than when adjuvanted with aluminium hydroxide alone. In addition, AS04 allowed for higher and sustained concentrations of neutralising antibodies, as well as higher frequencies of memory B-cells.¹

New vaccine technologies have opened the door to vaccination against diseases that were not preventable before. GSK has formulated its cervical cancer vaccine with AS04 to address the need for long term protection against oncogenic HPV, a virus that typically hides from the immune system and for which the disease remains silent for years, if not detected by classical screening methods such as PAP smears.

¹Giannini SL, et al. *Vaccine* 2006;24:5937-49.

Final abstract number: 35.004

Session: Cervical Cancer Vaccination: The Need for Strong and Sustained Protection (invited)

Date/time: Saturday, 21 June, 2008, 15:45 - 17:45 hrs

Room: Plenary Theatre

Implementation of Cervical Cancer Vaccination. Reaching Girls and Women: Challenges and Opportunities

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Cervical cancer is the most common cancer in women in many parts of Asia. Indeed, 54% of the world's cervical cancer burden is in Asia. Although cervical cancer screening with Pap smears has been effective, most Asian countries don't have the resources to implement a comprehensive screening programme. Implementation of vaccination provides a realistic approach to improve cervical cancer control in these countries.

In Asia, successful implementation of cervical cancer vaccination can present more of a challenge than it does on other continents. Experience following the introduction of vaccination against common childhood infections highlights several practical issues, particularly concerning vaccination policy, financing and system capacity for vaccine delivery and inoculation. While the efficacy and tolerability of anti-HPV-16/18 vaccines are well established, policymakers in many Asian countries aren't ready to formulate a national policy.

Implementation of anti-HPV-16/18 vaccination in Asia is likely to start with opportunistic vaccination of individual women. Physicians will introduce the vaccine to their patients seeking cervical screening or attending consultations for other reasons. Caretakers will also discuss the benefits of vaccination for their adolescent daughters with these patients. In some Asian regions, opportunistic cytology screening has reached a high level of penetration and cervical cancer incidence is declining. Opportunistic anti-HPV-16/18 vaccination may gain momentum in a similar manner to cytology screening. Once sufficient demand from individuals for anti-HPV-16/18 vaccines is reached, policymakers are likely to adopt national policies for mass vaccination of targeted populations.

An important first step in implementing anti-HPV-16/18 vaccines in Asia should be to focus on heightening awareness of the need for effective strategies for cervical cancer prevention and the role of opportunistic vaccination among the general public and primary healthcare workers. In a two-pronged approach, a private-public partnership between industry and global charity organisations on competitive financing will further catalyse the wider acceptance of cervical cancer vaccination.

Final abstract number: 36.001

Session: Macrolides - Yesterday, Today and Tomorrow (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

RTI: Treatment Challenges

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Severe community-acquired pneumonia (CAP) treated in intensive care units (ICU) represents a great therapeutic challenge. There is growing evidence on the importance of atypical pathogens and combined infections as causes of severe CAP. Data from our single-center study show that *Legionella* and atypical pathogens are associated with over 20% of CAP. That is why combined ceftriaxone and parenteral azithromycin therapy became a standard treatment in our ICU. This is congruent with a majority of contemporary treatment guidelines which recognized the importance of a combined treatment of severe CAP. Evidences on the role of atypical pathogens, particularly *C. pneumoniae*, in the etiology of nosocomial pneumonia (NP), including ventilator-associated pneumoniae (VAP), are also emerging. These pathogens are not so well recognized as possible pathogens and considered in present treatment guidelines of NP. Further surveillance is needed which might change our initial therapeutic approach in patients with NP.

In pediatric patients, *Mycoplasma pneumoniae* and *Chlamydothila pneumoniae* seem to play a more significant role in causing respiratory tract infections than previously thought. These atypical bacteria have been associated with acute tonsillopharyngitis (AT) and, unless adequately treated with antimicrobial therapy, it has been demonstrated that they can cause recurrent episodes of this disease. Moreover, it has recently been observed that the great majority of the children with a history of severely recurrent AT (and therefore considered eligible for elective tonsillectomy) are infected by atypical bacteria and that tonsillectomy seems to be effective in reducing the recurrence of both AT and acute respiratory disease in the presence of such infections. This means that treatment with macrolides can solve the acute illness and reduce the risk of new recurrences in the case of *M. pneumoniae* or *C. pneumoniae* infections and that appropriate treatment might postpone or abolish the need of tonsillectomy.

Final abstract number: 36.002

Session: Macrolides - Yesterday, Today and Tomorrow (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Chlamydia trachomatis: Area Under the Iceberg

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In both sexes, genital *Chlamydia trachomatis* infection is still the most commonly reported bacterial sexually transmitted infectious disease worldwide. The prevalence is highest in persons aged less than 25 years. In females, up to 40% of chlamydial cervicitis might ascend to the endometrium, and is responsible for the etiology of endometritis and salpingitis. Late sequels of Fallopian tube involvement include pelvic inflammatory disease, ectopic pregnancy, tubal factor infertility and chronic pelvic pain. Since the overwhelming majority of primary infections (urethritis in men and cervicitis or urethritis in women) are asymptomatic, early diagnosis should essentially rely on annual screening of sexually active young women as well as men at high risk sexual behavior. At present, nucleic acid amplification techniques (NAAT) are the most sensitive tests for the detection of the pathogen in male and female biological samples. Over the last decade, administration of a single oral dose of 1000 mg azithromycin is the recommended treatment for uncomplicated primary genital chlamydial infection in men and women. In addition, azithromycin was shown to be as effective as amoxicillin or erythromycin for the eradication of *C. trachomatis* infection in pregnant women and this regimen resulted in less adverse events. In a recent multicenter study in Central and Eastern Europe, prevalence of endocervical chlamydial infection in women aged less than 25 years was 6%, with significant differences of frequencies among some geographical areas. Risk factors of infection were in accordance with those reported from other parts of Europe.

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Session: Macrolides - Yesterday, Today and Tomorrow (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Acne vulgaris - Old/New Treatment?

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Acne vulgaris is one of the most frequent skin diseases affecting predominantly adolescents. The therapy depends on the severity of the disease. Systemic antibiotics in acne treatment have always been a controversial topic, as deprecated and respected at the same time. Pulse azithromycin therapy has devoted attention of many dermatologists. Several studies on this therapy were published so far, but dosage regimens in pulsed azithromycin therapy slightly differ between studies. However, all of them present that azithromycin has better clinical efficacy and safety than systemic minocycline or tetracycline. At our department, azithromycin has been administered and studied for four and half years now, with remarkable results. We have compared the effect of azithromycin against quinolones and tetracyclines. Three groups (30 patients each) of comparable age (aged 14-18 years) and gender suffering from moderate acne papulopostulosa (Cook's acne severity grading scale 2-6) were observed. Azithromycin was administered 500 mg orally during three subsequent days, followed by 500 mg weekly for the following six weeks. Ofloxacin was administered 100 mg for five days, 100 mg once daily following 10 days and 50 mg once daily during five weeks. Doxycycline was administered 100 mg twice daily for five days, 100 mg once daily for 10 days and 50 mg once daily following five weeks. Topical agents containing ichthamol and azelaic acid were applied. Significantly better results (reduction in inflammatory lesions) were observed after the third treatment week in the azithromycin group. The results remained significant even after therapy termination and at the follow-up visit (five months after therapy termination). Also, no adverse events were recorded in the azithromycin group.

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Session: Macrolides - Yesterday, Today and Tomorrow (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Acute Infectious Gastroenterocolitis: Use or Not to Use Antibiotics?

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Travelers' diarrhea (TD) is the leading cause of morbidity in travelers. This lecture will primarily address pediatric TD by discussing existing data on children as well as extrapolation of appropriate adult data and will propose reasonable therapeutic parameters for infants and children. TD is rarely associated with mortality though it is responsible for significant morbidity in traveling infants and children. Untreated, TD in children may last for days or even weeks. Prevention of TD generally includes dietary counseling and occasionally the use of chemoprophylaxis. The use of antimicrobial and antidiarrheal agents for the treatment of TD in children is controversial and there is still little data published and no firm recommendations available to guide the clinician. Modern macrolide, azithromycin, is now commonly used as a sole agent for TD and is particularly effective against *Shigella spp.* and *Campylobacter spp.*, including *Campylobacter spp.* resistant to fluoroquinolones. A single-center, randomized, no treatment-controlled parallel group, assessor-blind trial was performed in children with *Campylobacter enterocolitis* treated at the University Hospital for Infectious Diseases "Dr Fran Mihaljevic", Zagreb, Croatia. The primary objective was to evaluate the efficacy of a single oral azithromycin dose vs. standard oral erythromycin regimen or no antibiotic for *Campylobacter enterocolitis* in children ≤ 12 years of age. The results of our study have shown that a single azithromycin 30 mg/kg administration early after disease onset effectively eradicates the pathogen and accelerates clinical cure in childhood *Campylobacter enterocolitis*. It is clinically superior to an early commenced 5-day erythromycin regimen.

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Session: Biodiversity (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 304/305

Diversity of Human Microbial Pathogens and Commensals

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Complex microbial ecosystems occupy the cutaneous and mucosal surfaces of humans. Recent advances have highlighted both the tremendous diversity of these communities and their importance to host physiology, yet, we have only scratched the surface. Questions remain about the ecological processes that establish and maintain the human microbiota throughout life. Furthermore, basic features of the human microbial ecosystem remain poorly described, including variability in diversity, in space and time. Host individuality imposes a strong signature on patterns of diversity. In turn, our indigenous microbial ecosystem defines who we are as individuals. Assembly of the oral and the gut microbiota may also involve both stochastic historical events and contemporary environmental factors. Approaches that combine community ecology, molecular microbial ecology, and metagenomics may improve our understanding of health and disease within the communal human organism. By understanding the patterns of diversity associated with human health, we may be able to preserve and restore health more effectively. By recognizing the early signs of impending disturbance, we may be able to predict and avoid disease.

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Session: Biodiversity (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 304/305

Evolution of Diversity in Pathogen Populations

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Using sequencing or chip-based genomic approaches it is possible to gain insights into the genetic diversity and genome dynamics of bacterial pathogen populations. We study *Bacillus anthracis*, *Yersinia pestis* and *Escherichia coli* as model systems, all of which have several representative genome sequences available, allowing for the comparison of both clinical and environmental isolates. It allows to analyze the types of host variation, selection and adaptation occurring during the time course of a single or multiple outbreaks of human disease. Comparative analyses of the respective genome inventories and those of neighboring taxa and phyla, allows for the discovery of species- and lineage-specific microevolutionary traits and further elucidates common and unique traits in genome evolution and speciation. Applying SNP-based genotyping and resequencing methodologies, we were able to reconstitute a detailed evolutionary history of the *B. anthracis*, *Y. pestis* and the *E. coli* O157:H7 lineage and resolve highly clonal and monomorphic population structures. To study these subtle but important genetic variations, we have developed a bioinformatics pipeline that facilitates the discovery and validation of rare polymorphisms using genome sequence read coverage and quality. Analysis of the data led to an estimate of the degree of reductive evolution or the extent of influx of genetic material via horizontal gene transfer in these dynamic bacterial populations. In addition, it is possible to assess the impact of such alterations on the bacterial fitness, environmental survival and individual pathogenic potential. Although there is a stringent correlation between the absence of certain genes and a potential physiological function, the opposite does not hold true. Therefore, by studying the pan-genome of these important bacterial species, we can better define commensalism and pathogenicity as well as establish more accurate genetic species borders. Understanding genetic diversity and genome dynamics in bacterial pathogen populations has major impacts on the molecular epidemiology and microbial forensic communities and provides critical insights into the evolutionary and ecological niches of these human pathogens.

Final abstract number: 37.003

Session: Biodiversity (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 304/305

Retroviral Biodiversity: Practical Consequences for HIV Treatment and Prevention

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Background: Retroviral diversity is attributable both to the infidelity of the reverse transcriptase (RT) enzyme that is responsible for transcribing the viral RNA genome into DNA as well as to a high viral replication rate. In the case of HIV-1, the error rate of RT is approximately 5×10^{-5} . Given a genomic length of 9.2kb, this means that a mutation is likely to take place almost every time that HIV replicates; consequently, mutations are found throughout the HIV genome infected individuals. These mutations include those responsible for escape from immunological pressure as well as those associated with drug resistance. HIV replication patterns in different areas of the world have also given rise to a series of subtypes and recombinant forms that predominate in different geographic locales. Proper interpretation of drug resistance mutational patterns has potentiated both the sequencing of drugs within a given drug class, as well as the use of drugs from classes that have not previously been used in treatment of a given patient. Drug resistance is today acknowledged to be both a key cause as well as outcome of HIV treatment failure.

Results: In recent years, however, the field of HIV resistance testing has become complicated by the fact that different viral subtypes may sometimes express different mutations that are associated with resistance to the same compound. In some cases, this may be due to the redundancy of the genetic code and the fact that different viral subtypes may employ different codons in order to express the same amino acid. An example of this is the V106M mutation that encodes resistance against NNRTIs in subtype C viruses, as opposed to V106A in subtype B. In other instances, viral RNA template sequences may vary between subtypes such that certain mutations are preferentially selected under drug pressure. As an example, subtype C viruses seem more prone to develop the K65R mutation that causes broad cross-resistance to a range of nucleoside compounds, whereas this mutation is very rare in subtype B viruses.

Conclusions: These findings have relevance for both treatment and prevention strategies in countries in which subtype C viruses are predominant.

Final abstract number: 38.001

Session: AIDS in Asia: The New Tsunami (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 302/303

AIDS in India

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HIV infection in India was first detected in 1986 among female sex workers in Chennai. Today it is estimated by National AIDS Control Organization (NACO) that there are about 3 million infections in India. Data clearly show that HIV has spread to all strata of Indian society. But unfortunately 80% of those who are infected are not aware of their status. Most diagnosis occurs at late stage of the disease in spite of more than 700 Voluntary Counseling and Testing Centre (VCTC) in the government and NGO sectors. This may be attributed to the persistence of stigma surrounding HIV and the belief that it is a disease of 'immoral' people like FSW, MSM, IDU etc. Although the epidemic was initially described among sex workers, the prevalence of HIV among them stabilized, because of targeted interventions for the last 10 years. The housewife is becoming the new face of AIDS as they are primarily put at risk by their husband's behavior.

The National AIDS Control Program (NACP) I in 1992 estd. NACO with the objective of HIV prevention, awareness and building capacity. NACP II in 1999 aimed to reduce blood borne HIV infections to less than 1%, increase awareness and condom use to more than 90% among those in sexually active age groups and Targeted Interventions for those at high risk. They also had established a strong political commitment by 1999. In 2007 the NACP III focused on care, support and treatment, strengthen infrastructure and put in place strategic information management system.

The Government of India rolled out free ART on April 1, 2004 and in three years there were 75,000 patients in the public sector on ART. The success and challenges faced in the fight against HIV epidemic in the public and NGO sector will be discussed.

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Session: AIDS in Asia: The New Tsunami (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 302/303

AIDS in Thailand

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HIV infection has been in Thailand for over 2 decades and has gone through series of changes both in a positive way and a negative way. After several years of initial denial, Thai government finally took a serious action against AIDS in 1990. The 2 main driving forces were the findings from the nationwide sentinel surveillance and the strong government leadership. Raising public awareness and mass prevention campaign were the strategic approaches. VCT centers were established throughout the country as well as the well known 100% Condom Use campaign. This resulted in drastic reduction of STD and new HIV infection. HIV prevalence in all risk groups as well as in general population reduced significantly except in IDU. New HIV infection reduced from as high as 150,000 per annum in early 1990's to 20,000 in mid-1990's. Large-scale antiretroviral treatment (ART) started in early 2,000's when the Thai Government Pharmaceutical Organization could produce several cheap generic antiretrovirals (ARV). Universal access to ARV became a policy since 2007. As of March 2008, 120,000 Thais are on government-subsidized ART program.

In spite of the all successes as mentioned, Thailand is facing many challenges. Continued political commitment is one of the most important challenge, especially the balance between prevention and care. It should implement each other instead of being mutually exclusive. Prevention effort has been severely weakened during the last 5-7 years resulting in recent rapid increase in STD and HIV prevalence among certain risk groups such as men having sex with men, youth and female sex workers. Late diagnosis of HIV infection is still a problem. Strategy towards provider-initiated HIV counseling and testing needs to be developed and implemented. HIV-related stigma and discrimination is one of the barriers for HIV testing as well as for accessing care. On the care side, treatment failure begins to emerge which will result in the need for the more expensive second-line drugs. Healthcare resources will become a big issue in the near future.

HIV/AIDS in Thailand can be lessons learned for many other countries although continued success needs regional and global efforts and advocacy.

Final abstract number: 38.003

Session: AIDS in Asia: The New Tsunami (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 302/303

AIDS Control in China

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HIV/AIDS were first detected in China in the mid 1980s among foreign travelers and hemophilia patients. The epidemics started among IDUs in southwest China in the late 1980s. The 2nd wave of the epidemic was in the paid plasma donors in central China in the mid 1990s. While the IDU epidemic keeps at a high but relatively stable level, sexual transmitted HIV cases in both CSW and MSM have increased rapidly in recent years. In 2007, sexual transmission has become the largest portion of newly reported HIV infection for the first time. All signs indicate that the HIV epidemic in China is at a turning point, spreading from high risk groups to the general population. By the end of 2007, the estimated number of HIV infected people in China was 700,000. In order to control AIDS, China has launched an impressive AIDS campaign, called Four Free One Care (free VCT, ART, PMTCT and education for AIDS affected children, living assistants to AIDS family). More high risk population has been tested and the positive ones have received various intervention package, including condom, methadone substitutions and needle exchange programs. More than 40,000 patients have been experienced triple drugs therapy and thousands of lives have been saved. Even though progress has been made, challenges remain at both societal and technical levels. The rapid increasing STI cases indicate further spread of HIV in the future. Due to drug toxicity and HIV resistance, over 20% of patients have stopped treatment. Additional effort and strategy are needed to further increasing prevention coverage in both high risk groups and general population. Only with enhancing scientific research and evidence-based strategy, can China seize the opportunity to stop AIDS at the critical time in China's AIDS control history. International collaboration between scientists, NGOs and governmental agencies will help China reaching her AIDS control goal earlier and better.

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Session: AIDS in Asia: The New Tsunami (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 302/303

AIDS in Malaysia

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Like many countries in the region, Malaysia's HIV epidemic has been predominantly driven by injecting drug use although latterly heterosexual transmission and transmission amongst MSM have been on the rise. The estimated adult prevalence of HIV infection is 0.4% with the last few years seeing a significant trend in the percentage of women becoming infected with women and girls making up almost 25% of newly reported HIV infections nationwide by the end of 2006. The estimated HIV prevalence amongst injecting drug users who are predominantly male range from 16-40% with continuing high rates of needle sharing and low usage of condom during sexual interactions.

Scaling up HIV prevention in Malaysia remains a significant challenge due to the existence of legislative and socio-cultural barriers. Nonetheless in recent years, harm reduction programs have become possible including the piloting of methadone maintenance and needle exchange programs. Efforts at scaling up both these programs nationwide are currently underway.

On the treatment front, Malaysia took the bold step of issuing compulsory licensing in 2001 and together with direct negotiation with pharmaceutical companies saw a marked decrease in the cost of many antiretroviral agents. This enabled free access to first line HAART therapy to those infected since. Nevertheless a large proportion of those eligible to treatment remain untreated due to various factors including poorer access in rural areas and the pervasive stigma and discrimination that prevents many from coming forward for medical care.

In conclusion, although significant progress has been made in the country's response to HIV/AIDS, scaling up prevention, treatment and care to meet Universal Access goals remain a challenge in this country.

Final abstract number: 39.001

Session: Antibiotic Practices and Resistance in Areas of Unstable Health Infrastructures (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 301

Antimicrobial Practices and Resistance in Pediatrics in an HIV Endemic Area of Cambodia

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Background: Major health problems of Cambodia include TB with 400-600 new cases per 100000/year, HIV/AIDS and *P. falciparum* resistant malaria. Concerning antibiotic policy, Ministry of Health guidelines exist and also WHO/UN/CDC guidelines are adopted in the clinical practice. The number of physicians is low due to genocide 25 years ago when 1,8 million of inhabitants and virtually all doctors, nurses and health care workers were executed. All antibiotic classes are available in the market, 90% of them generic, however with good quality, manufactured in Thailand and India and containing 85-100% of the original substances. Antiretrovirals, but not antibiotics, antituberculous and antimalarials are available for free from the government or NGO's.

Methods: Study participants were HIV positive Cambodian children treated with HAART (stavudine, lamivudine and nevirapine or efavirenz). We assessed antibiotic resistance rates in respiratory tract isolates (nose, pharyngeal, ear swabs) from 93 Cambodian previously ART naive children.

Results: Antibiotic resistance rates investigated in 93 Cambodian HIV infected children in 2007 were extremely high, including ESBL and Ciprofloxacin resistance in Enterobacteriaceae spp. up to 100% and MRSA up to 80% with biphasic tendency and sustained decrease of resistance with the increase of the population receiving HAART.

Conclusion: Reversibility of resistance among isolates from respiratory system was probably due to the reconstitution of their immune system due to the HAART and therefore less exposition with therapeutic antibiotics.

Final abstract number: 39.002

Session: Antibiotic Practices and Resistance in Areas of Unstable Health Infrastructures (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 301

Antibiotic Practices and Resistance in Genocide Areas of Darfur and Southern Sudan

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Background: Due to 21 years of civil war in southern Sudan and 5 years conflict of Darfur, health care infrastructure in southern and western Sudan was destroyed. St. Elizabeth University Tropical programmes involve 2 hospitals in South Darfur (Nyamlell, Gordim) and 2 in Bahr Al-Gazal in southern Sudan (Mapuordit, Marialou), with patient flow of 35.000 a year. Antibiotic policy is based on WHO guidelines in those hospitals but no community health service is available yet and vaccination was sporadic or none.

Methods: On the market 4 antimicrobial drugs are available as OTC - Doxycyclin, Ampicillin, Cotrimoxazole and Cloroquine. We have tested 400 isolates from patients from this area as of antibiotic free environment.

Results: All isolates of *Str. pneumoniae* were Penicillin susceptible, all *S. aureus* Oxacillin susceptible and all *S. pyogenes* Erytromycine susceptible. All *H. influenzae* isolates were susceptible to Ampicillin and all *E. coli* to Ciprofloxacin, all but one to Cotrimoxazole.

Tetracycline resistance vice versa in *S. aureus* and Streptococcus spp. isolates was up to 33%.

Conclusion: Antimicrobial resistance in respiratory pathogens is extremely low due to lack of antibiotics because of isolation during civil war. Tetracycline resistance is high because Doxycycline is extremely cheap and available.

Final abstract number: 39.003

Session: Antibiotic Practices and Resistance in Areas of Unstable Health Infrastructures (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 301

Antibiotic Practices and Resistance in a Rural Haitian Population Isolated by Previous Civil War Conflicts

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Background: Haiti was suffering from about 40 years of focal civil war conflicts when changing the dictatorship to a democratic government until 2004 and some rural areas have been cut from supply of health care services for several years. Antibiotics for infection were used only exceptionally except of TB which was merged in specialized state supplied TB centres.

Methods: We have cultured 500 consecutive outpatient department patients from Community Health Centre in Mole St. Nicolaus in north Haiti, in a rural area without road and only boat access. 139 respiratory isolates were transported by air to National Reference Laboratory of Antimicrobial Resistance in Nitra.

Results: All *S. aureus* isolates were Oxacillin and Rifampicin susceptible, all pneumococci were susceptible to Penicillin and 94% also to Doxycyclin. All but one of 32 *Str. pyogenes* were susceptible to Erytromycine.

Conclusion:

The incidence of antimicrobial resistance in rural Haiti is exceptional because of limited access to pharmacy and shops or gasoline stations selling antibiotics as OTC.

Final abstract number: 39.004

Session: Antibiotic Practices and Resistance in Areas of Unstable Health Infrastructures (invited)

Date/time: Saturday, 21 June, 2008, 15:45-17:45 hrs

Room: 301

Antibiotic Practices and Policies in Slums of Nairobi and Among Economic Refugees in Turbana Area

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Background: About one third of 6 million slum population in Nairobi live without regular access to drinking water and toilets. Gastrointestinal infections (both bacterial and parasitic) and respiratory diseases due to overcrowding, pollution and malnutrition are very common. All antibiotics are OTC and available from pharmacies owned by Indian pharmacists with good education, who often supply doctor advice, because the number of doctors is very limited.

Methods: Antimicrobial resistance was surveyed regularly in 1999-2007 at Mary Immaculate Clinic in Nairobi. Swabs were transported to the reference laboratory for antimicrobial resistance in Slovak Republic at University Hospital Nitra and tested with disc diffusion method according to the NCLS standards.

Results: We discovered increasing resistance in *Str. pneumoniae* to Penicillin, *S. aureus* to Oxacillin and *E. coli* to Cotrimoxazole. Prevalence of HIV was 12-16% with decreasing trend and major opportunistic infection was TB, candidiasis and *Salmonella/Amoeba* diarrhoea.

Conclusion: Factors that contribute to unfavourable trends in antimicrobial resistance has to be addressed by preventing the transmission of commonest infectious diseases and implementing proven effective rational drug use strategies (IMCI, DOTS). Unregulated drug availability, inadequate antimicrobial drug quality and surveillance must be addressed as well.

Final abstract number: 51.001

Session: The Role of Neutrophils in Infection (invited)

Date/time: Sunday, 22 June, 2008, 09:00-9:45 hrs

Room: Conference Hall 1-3

The Role of Neutrophils in Infection

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Polymorphonuclear leukocytes (PMN) represent the dominant cellular contributor to innate host response to infection, dramatically evidenced by the increased frequency and severity of infections in individuals with compromised numbers of normal PMN. In circulation, the unstimulated PMN remains in a resting state, with critical components of its antimicrobial machinery segregated into different subcellular compartments. Upon exposure to soluble host factors, microbial products, or microbes, the PMN phenotype rapidly transforms; first ingesting the microbe and thereby sequestering it in the phagosome, and then recruiting and activating a variety of responses targeted to kill and degrade the trapped microbe. This presentation aims to discuss some of the mechanisms underlying specific features of the PMN response within the context of innate immune response to and resolution of infection. Concomitant with PMN activation, membrane-bound granule compartments fuse with the nascent phagosome, thereby delivering enzymes as well as antimicrobial peptides directly to the microbe. Concurrently, the NADPH oxidase is assembled and activated at the phagosome membrane, generating reactive oxygen species that directly and indirectly contribute to microbial killing and degradation. Collectively, these orchestrated responses of the PMN create an intraphagosomal environment inhospitable to the phagocytosed microbe. The mechanisms underlying the generation and antimicrobial action of several bioactive species will be highlighted, as will the specific synergies between soluble circulating proteins and PMN responses that collaborate to eradicate invading microbes. PMN contribute to host defense in ways other than those directly associated with phagocytosis, as they release IL-8 and other chemokines to recruit additional immune cells to the fray and to modulate the antimicrobial activities of resident cells at the site of infection. Lastly, PMN direct biochemical and cellular events that contribute to the subsequent resolution of the inflammatory response, an essential step in returning to a homeostatic, resting state.

Final abstract number: 52.001

Session: Community-Acquired MRSA: What in the World is Going on? (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

The Origin and Evolution of MRSA

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Since the identification of the first methicillin resistant *S. aureus* (MRSA) isolate in 1961, there is extensive literature on its successful spread in the nosocomial setting, its incremental rise in antibiotic resistance and more recently, its emergence as a community associated pathogen spreading in otherwise healthy populations. Extensive genotyping of *S. aureus*, including genome sequencing of six MRSA strains, and determining the organization of the staphylococcal chromosomal cassettes that harbor the methicillin resistance gene, *mecA*, have identified six major pandemic clones that have spread along epidemic waves, consistent with the historic outbreaks caused by penicillin resistant in the 1950s. The current epidemic strain, commonly referred to as USA300, has aggressively spread across the United States causing an inordinate number of skin and soft tissue infections in diverse healthy populations ranging from children to senior citizens. Comparative genomic sequencing of 10 chosen USA300 isolates representative of different types of infections and from different regions of the US revealed the molecular scars of an epidemic strain that is rapidly changing. This lecture will discuss *S. aureus* epidemic waves and the current emergence of community associated MRSA.

Final abstract number: 52.002

Session: Community-Acquired MRSA: What in the World is Going on? (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

Evasion of Innate Host Defense by *Staphylococcus aureus*

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Human polymorphonuclear leukocytes (PMNs or neutrophils) are essential to the innate immune response against invading microorganisms. Although most bacteria are killed readily by PMNs, pathogens such as *Staphylococcus aureus* have evolved multiple mechanisms to circumvent destruction by neutrophils and thereby cause human infections. Notably, prominent community-associated methicillin-resistant *S. aureus* (CA-MRSA) strains have enhanced ability to evade killing by human PMNs and rapidly destroy these critical innate immune cells. CA-MRSA immune evasion is multifactorial and includes resistance to antimicrobial peptides, detoxification of neutrophil reactive oxygen species, production of cytolytic molecules, and reprogramming of normal neutrophil apoptosis or turnover. Collectively, the current data indicate enhanced CA-MRSA virulence is linked to evasion of killing by neutrophils, which likely underlies (at least in part) the ability of prominent CA-MRSA strains to cause disease in individuals without known risk factors for infection.

Final abstract number: 52.003

Session: Community-Acquired MRSA: What in the World is Going on? (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

Microbial Pathogenesis of Community-Acquired MRSA Infections

T.J. Foster

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Staphylococcus aureus is a commensal of the anterior nares. It permanently colonizes the moist squamous epithelium of about 20% of the population and intermittently colonizes another 60%. Several different bacterial surface proteins promote adhesion to desquamated nasal epithelial cells. Clumping factor B and iron-regulated surface determinant IsdA have been shown to stimulate efficient colonization of the nares of rodents, and in the case of ClfB, humans. ClfB binds to host cytokeratin 10 which is exposed on the surface of desquamated epithelial cells. When *S.aureus* breaches the skin it can cause both localized and invasive infections. The bacterium can express a plethora of surface-located and secreted molecules that promote infection. Surface proteins promote adhesion of bacteria to host cells and tissues. Surface polysaccharides and proteins help the bacterium to evade innate immune responses by inhibiting phagocytosis by neutrophils. The organism secretes proteins that can interfere with neutrophil migration and with complement fixation which reduces the level of opsonins. It can co-opt host proteases to destroy opsonins on the bacterial surface. Several different pore-forming toxins are secreted, some of which destroy neutrophils (alpha-toxin and Panton Valentine Leucocidin). If taken up by phagocytic cells *S.aureus* can resist intracellular killing mechanisms such as lysozyme, free oxygen radicals and antimicrobial peptides. *S.aureus* can secrete proteins called superantigens which trigger the activation of T cells in a manner that lacks the specificity of antigen presentation. This causes depletion of immune cells and the failure to mount a robust response with immunological memory and may help explain the recurrent nature of infections. This presentation will review current knowledge of the phenomena of colonization and disease pathogenesis gathered from studies with many strains of *S.aureus*. Reference will be made to CA-MRSA where appropriate.

Final abstract number: 52.004

Session: Community-Acquired MRSA: What in the World is Going on? (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: Conference Hall 2

Clinical Aspects of the Community-Acquired MRSA Epidemic

H. Chambers

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Prevalence of methicillin-resistant *Staphylococcus aureus*(MRSA) in the community is high and rising both in the United States and in other countries. USA300 and USA400, are the predominant community-associated MRSA (CA-MRSA) clones circulating in US communities. Enhanced transmissibility and fitness, and hypervirulence characterize and probably drive emergence of MRSA in the community. The burden of disease caused by MRSA in the community exceeds that occurring in hospitals. In addition, community strains of MRSA are now a major cause of hospital-onset infections. Identification of multiple-drug resistant variants of community MRSA strains is of particular concern. Emergence of CA-MRSA has a profound impact on choice of therapy for treatment of all staphylococcal infections. For those treated as out-patients, clinicians must increasingly rely on second line agents, often in the absence of good data supporting their effectiveness. For hospitalized patients, an inevitable consequence is even greater use of vancomycin. This will increase the already considerable pressure for selection of vancomycin non-susceptible strains. Use of vancomycin will likely be accompanied by a higher rate of treatment failure. Several alternative drugs are available for treatment of MRSA, but none of these has yet been shown to be superior to vancomycin. The search for new approaches to prevention and treatment of staphylococcal infections has never been more important.

Final abstract number: 53.001

Session: Partnering in R&D to Develop New Drugs for the Most Neglected Diseases (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: Plenary Theatre

OVERVIEW ABSTRACT FOR THE SYMPOSIUM:

Partnering in R&D to develop new drugs for the most neglected diseases

Description:

Tropical diseases such as chloroquine-resistant malaria, leishmaniasis, lymphatic filariasis, Chagas disease, human African trypanosomiasis (HAT), dengue fever, and schistosomiasis continue to cause significant morbidity and mortality worldwide. With few new treatments that tend to be unaffordable and poorly adapted to the field, physicians are forced to use old tropical medicines that are increasingly ineffective due to inevitable drug resistance. Together with tuberculosis and HIV/AIDS, these disabling and/or life-threatening diseases represent an enduring unmet medical need and are collectively called "neglected diseases".

Of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4% of the global disease burden. With exponential progress made in the basic knowledge of many infectious diseases, it is ironic that the drugs currently used to treat kinetoplastid diseases were discovered decades ago. With few exceptions, the wealth of basic research knowledge of these parasites is not being translated into practical applications.

Although the R&D landscape has significantly changed for neglected diseases since 2000, the need remains for new field-adapted drugs for the kinetoplastid diseases. Founded in 2003 to address the needs of patients with these most neglected diseases, DNDi (Drugs for Neglected Diseases initiative) is a collaborative, patients' needs-driven, not-for-profit drug R&D organization that is currently developing new treatments against sleeping sickness (human African trypanosomiasis, HAT), visceral leishmaniasis (VL), Chagas disease, and malaria.

The only way to improve control is to develop innovative new drugs and diagnostics and ensure they are available to patients. This symposium aims to review the opportunities and challenges ahead in the different phases of research and development of new drugs for the most neglected diseases.

Final abstract number: 54.001

Session: Extensively Drug-Resistant TB: New Name or New Problem (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: Banquet Hall

The Epidemiology of XDR TB in KwaZulu Natal South Africa: A New name or a New Problem

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Introduction: The description of the AIDS-related "Tugela Ferry" Outbreak (TFO) of XDR TB in KwaZulu Natal focused international attention on this province of South Africa as an epicenter of an XDR TB epidemic of unknown proportion. Similarly the global burden of TB drug-resistance, particularly in countries with the highest incidence of HIV and TB is for the most part unknown. Of >100 countries that are not capacitated to report TB resistance surveillance to WHO, the majority reside in Africa. Global estimates are therefore extrapolated from different sources. The South African MDR/XDR TB burden is similarly estimated and for the most part incomplete.

Discussion: An MDR TB survey of 2001 (MRC) estimated the burden of MDR TB at levels between 1-3% with isolated hotspots. It was not designed to estimate XDR TB and was a classic "point prevalence" study that sampled from limited sites. KZN has been the only South African province with an expanded portfolio of routine susceptibility testing for second-line drugs for all clinical isolates. "XDR" TB has been documented since the late 1980's and described in treatment cohorts admitted for care. These results will be presented. The TFO however recorded the highest cluster of individual cases ever reported and exposed the limitations of the current surveillance strategy that depended on periodic cross-sectional surveys. As a result the MRC has embarked on a rapid surveillance project identifying regions in the province where XDR TB has been identified and targeting these settings for an in-patient and out-patient surveillance project.

Conclusions: The recommendation for a continuous, expanded, country-wide surveillance system is self-evident if only to accurately inform the currently straining programmatic management of drug-resistant TB and to provide the early warning signals of programmatic failure.

Final abstract number: 54.002

Session: Extensively Drug-Resistant TB: New Name or New Problem (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: Banquet Hall

MDR-TB and XDR-TB in Asia

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It is estimated that there were 149,615 (95% CLs, 114,780-217,921) incident MDR-TB cases in South East Asia in 2006, 74% were in India while there were 152,694 (95% CLs, 119,886-188,014) incident MDR-TB cases in the the Western Pacific region in 2006, with almost 85% of these cases estimated to be in China. The proportion of XDR-TB among MDR-TB was highest in Japan, 30.9% followed by 14.6% in Hong Kong, SAR, 3.4% Philippines, 1.8% Korea, 1% Bangladesh, and one case each in Vietnam, India, China and Nepal. Population-based studies still have to be undertaken to know the real magnitude of XDR-TB.

Extensively drug-resistant TB (XDR-TB) was first described in 2006 in 40 Of 49 countries studied with 4% of MDR-TB isolates in the USA, 19% in Latvia and 15% in Korea among chronic cases. An outbreak of XDR-TB among 54 patients with a high prevalence of HIV in South Africa reported in 2006 was characterized by high early mortality of 98% and nosocomial transmission as well as transmission in the community. This outbreak demonstrated that XDR-TB is a threat to both TB and HIV control and emphasized the need for infection control measures in health facility settings. XDR, defined as MDR-TB plus simultaneous resistance to a fluoroquinolone and an injectable second line anti-TB drug, showed a cure rate that was significantly low and a failure rate that was high compared to other MDR-TB patients in Latvia. To respond to this crisis, the WHO Global Response plan 2007-2008 emphasized the need to strengthen basic DOTS and HIV programs, to scale up the programmatic management of MDR-TB, strengthen laboratory services to support M(X)DR-TB diagnosis, expand M(X)DR-TB surveillance to study trends and link with HIV, foster sound infection control, promote research on the development of new diagnostics, drugs, and vaccines. Much like MDR-TB which is the consequence of poor DOTS, XDR-TB is the consequence of poor MDR-TB management.

Final abstract number: 54.003

Session: Extensively Drug-Resistant TB: New Name or New Problem (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: Banquet Hall

Rapid Diagnosis of MDR-TB in Low-resource Settings

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According to the inverse-care law, the highest standard of care is least available to those most in need. Diagnosis of drug-resistant TB has long been a clear example of this phenomenon. In recent years a number of candidate diagnostic tests have been developed in both the academic and commercial sectors which present potential opportunities to aggressively address this inequity. This talk will discuss some of the currently available tools that are suitable for resource-limited settings, their relative merits and drawbacks, and a number of implementation challenges common to all, drawing on experience from Peru.

Final abstract number: 54.004

Session: Extensively Drug-Resistant TB: New Name or New Problem (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: Banquet Hall

The Epidemiology of MDR-TB in Peru

E. Gotuzzo

Instituto de Medicina Tropical 'Alexander Von Humboldt' , Lima, Peru

TB in Peru has been known since the pre-hispanic period in mummies.

Peru and Haiti has had the highest rate of prevalence in America (> 160 x 10⁵ per habitant), where more than 65% of cases of pulmonary TB has sputum positive.

Recently, the WHO recognized the Peruvian DOT as one of the best worldwide programs to have reach the two goals of the DOT (Diagnosis in more than 90% cases and cure rate more than 90%) decreasing the incidence in 5-6% per year in the last 10 years.

However, in the shanty towns of Lima, the rate of MDR-TB has being increasing in an important way, spreading to urban parts of the big cities. Leaving in the North of Lima has been noted as a risk factor, where the primary rate of MDR TB is 6%, while in the South of Lima is just 2%. The most know risk factors are having an intra-domiciliary TB contact and a treatment failure in the second of month of the first line therapy; others include Diabetes Mellitus, AIDS/HIV and health care workers. Also, 10-15% of MDR TB cases are XDR. This form of resistance has been detected in Peru since 1996.

We have an excellent DOT with very good outcomes, however, the paradox of having a sensible TB and a growth of MDR TB is no easy to explain.

We could try to explain the reasons due to a low prevalence of Beijing strain (<10%) and administrative delay in starting specific treatment of 12-15 months detected in the period of 1995 to 2003. This administrative delay happened because after a treatment failure to first and second line therapy, an overall of 12 months; at this moment, cultures and diagnosis for INH/Rifampin resistance were taken. The results took about 3 months, and it was then when we could start a specific treatment.

During all this time, is estimated that a TB patient could infect between 2 to 25 people. This situation could be the cause of infection in the homes, health centers care, patients in the ER with predisposition like AIDS/HIV and Diabetes, and Health Care Personnel that took care of this patients without an adequate protection. Newcomer's molecular studies could help to find the answers to this special situation.

Final abstract number: 55.001

Session: Controlling Japanese Encephalitis: Advances in Detection and Prevention (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: 304 / 305

Measuring Japanese Encephalitis Disease Burden: Challenges in Surveillance and Diagnostics

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Japanese encephalitis (JE) is a significant but solvable public health problem. Safe, effective, and affordable vaccines are available to prevent this devastating disease. However, the introduction or expansion of JE immunization programs is often delayed because disease burden is unknown or underestimated. In several countries where JE virus transmission has been proven and sporadic cases have been recognized, JE surveillance does not exist. In other countries, the quality and accuracy of existing surveillance data are uncertain. Although WHO has published JE surveillance standards, these guidelines have yet to be implemented in most countries.

Therefore, the numbers and characteristics of JE cases cannot be easily compared between countries or over time. In addition, long-term sequelae associated with JE are often not measured, resulting in an underestimate of the full economic and social impact of the disease. Most JE cases are diagnosed based on clinical syndrome (i.e., encephalitis) without laboratory confirmation. This practice can perpetuate established biases in the epidemiology of JE because cases are only reported from known endemic areas during predefined transmission seasons. As a result, JE may be underreported from areas that lack well-defined seasonal peaks in encephalitis cases, or among patients with unique clinical presentations (i.e., acute flaccid paralysis) or demographics (i.e., adults). In addition, encephalitis cases due to other etiologies are erroneously attributed to JE virus infection and sometimes misclassified as vaccine failures or vaccine-associated adverse events. Although many laboratories perform JE diagnostic testing, several steps are needed to ensure the accuracy, reliability, and comparability of the results. Laboratories supporting surveillance efforts should use validated diagnostic assays and standardized testing protocols with strong quality assurance and quality control programs. Improved surveillance with accurate laboratory-based diagnostics is an essential step for better understanding the epidemiology and true burden of JE, and for directing and evaluating effective immunization strategies.

Final abstract number: 55.002

Session: Controlling Japanese Encephalitis: Advances in Detection and Prevention (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: 304 / 305

Japanese Encephalitis in Indonesia: New Findings on Geographical Extent and Disability from the Disease

E.R. Sedyaningsih¹, S. Ompusunggu¹, S. Hills², N.K. Susilarini¹, V. Moniaga², A. Sasmito², D. Yuwono¹, G. Wahyuhono¹, M. Sembiring Maha¹, A. Suwandono¹

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Background: A two-year prospective study was conducted from January 2005 to December 2006 to estimate the magnitude of Japanese encephalitis (JE) disease burden in Indonesia. All children 15 years of age and under presenting with acute encephalitis syndrome (AES) to selected hospital and health center sites were identified and laboratory testing was conducted to confirm the proportion of cases due to JE virus infection. Epidemiological data were collected to improve understanding of JE disease in Indonesia.

Methods: Six provinces with different assumed risks for JE virus transmission were included. At fifteen hospital and health center sites, paired sera, cerebrospinal fluid samples, and at some sites filter paper specimens, were taken from patients who met the WHO criteria for AES. They were tested for antibody to JE and dengue viruses using immunoglobulin M antibody capture ELISA at the National Institute of Health Research and Development in Jakarta.

Results: 1496 AES patients (1401 from hospitals, 95 from health centers) were recorded. 74.9% (n = 1120) were <5 years old, and 57.6% (n = 862) were male. 82 patients (5.5%) had IgM antibody to JE virus: of these, 70.7 % (n = 58) were aged <5 years, and 56.1% (n = 46) were males. The average length of hospitalization of JE positive patients was significantly longer than those who tested JE negative (12.7 days and 8.8 days, respectively; p = 0.03); they were also more likely to suffer from sequelae than those without JE (RR = 3.12 ; p <0.001). Having pig rearing nearby (less than 5 km from the house) was the main risk factor associated with acute JE infection (p = 0.004). However, about half of the JE patients did not live close to a pig population, suggesting that other amplifying hosts such as water birds are also involved in JE virus transmission in Indonesia.

Conclusion: JE patients were found in all study sites, and sequelae were found in a high proportion of patients. A national program of JE vaccination is certainly worth consideration.

Final abstract number: 55.003

Session: Controlling Japanese Encephalitis: Advances in Detection and Prevention (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: 304 / 305

The Landscape of New Vaccines for Japanese Encephalitis: Country-Level Strategies for Introduction

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The first recorded major outbreak of Japanese encephalitis (JE) in Sri Lanka occurred in 1985-86 with 385 cases and 64 deaths in the North Central province. Outbreaks occurred in 1986-87 and 1987-88, the latter being the largest with 812 cases and 192 deaths in three adjoining districts. Cases occurred in rice cultivating areas with a network of irrigation canals supported by seasonal, moderate to heavy rainfall. Children aged 5-9 and young adults aged 20-24 years were predominantly affected.

JE was also spreading to new areas with previously low transmission. To cope with this emerging challenge, the Ministry of Health's Epidemiology Unit initiated phased JE immunization in 1988. Children aged 1-10 years were offered three primary doses and a booster of inactivated vaccine in the interpandemic period through a campaign approach. Over the years, JE incidence decreased as immunisation coverage increased. However, cases and occasional outbreaks were reported in other districts where immunization was not carried out, and the programme ultimately expanded to 18 districts. An increasing trend of adverse events following immunization with the inactivated JE vaccine threatened repercussions to the programme. Another obstacle was the increasing cost of the inactivated vaccine-US\$4.50 per dose in 2006, a prohibitive factor to programme sustainability. Identifying an affordable, safe and immunogenic vaccine alternative was a high priority.

The live, attenuated SA 14-14-2 JE vaccine (LJEV) appeared to be an appropriate, low cost, safe and potent alternative. With support from PATH, the Epidemiology Unit initiated a clinical trial in 2007 to ascertain the safety and immunogenicity of LJEV. Based on preliminary results, the government decided to introduce LJEV in place of the inactivated vaccine, hopefully expanding to routine EPI very soon.

Currently, the Ministry of Health is negotiating a public sector price for procurement of LJEV and finalizing the recommended schedule. Cost savings from transitioning to LJEV will enable the introduction of new vaccines and will extend the JE immunization programme to adults in high endemic areas

Final abstract number: 55.004

Session: Controlling Japanese Encephalitis: Advances in Detection and Prevention (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: 304 / 305

Japanese Encephalitis Control: What Can Be Achieved?

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World Health Organization, Geneva, Switzerland

JJE is the leading cause of viral neurological infection (encephalitis) in the Asian region, primarily affecting children aged 1-15 years in rural areas. JE vaccination has been successful in effectively controlling the disease in many countries where JE was identified as a public health problem, often linked to epidemic manifestation. These experiences show the way to successful JE control and, recently, several additional countries have started to introduce JE vaccination. Today, there is great opportunity to sustain and expand momentum for JE control through vaccination, building on recent advances achieved through country, WHO and partners' efforts, in particular PATH. Increasingly, countries are establishing surveillance to document the burden of disease. Live, attenuated vaccine has shown great potential in preventing disease and is becoming available in large volume at a highly preferential public-sector price. Additionally, promising JE vaccines under development should become licensed for pediatric use during the coming years. Moreover, cost-effectiveness analysis gives favorable figures in many country settings (estimated 75\$/DALY loss averted for GAVI-eligible countries), providing a strong rationale for vaccine introduction. Most important, however, is public and government recognition of the JE problem, and the will to take action.

To advance sustainable introduction of JE vaccination where it matters, priorities include documentation of disease burden -in particular in countries with no visible epidemics-and the establishment of a public sector reporting system. Building local capacity for strengthening JE surveillance, including quality-assured diagnostic laboratories, is key. The decision on vaccine introduction and optimal immunization strategy has to follow a rationale process as recommended for any other vaccine, with a particular emphasis on cost-effectiveness analysis and financial and managerial planning to sustain the effort beyond initial campaigns. This includes an assured vaccine procurement plan and an AEFI system to monitor vaccine safety.

Countries have shown leadership in introducing JE vaccination. Targeted financial and technical support from the international community can sustain and expand this momentum to develop a comprehensive control effort in all disease-endemic countries.

Final abstract number: 56.001

Session: International Perspectives on Palliative Care for People with HIV/AIDS (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: 302/303

International Perspectives on Hospice and Palliative Care for HIV/AIDS

S.R. Connor

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Hospice and palliative care is an essential component of the continuum of care for people living with HIV/AIDS. There is considerable symptom burden associated with HIV/AIDS throughout the course of the illness and palliative care is valuable both in optimizing functioning as well as at the end of life. In this presentation we will explore the extent of the need for palliative care in HIV/AIDS, the problems that are responsive to palliative care, the range of available palliative interventions, and how palliative care can be incorporated into ongoing anti-retroviral therapies. We will examine the differences between supportive and palliative care as well as the public health implications for palliative care. Where ever possible palliative care must not be a substitute for active disease therapy. Appropriate palliative care as defined by WHO, must include impeccable assessment and treatment of pain and other symptoms using an interdisciplinary team skilled in addressing all the dimensions of the human experience for PLWHVA's and those who care for them.

Final abstract number: 56.002

Session: International Perspectives on Palliative Care for People with HIV/AIDS (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: 302/303

Clinical Issues in Palliative Care for HIV/AIDS

E. Hamzah

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Over the past 40 years, palliative care has made inroads in healthcare services. Although it has its roots in the care of the dying and advanced cancer, it is slowly making an impact in the struggle against HIV/AIDS.

Clinical issues in dealing with HIV/AIDS needs to be considered along with the psychosocial, cultural, ethical and specific nature of the HIV/AIDS illness. The myriad of symptoms that may present in a patient needs to be individualised and take into account the resources available, the desired outcomes and whether the patient is in a hospital or community setting. The aim is to minimise the symptom load to improve the quality of life but palliative care services need to be tailored to the fluctuations of the disease as well as consider the possible reversibility of associated conditions.

In the setting of providing palliative care for HIV/AIDS in developing countries, much of the suffering of such patients could be addressed by integrating palliative care into the disease management programme of current service provision. Palliative Care complements the other medical treatments and with a holistic approach could assist those with controlled illness but also with those with advanced and dying of the illness.

Final abstract number: 56.003

Session: International Perspectives on Palliative Care for People with HIV/AIDS (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: 302/303

Successful Development in Hospice and Palliative Care in Asia

C.R. Goh

Lien Centre for Palliative Care, Singapore, Singapore

Hospice and Palliative Care services in Asia developed in the more economically developed countries in the 1980s. Countries like Japan, South Korea, Taiwan, Hong Kong and Singapore have relatively well developed palliative care services. In the 1990s services started developing in Malaysia, Indonesia and the Philippines, and good progress has been made in various centres in these countries, though overall coverage still needs to be improved. The Asia Pacific Hospice Palliative Care Network is a regional network of individuals and organizations which act as a resource for palliative care. Faculty from established palliative care services travel to resource-poor countries to help train trainers at the invitation of local organizations. One such project is in Vietnam where a 3-year Training of Trainers project organized by the Singapore International Foundation provided training in two palliative care units in Ho Chi Minh City and Hanoi in Vietnam. Together with simultaneous efforts by the Vietnam-CDC-Harvard group to provide a National Palliative Care Program for Vietnam, palliative care services for both cancer and HIV patients have been developed, and Vietnam is in the process of establishing its own National Association for Palliative Care. A further example of palliative care development in Thailand will also be presented.

Final abstract number: 56.004

Session: International Perspectives on Palliative Care for People with HIV/AIDS (invited)

Date/time: Sunday, 22 June, 2008, 10:15-12:15 hrs

Room: 302/303

National and International Measurement Opportunities

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The growing field of hospice and palliative care has been promoted most effectively in industrialized countries, where it has focused primarily on chronic illnesses such as cancer. However, in underdeveloped countries, HIV/AIDS represents a major public health problem. Despite aggressive prevention efforts and growing access to antiretrovirals, HIV/AIDS remains a fatal disease for many people. Therefore, there is growing international interest in applying principles of hospice and palliative care to improve the care that patients with HIV/AIDS receive near the end of life.

This symposium will provide an overview of worldwide hospice and palliative care efforts in HIV/AIDS, identifying key opportunities and challenges. First, presenters will describe common palliative care needs in this population, including estimates of the prevalence of pain and other symptoms. Next, presenters will trace the growth and development of HIV/AIDS-focused efforts to provide hospice and palliative care in resource-poor settings. Finally, presenters will describe two case studies of successful HIV/AIDS hospice programs in Southeast Asia.

Final abstract number: 58.001

Session: Emerging Infections: What Have We Learned After 15 Years? (invited)

Date/time: Sunday, 22 June, 2008, 14:30-15:15 hrs

Room: Conference Hall 1-3

Emerging Infections: What Have We Learned After 15 Years?

D. Heymann

WHO, Geneva, Switzerland

Infectious diseases are complex, dynamic, and constantly evolving. Examples during the past 15 years range from changes in transmission patterns of human monkeypox and dengue; more frequent re-emergence of cholera, legionnaire's disease, *E. coli* 0157, hepatitis C and, the haemorrhagic fevers - Marburg, Lassa and Ebola; and emergence of bovine spongiform encephalopathy (BSE), severe acute respiratory syndrome (SARS) and H5N1 influenza. Causes of emergence and re-emergence include weakened public health infrastructure, increases in human and domestic animal populations, rapid urbanization, and effects on the environment from global warming to deforestation and flooding. Human behavior also plays a major role, ranging from unsafe sexual practices to over- or under-prescribing of antimicrobial drugs, patient adherence, unregulated sale, and indiscriminate use in humans, plants and animals.

Emerging and re-emerging infections occur in a world where international travel and trade facilitate their spread, and where their impact affects economies as well as health. Attempts at regulation to prevent their international spread occurred first in the 14th century quarantines in Venice. They continued during the 19th and 20th centuries in Europe and the Americas through a series of conferences and conventions leading to the International Health Regulations. The goal of the Regulations is to strengthen national capacities to detect and respond to emerging or re-emerging infections when and where they occur, with the guarantee of a safety net of collective detection and response should they cross international borders.

The lesson over the past 15 years - whether from the global response to SARS or preparations for the next influenza pandemic - is that collective action will decrease our vulnerability, and increase our public health security. The challenge is to ensure resources for our collective action under the framework of the International Health Regulations.

Final abstract number: 59.001

Session: Treatment of Acute Otitis Media in Children - Never Simple (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

How to Evaluate Response to Treatment in AOM

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Background : Several studies have shown that watchful waiting management of acute otitis media (AOM) can be an alternative to immediate antibiotics. In practice, clinicians may be more comfortable using the watchful waiting option when the child has mild symptoms and the ear is not severely inflamed. Regarding clinical trials, standardized criteria for the diagnosis of AOM, and a clear description of TM findings has often been lacking, making interpretation of study results somewhat difficult. The objective of this paper will be to define AOM, review the development of an Ear Card methodology for assessing the child with AOM, and describe the effective use of the Ear Card in a clinical trial.

Methods : The Ear Card system for assessing the child with AOM was evaluated for concurrent correlation, sequence validity and reliability against previously published questionnaires. Responsiveness was assessed during a randomized clinical trial.

Results : The system demonstrated excellent sequence validity, concurrent correlation and reliability.

Conclusions : The Ear Card combines a parent assessment of severity using a faces scale and the clinician's assessment of the tympanic membrane to provide an evaluation of total AOM severity that can be used to characterize AOM signs and symptoms at enrollment and to evaluate a patients progress during treatment. For research, clinical investigators can be reliably trained using the Ear Card, so that clinical characteristics at enrollment and follow-up can be clearly defined and scored. The method is sufficiently sensitive to detect small differences in outcomes between treatment groups. The Ear Card has also been useful in teaching residents and students to accurately assess the tympanic membrane.

Clinicians, AOM researchers, and clinical educators from around the world have requested our copyrighted electronic version of the Ear Card, which may be freely used for patient care, teaching and research.

Final abstract number: 59.002

Session: Treatment of Acute Otitis Media in Children - Never Simple (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

Summary of Studies With New Antibiotics in AOM in Last Decade - Where Are We?

A. Arguedas

Instituto de Atención Pediátrica, San Jose, Costa Rica

In the last decade multiple clinical antimicrobials with new antibiotics have been performed in children. During this time, the design of the clinical trial improved dramatically to take into consideration multiple factors but always keeping as the most critical factor the resolution of signs and symptoms from the participant children. In this regard, trials have taken into consideration the use of innovative additional surrogate markers such as the value of a during treatment second tympanocentesis, the impact of the study medication on the nasopharyngeal flora and more recently the parents and children response to specific questions as a way to evaluate time to clinical resolution between agents or against placebo. Importantly, clinical trials have focused on those children that most likely require antimicrobial therapy either because they have a recurrent otitis media or they are therapeutic failures to standard OM therapy making these two sets of patients at high risk of having a resistant pathogen in the affected middle ear. Completed clinical trials have been presented or published in peer review journals with the main focus been the impact of these new compounds against resistant *S. pneumoniae* strains and against the other target MEF pathogens. In this regard, some of the trials that were performed and that will be described in detail in the presentation, include a study using single dose azithromycin, a regimen approved by the FDA but with current large limitation because of the rates of macrolide resistance; a high dose twice a day cefdinir that showed disappointing results against resistant *S. pneumoniae* and for *H. influenzae*; a new azithromycin formulation used as a larger dose that showed low eradication rates against macrolide resistant *S. pneumoniae* but a better eradication rate against *H. influenzae*; a recently completed trial with an oral carbapenem (faropenem) [results pending] and multiple trials with two promising quinolones for these problematic children presented as a pediatric formulation (gatifloxacin and levofloxacin) that showed a tremendous success but whose programs were put on hold by the sponsors. A pediatric program with telithromycin, a new ketolide with excellent invitro activity against penicillin and macrolide resistant *S. pneumoniae* was also put on hold by the sponsor. Currently the number of trials for otitis media are extremely limited however there are children with problematic antimicrobial resistant pathogens that need research programs in this area.

Final abstract number: 59.003

Session: Treatment of Acute Otitis Media in Children - Never Simple (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

What Do Antibiotics Really Do In AOM?

R. Dagan

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It is well recognized that appropriately chosen antibiotics enhance bacteriologic eradication in culture-positive AOM. It is also established that if bacteriologic eradication does not occur within 3-5 days of treatment, the risk of clinical failure at the end of the treatment increases ~ 5 fold. However, even with the 5-fold increase, over 50% of those from whom organisms were not eradicated after 3-5 days are still doing well at the end of treatment. New evidence demonstrates that among those who, despite failure of eradication after 3-5 days of treatment, have clinical improvement or cure at the end of treatment, recurrence of AOM occurs 35% more frequently than among those with eradication. Furthermore, in these cases only 34% will have new organisms, vs. 64% among those from whom bacteria were eradicated. New evidence also shows that nasopharyngeal (NP) carriage at initiation and/or at end of treatment is an independent major determinant of the outcome of AOM, with an independent additional role to that of MEF organisms. Antibiotics were shown to modify NP carriage at the end of treatment and thus play a major role in determining the nature of the following AOM in children. Thus, although the long term benefits of antibiotic use in AOM are not proven, the short term problems were demonstrated. This should be carefully weighted when deciding to treat a child with AOM.

Final abstract number: 59.004

Session: Treatment of Acute Otitis Media in Children - Never Simple (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: Conference Hall 2

Delayed Antibiotic Treatment of AOM - Risks and Benefits

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Delayed prescribing can take many forms but the Dutch originally developed the policy: their guidance was for no prescription for AOM unless there was significant otalgia and/or fever 72 hours after seeing the doctor, or if a prolonged discharge developed. They have shown in a large cohort study that if such an approach is used there are likely to be very few cases of complications. Delayed prescribing can help rationalise antibiotic use (with reductions in antibiotic use from 50-75%); changes beliefs in antibiotics - since prescribing antibiotics probably fuels a vicious circle of belief in antibiotics, subsequent reattendance, further antibiotic use etc.; achieves acceptable symptom control; and provides a back up and rapid access to antibiotics where there is uncertainty about which children will not recover quickly. There is weak ecological evidence from the UK and European studies that either localities or countries that have lower prescribing of antibiotics have higher admission rates for mastoiditis. Even assuming such ecological data does provide secure evidence of a genuine problem, the data suggests that several thousand prescriptions would be required to prevent one case of mastoiditis in affluent developed populations. The alternatives to delayed prescribing are all problematic: not to prescribe at all which is probably less safe; to prescribe in most or all cases which will lead to side effects, antibiotic resistance, and possibly more complications associated with antibiotic resistance; or to target antibiotics those likely to suffer prolonged illness or adverse events - but few clinical studies demonstrate such at risk groups, nor the benefit of antibiotics in such groups. Delayed prescribing can either be implemented in a number of ways - commonly by giving parents access to a prescription with clear guidance, or not to prescribe but advise patients to return for review if they are getting worse or not improving. The latter option provides the clinician with more control, but may result in higher reconsultation rates, and for no clear benefit.

Conclusion: Based on current evidence delayed prescribing has its place. If parents are provided with clear information - about the timing of antibiotic use, and what should trigger review, it is acceptable to parents, is reasonably safe, and provide a significant help in the battle against antibiotic resistance.

Final abstract number: 60.001

Session: Treatment of Infections Caused by Highly Drug-Resistant Bacteria (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Multi-resistant Enterobacteriaceae

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Resistance to multiple antimicrobial agents is becoming more frequently seen amongst the Enterobacteriaceae world-wide. Much of this is result of the accumulation of resistances inside integrons. Thus, resistance to penicillins, beta-lactamase inhibitor combination, cephalosporins, monobactams, carbapenems, fluoroquinolones, aminoglycosides, tetracyclines and folate antagonists can be found in various linked combinations within the family. The most problematic species is *Klebsiella pneumoniae* (KPNE), with *Escherichia coli* (ECOL) and *Enterobacter* species (ENTR) showing rising rates of multi-resistance. The increasing rates of linked resistance have created significant problems because of limited treatment choices. Options for treatment of serious infections caused by extended-spectrum beta-lactamase-(ESBL)-producing KPNE and ECOL include carbapenems, considered the drugs of choice by many, and, only if susceptible, fluoroquinolones. Aminoglycosides have not been favoured as the patients with multi-resistant strains are the most vulnerable to the toxic effects. Trimethoprim-sulfamethoxazole, if tested as susceptible, may be used for minor infections, but there is little published experience with its use in serious infections. Tetracyclines are generally not favoured for infections caused by Enterobacteriaceae. Carbapenems are also favoured for treatment of serious infections caused by ENTR. Again aminoglycosides have been used but have their attendant problems, including failure to prevent the emergence of stably-derepressed mutants when used in combination with third-generation cephalosporins. The recent emergence of carbapenemases in Enterobacteriaceae in some parts of the world, especially KPC series enzymes in KPNE and metallo-enzymes in a number of species, have left few viable options for treatment. Most experience has been gained with polymyxins, especially colistin methanosulfonate. However, doubts about the efficacy of this class remain, related both pharmacodynamics, and to the potential for resistance selection. The only readily available alternative is tigecycline, but there is limited experience with this agent and uncertainty about the adequacy of the current dosing regimens. The lack of novel agents active against Gram-negatives in the development pipeline heralds a bleak future for treating multi-resistant Enterobacteriaceae.

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Session: Treatment of Infections Caused by Highly Drug-Resistant Bacteria (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Carbapenem-resistant *Pseudomonas* and *Acinetobacter*

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Over the last decade infections caused by multi drug-resistant (MDR) gram-negative bacteria have become a continuing and growing problem in both developing and developed nations alike. Nosocomial infections caused by gram-negative bacteria, particularly *Klebsiella* spp., *E coli*, *P. aeruginosa*, and *Acinetobacter* spp. have become increasingly difficult to treat due to the rising incidence of drug resistance and the limited number of antimicrobial agents that are effective against them.

Acquired carbapenemases are increasingly reported in *Pseudomonas* and *Acinetobacter* isolates world wide. The emergence of these carbapenem-resistant *P aeruginosa* and *Acinetobacter* species has provided a particularly difficult challenge for clinicians with most carbapenemase producers being broadly resistant to beta-lactams, and many are also resistant to fluoroquinolones and aminoglycosides. Due to the lack of therapeutic options in these patients who are often critically ill, clinicians are often faced with using older and more toxic antibiotics such as polymyxins and minocycline. Sulbactam which has inherent activity against *A baumannii* has also been found to be useful in the treatment of these infections. Polymyxins are now being commonly used to treat these multi drug resistant *A baumannii* and *P aeruginosa* with variable success. Additionally, combination antimicrobial therapy is frequently employed to treat infections caused by such multidrug-resistant strains adding to the potential toxicity and cost of treatment. Clearly the ever growing threat of the rise MDR gram negative infections including carbapenem resistant *P. aeruginosa* and *Acinetobacter* spp cannot be answered by the development of new antimicrobial agents alone. A multi-pronged strategy that includes adherence to infection control principles and antimicrobial stewardship programs including rational use of current antimicrobial agents must remain the main stay of the response to this growing healthcare threat.

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Session: Treatment of Infections Caused by Highly Drug-Resistant Bacteria (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Ceftriaxone-resistant Salmonella

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Salmonella resistant to extended-spectrum cephalosporins (e.g. ceftriaxone) has become a worldwide problem, with over 43 countries reporting cases. These infections have been associated with increased risk of bloodstream infections, longer duration of hospitalization and pose a treatment challenge, particularly in children. Common mechanisms of this antimicrobial resistance are mediated by extended-spectrum beta-lactamases and plasmid-mediated cephalosporinases, with the CMY-2 being the most widely disseminated enzyme. In humans, Salmonella enterica serotypes Typhimurium, Enteritidis and Newport are the most common serovars associated with ceftriaxone resistance. The use of antimicrobial agents in livestock, including cattle, has been associated with the emergence of antimicrobial-resistant nontyphoidal Salmonella strains and with the dissemination and transmission of these strains to humans. In this presentation, an overview of the epidemiology, risk factors, antimicrobial resistance mechanisms and treatment outcomes of ceftriaxone-resistant Salmonella will be discussed.

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Session: Treatment of Infections Caused by Highly Drug-Resistant Bacteria (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: Banquet Hall

Fluoroquinolone-resistant Gonorrhea

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The rapid emergence of fluoroquinolone resistance among *Neisseria gonorrhoeae* isolates with a preexisting high prevalence of penicillin resistance in the past decade is of great concern. The prevalence of gonococcal resistance to ciprofloxacin has increased rapidly worldwide in the past few years, but this increase has varied considerably by country, ranging from 2.1% in Canada to 86.9% in China. In Taiwan, ciprofloxacin-resistant *N. gonorrhoeae* was first isolated in 1998. A remarkable increase in the prevalence of ciprofloxacin resistance was found between 2001 (66.7%) and 2003 (95.2%) at National Taiwan University Hospital. Previously established guidelines for the management of gonorrhea in adults in the United States and the United Kingdom recommended the use of a fluoroquinolone (e.g., ofloxacin, ciprofloxacin, or levofloxacin) as a first-line option for gonorrhea therapy. Failure of gonococcal infections caused by *N. gonorrhoeae* strains with resistance to ciprofloxacin to respond to treatment with these agents has been well documented. Accordingly, a fluoroquinolone is no longer a first-line option for the treatment of gonorrhea in many countries, particularly those with high incidence of fluoroquinolone resistance in gonococcal isolates. Spectinomycin and a cephalosporin (e.g., cefpodoxime or ceftriaxone) might be used as the first-line agent for the treatment of gonorrhea, although some gonococcal isolates exhibiting resistance to the above agents have been reported.

Final abstract number: 61.001

Session: Update on Clinically Significant Anaerobes (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 304/305

Antimicrobial Resistance Among Anaerobes -The European Experience

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Clinical usage of antimicrobial agents has been accompanied by the isolation of antimicrobial-resistant bacteria. During the last years there have been reports showing increasing numbers of anaerobic bacteria resistant to different antimicrobial agents in Europe. Resistance in anaerobic bacteria has a significant impact on the selection of antimicrobial agents for empirical therapy. The development of antibiotic resistance in anaerobic bacteria has been documented for beta-lactam drugs, clindamycin, macrolides, tetracyclines, fluoroquinolones and nitroimidazoles. The *Bacteroides fragilis* group is more resistant to antimicrobial agents than most other anaerobic bacteria. The *Bacteroides* genus and the genera *Prevotella* and *Porphyromonas* have become increasingly resistant to many anti-anaerobic agents. *Fusobacterium* strains resistant to beta-lactam drugs are relatively frequent. Resistant anaerobic cocci and *Propionibacterium acnes* have also been reported. Recently, fluoroquinolone-resistant *Clostridium difficile* strains producing three toxins (toxin A, toxin B and binary toxin) have been isolated from patients with severe *C. difficile* diseases.

The resistance mechanisms in anaerobic bacteria are: a) hydrolysis of the antimicrobial drug by several enzymes before reaching the site of action (most common, sometimes plasmid mediated); b) decreased permeability of the organisms; c) modification at the site of action of the antimicrobial agent; d) efflux mechanisms which eliminate the antimicrobial drug from the bacterial cell.

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Session: Update on Clinically Significant Anaerobes (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 304/305

Clostridium difficile Type O27, Coping with a More Virulent Strain

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Clostridium difficile (CD) is an anaerobic bacterium capable of forming spores which confer resistance to heating, drying and chemical agents, including disinfectants. Spores of CD may survive in the environment for long periods and are resistant to alcohol. More than 150 PCR ribotypes and 24 toxinotypes have been recognized; epidemic ribotypes may have enhanced sporulation. Since 2003, increasing rates of CD infections (CDI) have been reported in North America and Europe involving a more severe course, higher mortality, increased risk of relapse and more complications. The outbreaks are difficult to control and require a multifaceted approach. The most important infection control measures act on interruption of transmission of spores to vulnerable patients from infected patients and from the environment. Vulnerable patients are mainly patients who receive antimicrobial treatment, and therefore fewer antibiotic prescriptions should lead to less vulnerable patients. At present, no sufficient evidence exists to propagate the use of probiotics to vulnerable patients for prevention of CDI. Transmission of spores occurs mainly via contact of contaminated health care workers to patients, directly by patient-to-patient transmission or by transmission from the contaminated environment to patients. There is no direct evidence that patients or healthcare workers who are symptom-free but colonised with *C. difficile* in the intestinal tract are significant sources of infection. Early diagnosis of CDI, prompt isolation of symptomatic patients and reducing antimicrobial treatment are essential first steps. The infection control measures include recommendations to isolate infected patient on a single room with designated toilet, to apply proper hand hygiene with soap and water, to use appropriate protective clothing (gloves and aprons or gowns), to intensify environmental cleaning with a chlorine containing disinfectant and to take specific precautions for the use of devices (disposable or dedicated to individual patient). Patient isolation must continue at least until diarrhoea has ceased. Each hospital should have an appropriate surveillance system to recognize an increase of the incidence of CDI in an early stage. All infection control measures should be written in a local protocol so that additional measures can be carried out as soon as a problem with CDI arises. When outbreaks occur, additional recommendations include a reinforcement of general and hand washing measures, intensifying of testing patients with diarrhoea for *C. difficile*, reinforcement of environmental cleaning, information and education of health-care workers, cleaning department and visitors, cohorting of infected patients, and eventually closure of the unit followed by intensive environmental cleaning. Restricted antibiotic prescribing is also highly recommended to reduce polypharmacy and duration of administration. Second and third generations cephalosporins and more recently fluoroquinolones have been identified as potential risk factors. Although some hospitals report successes for enhanced environmental cleaning with potentially effective agents such as hydrogen peroxide vapour, the evidence is too scarce to consider this as an evidence-based approach.

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Session: Update on Clinically Significant Anaerobes (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 304/305

Molecular Biology of Protein Glycosylation in the Symbiotic Anaerobe *Bacteroides Fragilis*

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B. fragilis is one of the most abundant gram negative anaerobes living symbiotically in the human intestine, where it digests carbohydrates for the host and has been implicated in immune system development. It is also an opportunistic pathogen and a reservoir of antibiotic resistance genes. *B. fragilis* produces multiple capsular polysaccharides and fucosylated glycoproteins. Mutant strains deficient in production of either of these cannot compete with wild-type in colonization of germ-free mice, indicating that both types of molecule are vital for symbiosis. Here we characterize the molecular biology of the protein glycosylation system. A cell lysate was enriched for glycosylated proteins by lectin affinity chromatography and proteins identified by mass spectrometry. These candidates were expressed from a plasmid in *B. fragilis* with a C-terminal His tag, purified and glycosylation confirmed by periodate reactivity and release of oligosaccharides. The glycoproteins include a secreted lipoprotein and several soluble periplasmic proteins, the first time that the latter has been observed in a bacterial species. Deletion of a genetic region containing a gene resembling an O-antigen flippase and multiple glycosyltransferases reduced the MW of the glycoproteins, indicating that these genes are involved in protein glycosylation and suggesting that it occurs in the periplasm. The smallest and most abundant glycoprotein was investigated in detail. Similar glycans were released by beta-elimination and hydrazinolysis, consistent with O-linkage to Ser or Thr. Point mutations in peptides that were rarely or never observed by mass spectrometry, and therefore likely to be glycosylated, identified one Ser and three Thr residues as probable glycosylation sites. Deletion of the signal peptide prevented glycosylation of the protein, consistent with it occurring in the periplasm. We continue to investigate the biochemistry and genetics of the glycosylation system, the biological functions of the glycoproteins and the role of glycosylation.

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Session: Update on Clinically Significant Anaerobes (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 304/305

Anaerobes As Biofilms

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Although anaerobes are predominant in humans, largely outnumbering aerobic bacteria, experimental data concerning their biofilm forming ability are still relatively few and essentially focused on the anaerobic flora of the mouth (including dental plaque, buccal mucosa and tongue biofilm) and the vaginal mucosa.

As the oral environment is concerned, its complexity has induced the development of a number of artificial mouth models able to simulate the different conditions of microbial growth within the microcosms of the oral cavity. With regards to the vaginal mucosa, recent studies have elucidated that the biofilm phenotype confers to *Gardnerella vaginalis* a survival advantage in the presence of hydrogen peroxide and lactic acid producing resident lactobacilli; on the other hand, the ability of probiotic strains of *Lactobacillus* to interfere with *Gardnerella vaginalis* and disrupt its biofilm, has been recently reported as a promising tool to reduce the need for antibiotics in the treatment of bacterial vaginosis.

As the intestinal tract is concerned, investigations by microscopic and FISH techniques have shown that mucosal bacteria, including bacteroides and bifidobacteria, occur in microcolonies and are distributed throughout the mucus layer.

Our group is currently investigating the role of anaerobes in the occlusion of biliary stents. SEM observations revealed that biliary sludge occluding the lumen of the 18 so far examined polyethylene stents was constituted by a multispecies (aerobes and anaerobes) microbial biofilm immersed in an amorphous material containing also dietary fibers and crystals of bile salts. The ability of the isolated anaerobic strains, belonging to the species *Bacteroides*, *Clostridium*, *Fusobacterium*, *Peptostreptococcus*, *Prevotella* and *Veillonella*, to form biofilm has been assessed in vitro. On the light of the higher antibiotic-resistance reported in biofilm-growing bacteria, our findings on the role of anaerobes in the occluding process should be considered in selecting and dosing antibiotics for the prophylaxis of biliary stent blockage.

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Session: Antiretrovirals for Prevention of HIV (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 302/303

Can Expanded Treatment Slow the AIDS Epidemic? The Public Health Perspective

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The introduction of antiretroviral therapy has changed the course of HIV disease by improving survival rates. But ART has equal potential for prevention, since it reduces the HIV RNA level and the probability of HIV transmission from an infected person to their sexual partners. Currently NIH is undertaking a large randomized clinical trial (HPNT052) in serodiscordant couples to study the effect of antiretroviral therapy in preventing HIV transmission to their partner. Although there have been no randomized controlled clinical trials on the subject, antiretroviral drugs are currently used in clinical practice for post-exposure prophylaxis after inadvertent occupational exposure or after sexual exposure to the virus. The success story in using antiretrovirals for HIV prevention has been shown from trials involving Mother to child HIV transmission interventions. Hence Can Expanded Treatment through the Public Health approach slow the AIDS Epidemic?

Final abstract number: 62.002

Session: Antiretrovirals for Prevention of HIV (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 302/303

Can Expanded Treatment Slow the AIDS Epidemic? The Behavioral Scientist's View

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This presentation explores existing and potential behavioral and social science contributions to consideration of the impacts of expanded antiretroviral (ARV) scale-up on the global HIV epidemic. Behavioral science literature commonly evaluates sexual behavior ("risk compensation") and medication adherence. While such analyses are critical to evaluation of overall impact and will be reviewed here, the presenter seeks to highlight approaches and empirical research that set (and sometimes problematize) such typically individually-based approaches in their social, cultural, political, economic, and human-rights/ethical contexts. It, furthermore, brings behavioral and social science contributions to bear on the critical question of: "how do we define and measure success?" The presentation addresses the ways in which interdisciplinary behavioral and social science work can illuminate key questions about feasibility and sustainability as well as "unintended consequences" of these biomedical interventions on non-biomedical HIV prevention interventions and social and health systems. From a practical standpoint, such analyses can 1) assist identification of appropriate methods and criteria to evaluate impacts; 2) assist targeting and revision of patient and community educational materials and involvement strategies; and 3) aid development of uptake, retention and medication and general program adherence schemes that more explicitly address economic, cultural, and social barriers. A systematic analysis of lay media (primarily print sources) about recent ARV scale-up will be used as a case study to demonstrate how social/behavioral science perspectives may shed light on popular conceptions of such programs and technologies, how scientific information is interpreted by media and the general public, and how consequential misconceptions may arise. In the overall presentation, special emphasis is placed on examination of approaches and perspectives that are likely to inform questions and solutions relevant to both ARV treatment and biomedical prevention technologies under testing, particularly implementation of ARV pre-exposure prophylaxis.

Final abstract number: 62.003

Session: Antiretrovirals for Prevention of HIV (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 302/303

Antivirals in Uninfected People: PrEP and PEP

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Background: With the exception of male circumcision and some behavioural interventions, randomised controlled trials (RCTs) of HIV prevention interventions have reported disappointing results. In this presentation, data on post-exposure prophylaxis (PEP, the provision of anti-retrovirals (ARVs) after exposure to prevent HIV infection) and pre-exposure prophylaxis (Pre-EP, ARVs provided before exposure to prevent infection) will be reviewed.

Methods: A guided literature review on the efficacy, cost-effectiveness, implementation policy and likely public health impact of PEP and pre-EP was conducted.

Results: No RCTs examining the efficacy of PEP were identified. Nevertheless, a variety of animal and observational evidence suggests that PEP prescribed within 72 hours of HIV exposure is likely to substantially reduce the risk of HIV transmission. PEP use at the population level is generally not cost-effective, unless its use is highly targeted towards the highest risk exposures. Despite these limitations, policies recommending PEP after sexual and other HIV exposures exist in many settings. Although it is possible that post-EP may prevent cases of transmission, a substantial public health impact on the HIV epidemic is unlikely. RCTs evaluating the efficacy of Pre-EP are currently underway in a number of settings. Animal data strongly suggest that Pre-EP will need to consist of combinations of more than one ARV. The cost effectiveness of Pre-EP will depend strongly on the risk setting. No locations were identified which currently recommend Pre-EP, and there has been little study of the potential public health impact of this preventive intervention.

Conclusion: PEP is being increasingly utilized as a form of HIV prevention, despite the lack of any efficacy data from RCTs. On the other hand, RCTs will soon establish whether Pre-EP is an effective means of HIV prevention. If Pre-EP is proven effective, there will be substantial challenges in formulating a policy framework to guide its use.

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Session: Antiretrovirals for Prevention of HIV (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 302/303

Antivirals for HIV Prevention

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The possibility that antiretroviral drugs may be useful for HIV prevention has been suggested by animal studies that have documented that if these medications are used before or after a retroviral challenge, they can protect against the development of HIV infection. Epidemiological studies in HIV discordant couples suggest that individuals with lower plasma RNA levels are less likely to transmit HIV to their sexual partners. These findings have lent support to new HIV prevention approaches that include the evaluation of the use of pre- and post-exposure prophylaxis (PrEP and PEP) in high risk HIV-uninfected persons, and studies of the use of antiretroviral drugs to lower plasma RNA in people who are in discordant couples, in order to decrease the likelihood of HIV transmission. Questions that remain to be addressed include whether the benefits of decreasing HIV transmission are offset by behavioral disinhibition, drug toxicities, and costs. An additional set of important considerations include the timing and duration of antiretroviral drug use and whether these compounds are best used as topical microbicides applied to the cervicovaginal or rectal mucosa, or whether oral chemoprophylaxis is more effective. Over the next few years, several thousand at risk persons will be evaluated in efficacy trials to address the optimal uses of antiretroviral medications for HIV prevention.

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Session: Emerging Rickettsioses in Asia (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 301

Spotted Group Rickettsioses in Asia

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Tick-borne rickettsial diseases are usually called spotted fevers. Their agents, rickettsiae from spotted fever group (SFG), are obligate intracellular bacteria widespread in nature and associated with parasitic blood-feeding arthropods. Ixodid ticks are common human parasites and they may host different microbial pathogens that are often transmitted via ticks feeding on humans. Humans are not natural hosts in rickettsial lifecycle, but due to high frequency of tick bites, the incidence of tick-borne diseases, including rickettsiosis, may be very high. A vast Asiatic territory with different biotopes harbors lots of natural foci of multiple tick species. For the moment, 9 rickettsial diseases are more or less regularly reported in Asia and 2 more rickettsial species potentially associated with human illnesses were found. Rickettsiae recognized as human pathogens are *R. conorii indica*, agent of Indian tick typhus (India), *R. sibirica sibirica*, agent of Siberian tick typhus (Eastern Russia, Mongolia, China), *R. heilongjiangensis*, agent of Far Eastern tick-borne rickettsiosis (Eastern Russia, Northern China), *R. japonica*, agent of Japanese spotted fever (Japan, Korea), *R. sibirica mongolitimonae* (Northern China), agent of LAR (Lymphangitis-associated rickettsiosis), *R. aeschlimannii*, unnamed spotted fever (Kazakhstan), *R. raoultii*, unnamed rickettsiosis (Eastern Russia), *R. honei*, Thai tick typhus (Malaysia, Thailand, Laos) and *Candidatus Rickettsia kellyi*, unnamed rickettsiosis (India). Suggested pathogenicity were reported for *R. helvetica* found in Japan and *R. tamurae* (Japan, Laos). Studies show that in some regions, the seropositivity rate for SFG is as high as 57% for certain population groups. The real role of tick-borne rickettsiosis in human pathology also may be shaded by lack of diagnostic facilities and methods in some countries, misdiagnosing with scrub typhus, murine typhus, dengue fever and other clinically resembling entities.

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Session: Emerging Rickettsioses in Asia (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 301

Scrub Typhus

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Scrub typhus is recently recognized as a common cause of acute fever in rural Asia. Clinical presentations of scrub typhus vary widely from acute flu-like syndrome, with or without signs of organ dysfunction such as jaundice or renal insufficiency, to multi-organ dysfunction mimicking sepsis syndrome. Acute undifferentiated fever (AUF) with or without organ dysfunction is the major clinical presentation of scrub typhus. The incidence of scrub typhus ranged from 1.1 to 19.3% in various studies conducted in indigenous patients who presented with AUF in rural hospitals in Malaysia, Indonesia and Thailand. The incidence of scrub typhus, murine typhus, and SFG rickettsioses was 7.8%, 2.4%, and 5% respectively in a recent study conducted in patients with AUF who presented with severe manifestations in Thailand. Jaundice, renal dysfunction, abnormal chest radiography on admission occurred in 21%, 35.7%, and 50% respectively in patients with severe scrub typhus. Multiorgan dysfunction or sepsis occurred in 14%. Clinical spectrum of severe murine typhus and SFG rickettsioses were similar to scrub typhus. The reported mortality of severe scrub typhus varied from 2.4% to 16.7%.

Awareness that scrub typhus is one of the common cause of AUF in adults in rural Asia improves the probability of an accurate clinical diagnosis. Early recognition and appropriate treatment reduce morbidity and mortality. Results from recent clinical studies from Thailand indicate that rational antimicrobial therapy would be doxycycline in mild cases and a combination of either cefotaxime or ceftriaxone and doxycycline in severe cases. Azithromycin could be considered as an alternative treatment when ever doxycycline allergy is suspected. This would be either curative, or have no ill-effect, in the majority of instances. Failure to improve or defervesce within the next 48 hours would indicate the need to a thorough reevaluation of clinical findings and initial laboratory investigation results and a need to change antibiotic.

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Session: Emerging Rickettsioses in Asia (invited)

Date/time: Sunday, 22 June, 2008, 15:45-17:45 hrs

Room: 301

Different Clinical Expression of Murine Typhus and Scrub Typhus

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The clinical epidemiology of scrub and murine typhus in Laos will be reviewed. Both diseases are common causes of uncomplicated fevers but also present with more severe disease - jaundice, dyspnoea and impaired consciousness. Patients with murine typhus had a lower frequency of peripheral lymphadenopathy than those with scrub typhus. Data on the differential distribution of IgG antibodies against these diseases, amongst Lao people, will also be presented.