Plenary & Symposia Abstracts

17th International Congress on Infectious Diseases
Hyderabad · India · 2016
Streptococcal lymphatic metastasis: Bacterial close encounters of the fourth kind

S. Sriskandan
Imperial College, London, United Kingdom

Abstract: Anatomists of the 17th century described the milky ‘vasa lymphatica’ as the fourth kind of vessel, the first three kinds being arteries, veins and nerves which were, at the time, considered as such. The subsequent centuries demonstrated a role for these in transport of interstitial fluid and cells, as well as a conduit for larger molecules and tumour metastasis. Long recognised as a barrier or as a conduit for infectious pathogens travelling within leukocytes, research has focussed on the interaction of the lymphatic system with intracellular microbes; from plague and tuberculosis, to viruses and parasites. The potential for extracellular bacteria to access this system has been largely ignored, as an accidental consequence of normal interstitial fluid transport. Group A streptococcus, a virulent human pathogen that is known for its capacity to disseminate systemically, can rapidly access the lymphatic system and local lymph nodes via a hitherto unrecognised but specific interaction between its hyaluronan capsule, and the lymphatic endothelial receptor LYVE-1. The consequences of this for infection pathogenesis and immunity, are emerging areas of research that are important not only for streptococci, but for other major bacterial pathogens.
Global burden of pneumonia

K. Thomas
Pondichery Institute of Medical Sciences, Vellore, India

Abstract: Global community his committed to achieving measurable Global Development Goals (MDG). MDG 4 is specifically dealing with reducing child mortality. Pneumonia and Diarrhea are perhaps two very important contributing causes of child mortality globally. While many developed countries have managed to achieve the MD4 targets, most of devolving countries far behind in achieving this important goal. Measuring pneumonia burden is difficult since there is wide variation in its presentation particularly in children and the multiple etiological agents associated with the disease. It is also well known that clinical signs of malaria and measles overlap with those of pneumonia and there is lack of clinical signs in malnourished children leading to misclassification error. However, a number of well conducted studies1,2,3,4,5 recently have made it possible to arrive at reasonable estimates of pneumonia burden particularly for preventable disease at both global levels and regional levels. Black et al1 through a systematic analysis of data on mortality as the starting point estimated that there is nearly 8.795 million under 5 mortality globally. Of this more than 726 million (52%) occurred in the Sub-Saharan region and in the Indian subcontinent contributed mainly by 5 countries, India, Nigeria, DR. Congo, Pakistan and Afghanistan. Global Pneumonia mortality was estimated to be 1.575 million globally. The Indian component of this global mortality was estimated to be 0.371 million (~23%). The Child Health Epidemiology Reference Group (CHERG) 2 established by WHO arrived at estimates not much different from the earlier results in 2012. They estimated the global burden of pneumonia death in under 5 to be 1.396 million. In this study India contributed to 43 million pneumonia episodes leading to 0.397 million under 5 deaths.
Community-acquired pneumonia in children under five years of age: An overview
S. Awashti
King George's University Hospital, Lucknow, India

Abstract: Burden of disease: South East Asia, and India in particular, is reported to have the highest burden of community-acquired pneumonia (CAP) in children <5 years of age. Annually there are about 43 million new CAP. According to NHFS-3, CAP in preceding 2 weeks was reported in 5.8% children. About 10% of acute respiratory illnesses are classified as CAP, translating into 0.2 -0.5 episodes per child-year and approximately 10 to 20 per cent of these episodes tend to be severe. India has a CAP mortality rate of about 322 per 100 000 under-five population. Mortality varies by severity of disease, ranging from 1% - 15.8%.

Health care seeking practices: Awasthi et al (2015) reported that fast breathing, an early sign of CAP, was not commonly recognized by care givers as well as grass root health care providers. Also, they did not look of respiratory rate and chest in-drawing. Village based rural medical practitioner was the preferred health-care provider. By the time the most serious cases reached a public tertiary-care hospital, children had been ill for a week and treated by 2-3 providers. Quality of care at government facilities was deemed poor by caregivers. Similar situation is seen across the country.

Causative organisms: A few studies done in India to assess the etiological organisms of CAP have reported low yield of blood cultures (about 2%) and higher yield of nasopharyngeal swabs (NPS) (13.7 - 40%) for bacteria, namely Streptococcus pneumoniae (SP), Hemophilus influenza and Staphylococcus aureus (SA)). In blood culture, however, the leading organism was SA followed by SP. The studies have reported high yield of viruses from NPS. Hence mixed viral and bacterial infections resulting in CAP presentation has been speculated.

Associates of mortality: In India CAP related mortality is associated with malnutrition, anemia, younger age, delayed care seeking, lower spO2 <95% and presence of consolidation on Chest X-ray.

Existing CAP Management scenario: The Government of India is largely moving from the use of co-trimoxazole to that of amoxicillin for the treatment of CAP, as recommended by the UNICEF. However, adherence of these guidelines is poor by medical practitioners. The public health facilities like the CHC and the PHC are not admitting cases of pediatric CAP in the high burden states of India.

Future Directions: It is essential to work for the primary prevention of CAP by adequate immunization, improving nutritional status and hygiene. Community awareness about CAP has to increase and public health system has to be responsive and patient friendly. There has to adherence to CAP treatment guidelines. These initiatives must be taken simultaneously, early and effectively.
Prevention of childhood pneumonia through vaccination

R. Dagan
Soroka University Medical Center, Beer-Sheva, Israel

Abstract: Pneumonia is the most important killer of children <5 years old nowadays and the most important bacterial organism in early childhood pneumonia is *S. pneumoniae*. When trying to determine the extent of potential reduction of pneumonia burden in children one encounters real difficulties, some of which are the absence of definition of pneumonia, the absence of radiologic diagnosis of pneumonia, the differences between populations, the paucity of positive cultures and environmental considerations that could determine outcome of pneumonia and antibiotic use. Initially, efficacy studies were aimed mainly at invasive pneumococcal pneumonia (*S. pneumoniae* usually isolated from blood or pleural fluid) or alveolar pneumonia (mostly identified with bacterial pneumonia when organisms were not included). However, using PCVs, we have learned within 2 decades from a variety of advanced studies and introduction to the National Immunization Program, that PCVs impact on prevention of respiratory infections much beyond what was expected (Using PCVs to learn about pneumococcal involvement in disease and vaccination impact is termed “PCV vaccine probe studies”). We currently can point out to the remarkable impact of PCVs on the following pneumonia-related endpoints: Reduction of invasive pneumococcal pneumonia, culture-negative alveolar pneumonia, all-cause pneumonia, all-cause lower respiratory infections, bacterial-viral mixed infections, pleuropneumonia and more. Moreover, PCVs reduce carriage and spread of vaccine type pneumococcal strains, resulting in protection not only among the vaccinated children but also from diseases in all ages (herd protection). Influenza vaccines may in turn reduce pneumonia through the reduction of acute influenza illness, often responsible for severe secondary bacterial infections. However, studies demonstrating this effect are lagging behind the studies with PCVs.
The path to pneumonia prevention in India - Call to action
R. Kumar
Reproductive and Child Health, Delhi, India

Abstract: (no abstract received from presenter)
The burden of dengue: Insights from large scale clinical studies

O. Brady
University of Oxford, Oxford, United Kingdom

Abstract: (no abstract received from presenter)
Recent update on dengue vaccine development

P. Pitisuttiithum
Mahidol University, Bangkok, Thailand

Abstract: (no abstract received from presenter)
Dengue vaccination impact: Perspective from modeling

T. Hladish
University of Florida, Gainesville, FL, USA

Abstract: (no abstract received from presenter)
Roadmap for dengue vaccination introduction in Mexico

M. Betancourt-Cravioto
Fundacion Carlos Slim, Mexico City, Mexico

Abstract: (no abstract received from presenter)
Non-molecular detection of carbapenemases in Enterobacteriaceae clinical isolates

L. Martinez-Martinez
Universidad de Cantabria, Santander, Spain

Abstract: Reliable and accurate detection of carbapenemase-producing enterobacteria (CPE) is based on both non-molecular (phenotypic) and molecular methods. The obvious first step is recognition of carbapenem resistance using clinical breakpoints (EUCAST/CLSI); however, as some susceptible enterobacteria can still produce a carbapenemase, screening criteria (as defined by EUCAST), whole pattern of β-lactam resistance and simultaneous resistance to other families should also be considered. Care should be taken when using automatic methods, which may produce false susceptibility results for CPE. Metallo-β-lactamases (MBL, Class B) do not hydrolyze monobactams, while OXA-48-like (O48L, Class D) enzymes cause resistance to temocillin and piperacillin-tazobactam and are poorly active against expanded-spectrum cephalosporins. Importantly, CPE may also produce other β-lactamases (i.e., extended-spectrum β-lactamases, ESBL), which determine very complex phenotypic patterns. KPC (Class A) carbapenemases are inhibited by boronic acid derivatives, while MBL are inhibited by EDTA, 1,10-phenanthroline, thiol compounds and dipicolinic acid. Comparison of zones around discs of carbapenems (usually meropenem) alone or with the indicated inhibitors will suggest the presence of a certain carbapenemase class, and help to exclude other mechanisms of carbapenem resistance (i.e. porin loss plus AmpC/ESBL production). Other smart approaches have also been designed based on the inhibition activity of the indicated compounds. Detection of carbapenemases can be made demonstrating their hydrolytic activity against carbapenems using bioassays (several variants of the modified Hodge test or the so-called carbapenem inhibition method), colorimetric assays (Carba NP and Carba Blue), MALDI-Tof or spectrophotometry. Immunochromatography assays (including commercial versions for some enzymes) have been designed for IMP-, OXA- and KPC-type carbapenemases. Recently, an electrochemical device (BYG carba test) has been designed for rapid carbapenemase detection. Carbapenemase-producing Enterobacteria can be selectively cultured using carbapenem-containing media. Clinical samples can be pre-incubated in a liquid medium with a commercial carbapenem disk, then subcultured on MacConkey agar with imipenem or on any of the multiple version of the commercially available chromogenic media (ChromID variants, Supercarba, CHROMagar KPC, HardyCHROM Carbapenemase, Brilliance CRE...). Once bacteria have grown, carbapenemase can be detected using phenotypic or molecular methods. Every laboratory should decide about the more convenient algorithm for detecting CPE, taking into account the incubation time needed for methods based on culture (including bioassays and disc approaches), the usefulness of rapid methods (such as colorimetric assays, MALDI-Tof or immunochromatography) and the need of molecular assays for definitive identification of concrete enzymes.
Molecular diagnosis of carbapenemase producing Enterobacteriaceae infection
Y. Ishii
Toho University School of Medicine, Tokyo, Japan

Abstract: The gold standard for diagnostics of infectious diseases and detection of antibiotic resistant organisms are culture and antibiotic susceptibility testing respectively. However, culture is sometimes unsuccessful because patients have been treated with antibiotics or are infected with unculturable or difficult to culture microorganisms. Antigen detection using an immunochromatographical technique is a simple and rapid method that has been used for the diagnosis of infectious diseases such as Legionnaires’ disease, pneumococcal infection, and Mycoplasma pneumonia. We have already constructed a system for detecting carbapenemases in Acinetobacter spp. such as the OXA-23 group, OXA-24/40 group, OXA-51 group and OXA-58 group. However, this system is not able to detect carbapenemases directly from clinical specimens. Multiplex PCR is a useful technique for active surveillance or targeted surveillance of carbapenemase encoding genes in Enterobacteriaceae. However, novel or mutated carbapenemase genes cannot be detected by PCR. On the other hand, next generation sequencing (NGS) is a powerful tool for the diagnosis of infectious diseases and enables a comprehensive search for antibiotic resistant genes. Whole genome sequence (WGS) data or Meta genome sequence (MGS) data is provided from bacterial colony or clinical specimens, respectively. In this presentation, I will discuss novel techniques for the diagnosis of infectious diseases caused by carbapenemase producing infections.
Control of carbapenem-resistant Enterobacteriaceae
S. Munoz-Price
Froedtert and the Medical College of Wisconsin, Milwaukee, WI, USA

Abstract: Given that treatment options for carbapenem-resistant enterics is limited, we should concentrate our efforts on prevention methods. These preventative interventions are usually combined into a bundle of interventions and include: increased hand hygiene compliance, active surveillance cultures, contact precautions, cohorting patients and hospital personnel, heightened environmental disinfection, limiting communal objects, and antibiotic stewardship. During this session we will review the most relevant papers on this topic and the most recent literature.
Appropriate therapy for carbapenem-resistant Enterobacteriaceae (CRE)

O. Abraham
Christian Medical College, Vellore, India

Abstract: CRE (KPC, NDM-1 and OXA-48 type carbapenemase producers) infections, increasingly encountered across the globe, are associated with substantial (up to 40%) mortality. Treatment options are limited due to in-vitro resistance to virtually all classes of antimicrobials. In-vitro, polymyxins (colistin and polymyxin B) and tigecycline remain active against majority of CRE isolates. Treatment recommendations are difficult to formulate due to absence of evidence from randomized clinical trials, and paucity of published studies on treatment outcomes in infections caused by NDM-1 producers; most of the studies have been on patients with KPC-producing *K pneumoniae* infections. Based on the review of available evidence (in-vitro and observational studies), the following strategies can be recommended for appropriate therapy of CRE infections: Optimal dosing of colistin and carbapenems: A loading dose followed by high-dose extended-interval colistin regimen has been reported to have good efficacy (clinical cure 82%) in treatment of CRE infections. For CRE strains with low MICs (up to 4 µg/ml), prolonged infusion of high-dose carbapenem has been shown to improve free time above MIC required for bactericidal effect of carbapenems. Carbapenem monotherapy may be considered in rare cases of infections caused by CRE strains with low-level carbapenem resistance, with adequate source control. Combination therapy: A recent systematic review has shown that combination therapy (≥2 antimicrobials active in-vitro – colistin with a carbapenem, tigecycline or gentamicin) results in better survival when compared to monotherapy. The mortality was lowest among patients who received carbapenem-containing combinations, and those with lower meropenem MICs. Tigecycline monotherapy is not considered a good option for treatment of serious CRE infections, as the serum concentrations achieved are well below the MIC of these organisms. CRE isolate remain susceptible to fosfomycin, which could be used for treatment of CRE urinary tract infections.

In summary, optimal dosing and combination of at least two antimicrobials, preferably colistin with a carbapenem seems to be the most appropriate therapy for severe CRE infections.
Making clinical sense of candida and aspergillus susceptibilities

N. Wiederhold
University of Texas Health Science Center, San Antonio, TX, USA

Abstract: (no abstract received from presenter)
Why prophylaxis for invasive fungal infections?

A. Pagliuca
King's College London, London, United Kingdom

Abstract: (no abstract received from presenter)
Risk stratification for treatment or prophylaxis of invasive fungal infections

M. Slavin
University of Melbourne Parkville, Melbourne, Australia

Abstract: (no abstract received from presenter)
New options for prevention and treatment of invasive fungal infections

R. Duarte
Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain

Abstract: (no abstract received from presenter)
Tuberculosis/HIV co-infection

S. Swaminathan
National Institute for Research in Tuberculosis (ICMR), Chennai, India

Abstract: Tuberculosis (TB) is the only opportunistic infection, which is transmissible to the healthy immunocompetent host. HIV is the most important known risk factor that promotes progression to active TB in people with *Mycobacterium tuberculosis* infection. The lifetime risk of tuberculosis in immunocompetent persons is 5% to 10%, but in HIV positive patients, there is a 5% to 15% annual risk of developing active TB disease. During the past two decades, TB has become the major opportunistic infection complicating the HIV epidemic worldwide, especially in Asia and Africa.

India has one of the world’s highest burdens of both TB (~2.1 million cases annually) and HIV infection (2.3 million prevalent cases). While TB occurs in all socioeconomic strata and ethnic groups, prevalence rates have been clearly linked to poverty. It has been estimated that undernutrition, HIV, smoking and diabetes are all strong risk factors for TB. Maternal TB in an HIV-infected woman is a risk factor for transmission of HIV to the infant and is associated with premature delivery or low-birth weight and with higher maternal and infant mortality.

Patients with advanced immunodeficiency are at high risk for acquisition of Rifampicin resistance when treated with twice-weekly or thrice-weekly regimens. This is possibly due to malabsorption and low blood levels of anti-TB drugs. Cure rates with standard anti-TB treatment regimens average 86%, but outcomes in HIV-infected individuals are worse than uninfected patients. Though most HIV-infected patients respond well to anti-tuberculosis treatment (ATT) initially, there is a significant risk of developing other opportunistic infections as well as recurrent TB, leading to increased mortality. Timely initiation of antiretroviral therapy (ART) has been shown to reduce mortality and improves TB outcomes. The choice of ART regimen is governed by the drug-drug interactions between anti-TB and antiretroviral drugs: rifampicin is an inducer of the cytochrome p450 enzyme system, which metabolizes NNRTI drugs nevirapine and efavirenz. The metabolism of the latter is less affected by rifampicin and hence efavirenz is the NNRTI of choice when combined with ATT.

The 4 “I” policy for addressing co-infection of TB and HIV includes intensified case finding, infection control, isoniazid preventive chemotherapy and integration of TB and HIV services within antenatal, PMTCT, family planning and immunization services. Since HIV has become a chronic, manageable condition, the challenge ahead is to provide services to patients in an integrated manner and strengthen health systems so that long-term care can be effectively provided. Research priorities include improved and more sensitive point of care diagnostics for TB, shorter and more effective TB treatment regimens with minimum drug interactions with antiretroviral drugs and a better TB vaccine that is safe and effective in HIV-infected populations.
Cryptococcal meningitis and beyond - Management of select opportunistic infections in Sub-Saharan Africa

G. Meintjes
University of Cape Town, Cape Town, South Africa

Abstract: In sub-Saharan Africa, despite successful scale-up of ART programmes, opportunistic infections remain a frequent cause of morbidity, hospitalization and death. Factors that contributed to this are delays to HIV diagnosis, late engagement in ART care, difficulties with ART adherence and many patients not remaining engaged in care. Although tuberculosis is the most frequent HIV co-infection in the region, other opportunistic infections also result in considerable morbidity and mortality.

The main focus of this presentation will be cryptococcal meningitis. National surveillance data from South Africa show that 6000-8000 cases of cryptococcosis have been diagnosed annually over the last decade. Case fatality rates remain extremely high, with around two-thirds of patients dying or being lost to follow-up in routine clinical settings and one-third in clinical trial settings. In terms of management, a randomized controlled trial conducted in Vietnam demonstrated that the induction antifungal therapy associated with the best survival was a combination of amphotericin B with flucytosine for 2 weeks. Flucytosine access is limited in sub-Saharan African countries, but this is being addressed by advocacy initiatives. Sertraline has anti-cryptococcal activity and is currently being evaluated as an addition to combination therapy. Over 60% of patients have raised intracranial pressure; this is managed with serial therapeutic lumbar punctures. Unlike TB, very early ART has been shown to increase mortality in patients with cryptococcal meningitis: in the Cryptococcal Optimal ART Timing (COAT) trial those participants who started ART 1-2 weeks after cryptococcal diagnosis had a 73% higher mortality rate compared with those started 5-6 weeks after diagnosis. Immune reconstitution inflammatory syndrome (IRIS) is reported in 20% of patients with cryptococcal meningitis starting ART; management of this condition will be discussed. Among all patients with CD4 counts < 100 presenting for HIV care in sub-Saharan Africa 2-20% are found to have cryptococcal antigenaemia even though most do not have clinical features of meningitis at the time. Observational data and findings of a cluster-randomised trial suggest that pre-emptive fluconazole for such antigenaemic patients may prevent meningitis and death. The optimal dose and duration of fluconazole for this indication needs to be defined.

Other important opportunistic disease contributing to HIV-related mortality in the region (pneumocystis pneumonia, Karposi’s sarcoma and chronic gastro-enteritis) will be discussed, but this presentation will not address HIV-associated tuberculosis.
Challenges in the management of opportunistic infections: Focus on Southeast Asia

A. Kamarulzaman
University of Malaya, Kuala Lumpur, Malaysia

Abstract: Late presenters into HIV care remain common in South East Asia. In an analysis of more than 3700 patients in an Asian observational cohort, more than 72% were late presenters i.e., presenting into HIV care for the first time with CD4 of < 200 cells/mm² or with an AIDS defining illness. Consequently, physicians in South East Asia continue to manage patients who present with a myriad of opportunistic infections including toxoplasmosis, CMV infection, disseminated fungal infections and tuberculosis. Advanced HIV infection also leads to an increased risk for immune reconstitution syndrome which may present as a diagnostic and/or therapeutic challenge in these patients.

Apart from late presentation, substance use disorder and coinfections with hepatitis B and C are also relatively common in the region and can lead to additional challenges in the management of opportunistic infections and provision of antiretroviral therapy. Drug-drug interaction and hepatotoxicity are amongst the difficulties that may be encountered in these patients.

A further important consideration when managing patients with opportunistic infections is the optimal timing for the initiation of antiretroviral therapy. In recent years, several large clinical trials have been performed to address this issue, especially in relation to tuberculosis. These and data from observational studies would suggest that early initiation of antiretroviral therapy in the setting of active opportunistic infections confer survival benefits with the exception of tuberculous meningitis and cryptococcal meningitis.

Despite the advances that have been made in antiretroviral therapy and a global call for early and immediate initiation of treatment on diagnosis, a large majority of patients continue to present with late stage disease with opportunistic infections. Physicians in South East Asia and other low and middle income countries need to continue be equipped with the ability to diagnose and manage these infections effectively.
The challenge of opportunistic infections: Focus on South America

J. Torres
Universidad Central de Venezuela, Caracas, Venezuela

Abstract: Some opportunistic diseases are either exclusive or more commonly observed in South American AIDS patients than in those from different parts of the world. Interactions between HIV and endemic parasitic and other locally prevalent pathogens occur frequently in South America. However, knowledge about the impact of these interactions has been accumulating only recently.

HIV infection may alter the natural history of tropical diseases in different ways. Diagnosis and treatment may be altered and an increased pathogen burden may augment morbidity and mortality. The impact that tropical diseases have on the course of HIV infection may also be deleterious. Many intercurrent infections increase the HIV viral load enhancing the progression of HIV disease and the risk of transmission of HIV to non-infected individuals. Similarly, chronic immunomodulation by pathogens, such as helminths and protozoa, may considerably accelerate the natural history of HIV infection.

Characteristics of coinfection in the region with HIV and some emblematic endemic pathologies, such as paracoccidioidomycosis, histoplasmosis, Chagas’ disease, visceral leishmaniasis, strongyloidiasis and HTLV1, as well as some unique challenges posed by them, are reviewed in detail.
Mers-CoV: From camels to humans

Z. Memish
Ministry of Health, Riyadh, Saudi Arabia

Abstract: The Middle East respiratory syndrome coronavirus (MERS-CoV) is a novel enzootic beta coronavirus that was first described in September 2012. The clinical spectrum of MERS-CoV infection in humans ranges from an asymptomatic or mild respiratory illness to severe pneumonia and multi-organ failure; overall mortality is around 37.5%. Bats harbor several beta coronaviruses that are closely related to MERS-CoV but more research is needed to establish the relationship between bats and MERS-CoV. The seroprevalence of MERS-CoV antibodies is very high in dromedary camels in Eastern Africa and the Arabian Peninsula. MERS-CoV RNA and viable virus have been isolated from dromedary camels, including some with respiratory symptoms. Furthermore, near-identical strains of MERS-CoV have been isolated from epidemiologically linked humans and camels, confirming intertransmission, most probably from camels to humans. Though inter-human spread within health care settings is responsible for the majority of reported MERS-CoV cases, the virus is incapable at present of causing sustained human-to-human transmission. Clusters can be readily controlled with implementation of appropriate infection control procedures. Phylogenetic and sequencing data strongly suggest that MERS-CoV originated from bat ancestors after undergoing a recombination event in the Spike protein, possibly in dromedary camels in Africa, before its exportation to the Arabian Peninsula along the camel trading routes. Amongst the important measures to control MERS-CoV spread are strict regulation of camel movement, regular herd screening and isolation of infected camels, use of personal protective equipment by camel handlers and enforcing rules banning all consumption of unpasteurized camel milk and urine.
Climate change and other drivers of infectious diseases - Focus on Asia and the Pacific
D. Harley
College of Medicine, Acton, Australia

Abstract: Infectious disease epidemiology is determined by characteristics of host, agent, and environment. Climate is one important environmental influence on the incidence and distribution of infectious diseases. But climate interacts with host characteristics at individual and population levels, pathogen biology, and other facets of the biotic and abiotic environment. This presentation will consider mechanisms via which climate influences infectious diseases and present empirical evidence for some associations. The interaction of climate with other environmental, as well as host and agent characteristics will then be discussed. Examples from Asia and the Pacific, including dengue and tuberculosis, will be used. The future for infectious diseases under climate change will be considered.
Viral hemorrhagic fevers: Ebola and beyond
L. Blumberg
National Institute for Communicable Diseases, Johannesburg, South Africa

Abstract: The viruses that cause the Viral Haemorrhagic Fevers (VHFs) are largely zoonotic. Consequently, the endemic areas for the various VHFs are limited to the distribution of their mammalian reservoirs and/or arthropod vectors. Ecological changes, agricultural and cultural practices, population migration and land use may have an affect on the emergence and occurrence of the VHFs. Consequently a ‘One Health’ approach is important in surveillance, response and control of outbreaks of Filoviruses (Marburg and Ebola), the Bunyaviridae (Crimean Congo haemorrhagic fever and Rift Valley fever) and Flaviviruses such as Kyasanur Forest fever. The 2013-2015 Ebola virus outbreak in West Africa (Guinea, Liberia and Sierre Leone) is the largest to date with 28,637 cases and 11,315 deaths. The likely index case was a child exposed to a bat in a remote part of Guinea. As is usual with Filovirus outbreaks, there was nosocomial amplification due to poor infection control in under-resourced health care settings as well as community spread due to direct contact with contaminated blood or body fluids in the context of providing care to sick family members in the community or during funeral rituals. Recent evidence strongly implicates fruit bats as the filovirus reservoir, with human infection likely from inadvertent exposure to infected bat excreta or saliva. Miners, spelunkers, forestry workers, and others with exposure in environments where bats typically roost are at risk. Non-human primates, especially gorillas and chimpanzees, and other wild animals may become infected through exposure to bats, and subsequently develop a severe and often fatal illness. They frequently serve as intermediate hosts that transmit filoviruses to humans through contact with their blood and bodily fluids, usually associated with hunting and butchering. Ebola Zaire virus has caused large die-offs of central chimpanzees and western lowland gorillas in central Africa. Crimean Congo hemorrhagic fever has a wide distribution in Africa, Asia and central Europe that coincides with the distribution of Hyalomma ticks. Livestock are the usual reservoir and specific high-risk occupations, including abattoir workers, veterinarians and farm workers, hunters, and taxidermists are infected through direct exposure to animal tissue or through tick exposure. Kyasanur Forest disease, a tick-borne VHF endemic to South Asia was first reported from the Kyasanur Forest, Karnataka in India in March 1957 with an epizootic outbreak among monkeys. Preventive measures include protective clothing and tick control with an attenuated live vaccine now available.
A multisectoral approach is needed for VHF surveillance, response and control of outbreaks.
Rabies: One Health in action

P. Cowen
North Carolina State University, Raleigh, NC, USA

Abstract: The control of rabies, where successful, is built on a One Health paradigm. In many instances, the control of human disease rests on programs designed to limit canine rabies. Early rabies programs were not only One Health based but simultaneously helped define, develop and operationalize the concept of One Health. The development of rabies control programs in the United States will be examined with a particular emphasis on the development of different elements of the One Health paradigm. A review of One Health based, creative approaches used by the early rabies programs and how these programs provided a template for other creative zoonotic and non-zoonotic control programs will be described. Selected other successful rabies control programs globally will be described and their One Health based strategies highlighted. The human-animal-wildlife interface resulting in the transmission of rabies to humans will also be described with a special emphasis on the incursion of wildlife rabies in North America. Finally, strategies for the prevention of over 55,000 human deaths a year globally from rabies will be assessed from One Health based perspective and the central role of intradisciplinary approaches appraised.
Challenges and opportunities in the management of chronic hepatitis B infection
C.-L. Lai
Hong Kong University, Hongkong, China

Abstract: HBsAg seroclearance before the age of 50 years of age is associated with decreased incidence of hepatocellular carcinoma. Studies of spontaneous HBsAg seroclearance select special population with low viral activities. However HBsAg seroclearance is only achievable in 8-11% of patients with the current treatment agents (interferon and nucleoside analogues [NAs]). The pattern of HBsAg level decline during NA treatment is variable.

In contrast, permanent suppression of HBV DNA levels to below PCR detectability is achieved in 98-100% of patients on long-term NAs, irrespective of whether the baseline HBV DNA levels are high or low. Entecavir and tenofovir are the 2 first line choices, with resistance rates of 1.2% and 0% respectively.

Hepatitis B virus (HBV) covalently closed circular (ccc) DNA, a minichromosome essential for HBV replication, is supposed to be resistant to NA treatment. In a pioneering study of 43 subjects on long-term NAs with continuous viral suppression for a median of 126 months, patients had three liver biopsies at baseline, after one year of treatment and at the last follow-up. At the time of the third biopsy, serum HBV DNA levels were undetectable in all but one patient. Compared to baseline levels, there was reduction of HBsAg levels by 71.46%, lHBV DNA levels by 99.84% and cccDNA levels by 99.89%, with 49% of patients having undetectable cccDNA. The median pregenomic RNA level, measured only in the third biopsy, was 0.021 copies per cell, with 40% of patients having undetectable pgRNA. Long-term nucleos(t)ide analogue treatment induced marked depletion of cccDNA in the majority of patients while serum HBsAg levels, though reduced, were detectable in all but one patients. Whether cccDNA depletion is sustained and associated with better patient outcome requires further study.

There are also several agents currently being investigated. These agents can be classified into two main subgroups, direct acting antiviral agents and host-immune-stimulating agents. The former group includes HBV entry-to-hepatocyte inhibitors, short interfering RNA (siRNA), nucleocapsid assembly inhibitors. The latter group includes therapeutic vaccine and toll-like receptor agonists. These agents are in Phase I/II studies. These upcoming agents may further optimize HBV control.
India's perspective on antibiotic resistance

A. Prakash¹, N. Ganguly²

¹New Delhi, India, ²Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India

Abstract: (no abstract received from presenter)
South Africa's perspective on antibiotic resistance

M. Mendelson¹, P. Matsoso²
¹University of Cape Town, Cape Town, South Africa, ²National Department of Health, Pretoria, South Africa

Abstract: (no abstract received from presenter)
Kenya's perspective on antibiotic resistance

**G. Revathi¹, C. Mailu²**

¹Aga Khan University Hospital, Nairobi, Kenya, ²Ministry of Health, Nairobi, Kenya

**Abstract:** History of AMR surveillance in Kenya goes back to late 1970s and early 80s when Kenyatta National Hospital and University of Nairobi, College of Health Sciences began compiling and following antibiotic susceptibility patterns of routine clinical isolates. 5th ICID held in Nairobi in 1992 gave birth to ICAK (Infection Control Association of Kenya) composed of pathologists, pharmacologists and nurses. Hospitals appointed IPC committees around the same time under WHO guidance. Lab based AMR surveillance was an IPC activity at that time. Except the national referral hospital and a few small private hospitals in Nairobi, hospitals cannot generate AMR data due to absence of microbiology labs. Almost all AMR data is generated by scientists of Kenya Medical Research Institute or other externally funded international research groups. Most of these projects focus on organism based AMR since they are proposed by scientists. There are no updates on AMR in clinical conditions like meningitis, pneumonia or bacteremia in the community due to lack of local funding support. Recognition of diagnostic laboratory capacity as an essential component of health care system for effective disease surveillance and control was still lacking at national level until the release of WHO white paper in 2008 declaring public health labs in Africa a top priority for funding. World Bank sponsored East African Public Health Laboratory Network (EAPHLN) Project covering Kenya, Tanzania, Uganda and Rwanda; ASM and CDC supported Lab Cap program are two bright examples. The Launch of GARP Kenya project in 2009 and compilation of situation analysis in 2011 are important milestones since this project brought together various professionals across the country and establishment of AMR focal person and IPC secretariat in the Ministry of Health. World health assembly resolution on AMR in 2014 paved way to development of WHO global action plan on AMR in 2015 which urged member states to make National action plans for dealing with AMR. Kenya is well prepared to face the challenge of AMR. EAPH Lab network is able to provide the infrastructure for AMR surveillance. Close partnerships between technical and clinical professionals and strong financial support from Local and National health care managers are crucial.
Nepal's perspective on antibiotic resistance

R. Chaudhary\textsuperscript{1}, P. K. Pokharel\textsuperscript{2}
\textsuperscript{1}Ministry of Health, Kathmandu, Nepal, \textsuperscript{2}B.P.Koirala Institute of Health Sciences, Dharan, Nepal

Abstract: (no abstract received from presenter)
Mozambique’s perspective on antibiotic resistance

B. Sigauque¹, M. Saide²
¹GARP, Maputo, Mozambique, ²Ministry of Health Mozambique, Maputo, Mozambique

Abstract: For the last two decades, health has been a high priority in Mozambique. Although antibiotic resistance was not a major focus, many of the measures taken, by the Mozambique government, will have helped preserve the effectiveness of antibiotics. These include reducing the burden of infectious disease by introducing new vaccines in the national immunization program, building health infrastructure in rural settings, increasing the paramedical and medical workforce at the district level, deploying community health workers in remote underserved settings, adopting Integrated Management of Childhood Illness (IMCI) in basic health facilities and encouraging the establishment of private pharmacies in the rural areas where most of the population lives. Mozambique was early among African countries to begin hospital infection control and prevention programs and to monitor hospital-acquired infections. Recognizing the problem of drug quality in Africa, a national laboratory for drug quality was built and well equipped.

Global Antibiotic resistance partnership (GARP) provided a framework to bring together many of the leaders of the programs that form components of a national antibiotic resistance plan. The GARP Mozambique working group brought them together with a shared purpose, including both veterinary and human health specialists including civil society ou consumer association. The development of the situation analysis was key to creating a national focus on antibiotic resistance, which has resulted in appointment of a focal person at the National Directorate of Health Care. It has also sparked collaboration of the Ministries of Health and Agriculture, a greater interest among students and researchers to fill information gaps, the beginning of AMR surveillance in three regions, and the development of a National Action Plan on antibiotic resistance. The seeds of this movement already existed in Mozambique and the development would have taken place eventually, but GARP accelerated progress and provided significant support as Mozambique has become part of a growing network.
Lessons learned
H. Gelband
Center for Disease Dynamics, Economics & Policy, Washington, DC, USA

Abstract: The Global Antibiotic Resistance Partnership (GARP) is a project started by the Center for Disease Dynamics, Economics & Policy in 2008, with funding from the Bill & Melinda Gates Foundation. GARP now includes eight low- and middle-income countries, including the ones represented in this session, and is set to expand further in Africa and Asia. The GARP model involves bringing together professionals already expert in aspects of antimicrobial resistance (AMR), and covering both human and animal antibiotic use and resistance in what we have called “working groups.” Although the working groups are free standing and uncompensated, where possible, they include representation from Ministries of Health and Agriculture. These groups become a national brain trust on AMR, working collaboratively with government. We have learned that this is a way for low-resource countries to start on an evidence-based path to national AMR plans without an initial government investment. A key tool that we have required working groups to produce is a situation analysis that includes all available (published and unpublished) information on antibiotic resistance in humans and animals in the country, enriched by contextual information, such as the burden of antibiotic-treatable disease in the country, the supply chain for antibiotics, access to antibiotics among the population, etc. Important to completing the situation analysis has been the requirement of a paid working group coordinator, in all cases a young professional, which brings the added benefit of capacity building. Building up to national AMR plans may take several years in countries that have not started the process, but the global imperative now evident may help to shorten that timeline. The GARP process of relying on local leadership through a working group is one model that has been successful and is available for other countries to borrow and improve upon.
Panel Discussion

R. Laxminarayan
Public Health Foundation of India, New Delhi, India

Abstract: (no abstract received from presenter)
India - National disaster and epidemic preparedness

V. C. Menon
National Disaster Management Authority (NDMA), New Delhi, India

Abstract: History provides us several illustrations where epidemic outbreaks have led to biological disasters. Accidental or deliberate release of harmful micro-organisms can also lead to biological disasters. With the advent of bio-terrorism, there is a growing realisation that biological agents can also be used as weapons of mass destruction. The spread of Spanish Influenza of 1917-18, the Human Immunodeficiency Virus (HIV) / Acquired Immuno Deficiency Syndrome (AIDS), Severe Acute Respiratory Syndrome (SARS), Swine Flu (H1N1), Avian Influenza (H5N1), Middle East Respiratory Syndrome (MERS), dengue, chikunguniya, Ebola outbreak in West Africa and the recent Zika outbreak in several countries tested the capacities of the public health delivery system in several countries.

In India, the spread of dengue, chikunguniya, swine flu, avian influenza in hitherto non-endemic regions in the past few years posed serious challenges to the health delivery architecture in the country. The fallout of the Methyl Iso Cyanide gas leak in the Union Carbide Plant in Bhopal in 1984, alleged plague outbreaks in Beed and Surat in 1994, the avian influenza outbreak in 2012 and 2013, swine flu in India in 2014 and 2015 have also been major challenges to the public health delivery systems in the affected areas. The National Disaster Management Authority (NDMA), Government of India released the “National Disaster Management Guidelines on the Management of Biological Disasters” in July 2008. The Ministry of Health and Family Welfare also disseminated the Guidelines on Ebola like Guidelines for Safe Handling of Human Remains of Ebola Patients, Hospital Infection Control Guidelines, Ebola Virus Fact Sheet, Guidelines on Contact Tracing and Management of Contact, Guidelines for Sample Collection, Storage and Transportation, Guidelines for Clinical case Management, Guidelines for healthcare providers, Advisory for Travellers visiting Countries Affected with EVD, Advisory for Families Staying and Travellers Visiting Countries Affected with EVD, Advisory for Airlines on EVD, Health Alert on EVD for Display at Airports etc. In the aftermath of the spread of Zika virus, the Ministry of Health and Family Welfare, Government of India also released on 2nd February 2016 “Guidelines for Integrated Vector Management for Control of Aedes Mosquito” and “Guidelines on Zika Virus Disease following Epidemic in Brazil and other countries of America” to strengthen preparedness and emergency response capacities in the event of any reported case of Zika virus in India.

The presentation provides an overview of issues related to the management of epidemics in India, including a critique on the levels of preparedness, emergency response capacities and the need for strengthening disease surveillance and monitoring of early warning signals.
Influenza preparedness including H1N1

M. Chadha
National Institute of Virology, Pune, India

Abstract: (no abstract received from presenter)
Conducting clinical trials in the outbreak setting - MSF’s perspective

H. De Clerck
Médecins Sans Frontières (MSF), Antwerp, Belgium

Abstract: (no abstract received from presenter)
WHO reforms and UN actions

D. Lucey
Georgetown University, Washington, DC, USA

Abstract: This presentation will summarize five reports and commissions released between July 2014-Feb 2015 that address the response to the catastrophic Ebola epidemic in West Africa and recommend changes to prepare better for future infectious disease outbreaks, crises, and emergencies. The focus will be on World Health Organization (WHO) reforms and actions by the United Nations (UN). These reports and commissions include, but may not be limited to: (1) July 7, 2015. Report of the Ebola Interim Assessment Panel. Chaired by Dame Barbara Stocking. (2) Nov 22, 2015 published online in the Lancet. Moon S. et al. Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSTMH Independent Panel on the Global Response to Ebola. (3) Jan 13, 2016. The Neglected Dimensions of Global Security: A Framework to Counter Infectious Disease Crises. Chaired by Peter Sands. (4) Jan 18, 2016 (Second and Final Report). Advisory Group on Reform of WHO's Work in Outbreaks and Emergencies. Chaired by Dr. David Nabarro. (5). Feb 2016 (anticipated publication): The United Nations Secretary-General's High-Level Panel on the Global Response to Health Crises. While awaiting implementation of much-needed WHO Reform, as revealed by the Ebola catastrophe in West Africa, the emerging pandemic of Zika virus, and possibly-related microcephaly, was recognized. Lucey and Gostin. The Emerging Zika Pandemic: Enhancing Preparedness. JAMA published online (Wednesday) Jan 27, 2016 (online) called on the WHO Director-General to apply one of the most crucial lessons that should have been learned from the delayed WHO response to the Ebola epidemic in West Africa, and to no longer delay convening the WHO Emergency Committee to advise whether to declare a Public Health Emergency of International Concern (PHEIC) related to the Zika virus crises and to provide global guidance and leadership accordingly.
Diagnostic advances in assessing drug resistant tuberculosis

C. Rodrigues
P. D. Hinduja National Hospital & Medical Research Centre, Mumbai, India

Abstract: (no abstract received from presenter)
Translating genomics research into control of MDR tuberculosis: Lessons learned and future prospects

M. P. Nicol
University of Cape Town, Cape Town, South Africa

Abstract: The global MDR-TB caseload is increasingly driven by primary transmission of MDR-TB in high burden countries. Control will require interruption of transmission through earlier detection, effective outbreak investigation, detailed resistance testing to guide tailored treatment for patients with highly resistant TB and development and rapid access to better drugs. Genomics research and the application of technologies enabled through genomic research and technological innovation can play a critical role in each of these areas. Early diagnosis is facilitated through rapid and sensitive molecular detection of resistance-conferring mutations, real-time whole genome sequencing is now being used to target outbreak investigation and to rapidly identify resistance to second-line drugs and drug development has been enabled through the development of sophisticated screening methods supported by genomic tools. However, the promise of the genomic revolution has not yet been translated to more effective control of MDR-TB, and significant obstacles and gaps in knowledge remain. This presentation will highlight recent advances in this area, describe where existing genomic technologies are already being applied in MDR-TB programmes and identify key knowledge gaps that remain.
Advances in the understanding and management of drug-resistant tuberculosis

R. S. Wallis
Aurum Institute, Johannesburg, South Africa

Abstract: Tuberculosis is the leading infectious cause of death worldwide, with 9.6 million cases and 1.5 million deaths in 2014. The World Health Organization (WHO) estimates 480,000 cases were multidrug-resistant (MDR). Less than half of the patients entered into treatment for MDR-TB successfully complete that treatment, due primarily to high rates of mortality and loss to follow-up. These in turn reflect weaknesses in current treatment regimens and national tuberculosis programs, coupled with operational treatment challenges. We here provide an update on recent developments in the tuberculosis drug-development pipeline, including new and repurposed antimicrobials and host-directed agents, as they apply to new regimens to shorten and improve outcomes of MDR-TB treatment. Several new or repurposed antimicrobial drugs are in advanced trials for MDR-TB, and two new antimicrobial drug candidates are in early trials. Several trials to reduce the duration of therapy in both MDR and drug susceptible tuberculosis are ongoing. A wide range of candidate host-directed therapies are currently under development, to accelerate cure, prevent new drug resistance and prevent permanent lung injury. As these agents have been approved for other clinical indications, they are now ready for repurposing for tuberculosis in Phase II clinical trials. At the same time we review risks associated with evaluation of new treatment regimens, and highlight opportunities for advancing tuberculosis research generally through regulatory innovation in MDR-TB. Progress in tuberculosis-specific biomarkers, including culture conversion, PET/CT imaging and gene expression profiles, can support this innovation. Several global initiatives now provide unique opportunities to tackle the tuberculosis epidemic through collaborative North-South partnerships for clinical trials training and research, allowing funders to coordinate multiple national and regional programs for greatest overall impact.
Multidrug-resistant tuberculosis in children: Special considerations

F. Qamar
Aga Khan University Hospital, Karachi. Pakistan, Karachi, Pakistan

Abstract: Tuberculosis is amongst the top 10 causes of mortality in children worldwide. Despite this fact, pediatric TB is not a priority in most national health programmes. In view of current Millennium Development Goals recommending a scale-up of pediatric TB detection and management globally, there is a dire need to improve pediatric TB programmes in high-burden countries. The diagnosis and management of pediatric TB is challenging. Tuberculosis in children is paucibacillary and the disease is rarely bacteriologically confirmed. Suspicion of MDR is based on either a history of contact with an adult with MDR TB case or clinical failure on first line therapy. It is therefore crucial to consider the epidemiological profile (i.e., contact with a known MDR-TB index case, or possible or likely infection in regions with high rates of DR-TB), or if the patient or index case clinically deteriorates during therapy despite strictly adhering to therapy. This makes case detection and contact tracing an essential aspect of the management of pediatric TB. Most research in TB diagnostics is focused on adults. There is a dire need to invest in improved TB diagnostics in children particularly in this era of MDR and XDR TB.

Regarding therapeutics, robust information on pharmacokinetic and pharmacodynamic properties, adverse effects and drug interactions of ATT is lacking in children. Children differ from adults in the way that drugs are administered, the manner in which they are metabolized and in the adverse effects experienced. Monitoring and describing adverse effects in children is challenging; young children cannot hardly available and all these pose challenges in the treatment of drug resistant TB in children articulate pain, nausea, vertigo, peripheral neuropathy, anxiety or confusion. Rashes are common due to a variety of etiologies and the testing of hearing and vision is more difficult than in adults. Furthermore, regimen for pediatric MDR treatment and the doses for second line drugs have not been systematically tested and reported. Pediatric formulations for second line drugs are hardly available. All the above highlighted issues pose significant challenges in the treatment of drug resistant TB in children.

Another important issue is the therapeutic choice for children who are contacts of an adult MDR /XDR TB case. The benefit of the currently recommended regimens of INH alone or INH plus rifampicin has not been tested in drug resistant cases. The option of prophylaxis with fluoroquinolone is recommended for adults but needs additional research to be included in pediatric guidelines.
The threat of antimalarial drug resistance

E. Ashley
Imperial College NHS Trust, London, United Kingdom

Abstract: History has shown us that wherever antimalarial drugs are deployed antimalarial drug resistance will follow. A pattern has emerged with the drugs falling to resistance first in South East Asia and subsequently in India, Latin America and Africa. The decline in chloroquine efficacy led to millions of avoidable deaths from malaria in sub-Saharan Africa throughout the 1980s and '90s.

Artemisinin based combination treatments (ACTs) are the recommended first line treatments for falciparum malaria worldwide. The unique properties of the artemisinin derivatives, in particular their ability to reduce peripheral blood parasitaemia rapidly, make them the most potent antimalarial drug class ever used. They are partnered with slower acting antimalarial drugs and given over 3 days. Resistance to both the artemisinin derivatives and their partner drugs (mefloquine and piperaquine) has emerged in South East Asia over the last decade. Now failure rates of the combinations exceed 30% at some locations. Alarmingly, malaria is on the rise again in western Cambodia where incidence rates had reduced dramatically over the last decade.

Genetic studies have identified several mutations in a gene encoding for a plasmodial kelch protein associated with artemisinin resistance. Sampling from several sites throughout Asia has suggested resistance may have emerged multiple times at different locations. This is unlike chloroquine resistance which is thought to have emerged only twice and then spread globally. This finding has implications for global surveillance and containment strategies.

Newer antimalarial drug compounds are in development but are still several years away from registration. The most practical solution to contain the threat of antimalarial drug resistance before the death toll from malaria rises is to intensify our efforts to eliminate falciparum malaria.
Declining efficacy of mefloquine-artesunate combination and relative role of drug-resistant molecular markers: Thai-Myanmar Border 2003-2013

A. P. Phyo
Shoklo Malaria Research Unit, Maesot Tak, Thailand

Abstract: Background: Mefloquine-artesunate treatment of Plasmodium falciparum malaria in the displaced population on the Thailand-Myanmar border led to a dramatic decline in transmission. Efficacy has fallen substantially in recent years, but the relative contribution of resistance to the individual drugs is unknown.

Methods: Patients with uncomplicated P. falciparum malaria receiving supervised mefloquine-artesunate treatment were followed for 42 days. Molecular testing was undertaken to determine baseline pfmdr1 copy number, K13 genotype and discriminate recrudescences.

Findings: 1005 patients were enrolled from 2003-2013, during which PCR-adjusted cure rate declined from 100% to 81·1%. The proportion of isolates with multiple pfmdr1 copies rose from 32·4% to 64·7% while infections with K13 mutation increased from 6·7% to 83·4%. K13 propeller mutations predominated after 2009. The PCR-adjusted failure rate of infections with both amplified pfmdr1 and K13 propeller mutation was 42·2% and the adjusted hazard ratio was 14·05 (p<0·001). Even without pfmdr1 amplification, K13 propeller mutation was a strong risk factor for recrudescence (AHR=5·73, p=0·009). The combined population attributable fraction of recrudescence associated with K13 mutation and pfmdr1 amplification was 82%.

Interpretation: Pfmdr1 amplification and K13 mutation act in combination to reduce the efficacy of mefloquine-artesunate but the rise in K13 propeller mutations was the decisive factor in the fall in efficacy to unacceptable levels. These findings confirm the strong link between artemisinin resistance and ACT failure, and demonstrate the relatively short timeframe in which ACT efficacy can be lost once artemisinin resistance is present.

Funding: Wellcome Trust–Mahidol University–Oxford Tropical Medicine Research Programme
Malaria prevention strategies

L. Von Seidlein
Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand

Abstract: Substantial gains have been made in the control of malaria; in many regions malaria has reached historically low prevalence. Still the global malaria burden remains unacceptably high and the spread of antimalarial and insecticide resistance threatens a resurgence.

A number of malaria prevention strategies have been evaluated since the turn of the century. Intermittent presumptive therapy (IPT) held initially great promise but has ultimately disappointed and has not been implemented. Seasonal malaria chemoprophylaxis has evolved from IPT and restricts presumptive therapy to the months with the highest malaria incidence. This strategy is finding increasing acceptance. Malaria vaccines have a long history but have yet to result in the roll-out of a safe, highly protective, long lasting product. The last candidate, RTS,S/AS01 held great hope but also has ultimately disappointed and the inclusion in the expanded program of immunisations has not been recommended at the end of last year. There are new vaccine candidates on the horizon but there is no reasonable hope that a vaccine can be used to prevent malaria on a population level in the near future. The ultimate hope to prevent malaria has to be the elimination of malaria. While considered unrealistic until recently a range of novel strategies aim now at the elimination of malaria.
Management of relapsing Plasmodium vivax malaria

C. Chu
Bangkok, Thailand

Abstract: Plasmodium vivax (P. vivax) endemicity covers large and diverse geographical regions. Transmission is lower than Plasmodium falciparum, however, relapses caused by hypnozoite forms increase the number of infections and sustain transmission. Resistance against chloroquine is increasing and assessment of efficacy is confounded because recrudescence, relapse and reinfection cannot be distinguished reliably. Background incidence of new P. vivax infections are needed for comparing efficacy of treatment regimens. Primaquine is the only currently widely available treatment effective against relapses (hypnozoite stage) of P. vivax and assessment of its radical curative efficacy using currently recommended dosing is required. Optimising primaquine regimens may be necessary to improve adherence in some populations. The assurance of primaquine safety in persons with glucose-6-phosphate-dehydrogenase (G6PD) deficiency is essential if deployed universally for malaria elimination.

Methods: Between March 2010 and July 2015 a series of studies were conducted in northwestern Thailand along the Myanmar border. In the first study, a rolling cohort of 200 healthy subjects with a history of P. vivax were given primaquine for radical cure and followed until a new P. vivax infection. The overall incidence of new P. vivax infection was 0.13 infections per person-year. In a parallel study 650 subjects with P. vivax malaria were randomized to artesunate, chloroquine or chloroquine+primaquine (only G6PD normal subjects) and followed for one year. At least one recurrence with P. vivax occurred in over 70% subjects in non-primaquine arms and in 18% subjects taking primaquine. The burden of relapse was calculated to be 78%. In a third study, 680 G6PD normal subjects were randomized to chloroquine+primaquine 7 days (1mg/kg/day), chloroquine+primaquine 14 days (0.5mg/kg/day), dihydroartemisinin-piperaquine+primaquine 7 days or dihydroartemisinin-piperaquine+primaquine 14 days. Recurrences within one year follow up with P. vivax were treated with a standard dose of chloroquine+primaquine 14 days (0.5mg/kg/day). Subjects with at least one recurrence were not significantly different between the 7 and 14-day primaquine regimens, although non-inferiority of the 7-day regimen was inconclusive.

Conclusion: Relapse contributes substantially to the burden of P. vivax malaria. High dose primaquine (7mg/kg) over 7 or 14-days are efficacious and universal deployment is likely necessary for P. vivax elimination. However, safety of these regimens in persons with G6PD deficiency requires confirmation.
Epidemiology and ecology of rickettsial infections

R. Premaratna
University of Kelaniya, Faculty of Medicine, Ragama, Sri Lanka

Abstract: Rickettsiae are obligatory intracellular bacteria, transmitted to vertebrates by arthropod vectors, primarily by fleas and ticks. A rapid increase in the incidence of four endemic rickettsioses; Rocky Mountain spotted fever, Mediterranean spotted fever, North Asian tick typhus, and Queensland tick typhus was noted since 1970s and for Japanese spotted fever, since its discovery in mid-1980s. As a result, spotted fever group of rickettsiae (SFG) currently include over 25 formally recognized species. Elevated attention to rickettsial diseases, advent and adaptation of new molecular tools used for field and laboratory studies in the 1990s and increase in funding support have lead to this second pronounced increase in the discovery of novel species and the increase in incidence of tick-borne rickettsial diseases in the last 40 years. Change in ecological factors which determine the vector species and their behaviour, particularly those driven by climate change or human activities such as deforestation, human behavioural changes such as recreational activities that involve close association with nature, human population increases and the improvements in surveillance methodologies may contribute to the change in rickettsial disease ecology and epidemiology. Since the use of molecular technologies, numerous rickettsiae from known to unknown or variable degrees of pathogenicity for humans are being found to co-circulate in overlapping geographic regions and demonstrated in the same tick species. Furthermore, the discovery and description of novel nosological entities caused by previously unknown SFG rickettsiae, ability of most rickettsiae to circulate in diverse sylvatic or peridomestic reservoirs without having obvious impacts on their vertebrate hosts or affecting humans, occurrence of rickettsiae in association with a wide range of hard and soft ticks which feed on very different species of large and small animals, their maintenance in these vector systems by both vertical and horizontal transmission has lead to a degree where the traditional views of tick-borne rickettsioses as endemic diseases with largely focal distributions, limited host and geographic ranges, predetermined seasonality and defined tick associations to become obsolete or at least very incomplete. Therefore, continuous vigilance, surveillance, research and funding are warranted in order to understand the changing ecology and epidemiology of rickettsial diseases.
Challenges and opportunities in the diagnosis and management of rickettsial infections in Southeast Asia
G. M. Varghese
Christian Medical College, Vellore, India

Abstract: Rickettsial infections are increasing in all regions of Southeast Asia where sought. Given the non-specific presenting symptoms resembling those of other endemic infections, diagnosis can be challenging, even to the most experienced clinician. Available tests have limitations, with no good gold standard diagnostic test. Serological tests are the mainstay of diagnosis with the IgM indirect immunofluorescence assay being the reference test. However, the enzyme-linked immuno-sorbent assay is used more commonly due to the ease of performance and a good sensitivity and specificity. Paired samples, obtained at least two weeks apart, demonstrating a minimum 4 fold titre rise, are needed for improved serologic specificity, limiting its clinical feasibility. Other methods of testing have become available, but at this time, these remain insufficient to provide the rapid point-of-care diagnostics that would be necessary to significantly change the management of this infection by providers in endemic areas. The mainstay of treatment is Doxycycline although the intravenous formulations are unavailable in several countries. Macrolides have proven efficacy in mild cases and intravenous Azithromycin is used along with oral Doxycycline in seriously ill with suboptimal gastrointestinal absorption and bioavailability. This presentation reviews the challenges in the laboratory diagnosis and management of rickettsial infections unique to Southeast Asia, and examines data on emerging resistance to antimicrobial drugs.
Abstract: An effective vaccine against scrub typhus is needed because of the high incidence (1 million cases annually is likely an underestimate), large geographic distribution in Asia and islands of the Indian and Pacific oceans, difficulty of diagnosis at the time of presentation as undifferentiated febrile illness, lack of an effective low-cost point-of-care diagnostic method to be deployed in rural areas, case fatality rate of 7-10%, and natural resistance to many commonly used antibiotics.

Scientific obstacles to development of a vaccine include great antigenic diversity of the immunodominant 56 kDa surface protein antigen that has four major variable domains; weak, short-lived cross protection against the numerous heterologous strains; loss of protection against even the homologous strain after a few years; and poor knowledge of the mechanisms of immune protection, which are mostly based on studies in an invalid animal model.

Current knowledge indicates that the target cells of intracellular Orientia tsutsugamushi are dendritic cells and macrophages in the mite feeding inoculation lesion (eschar) and mainly endothelial cells, and secondarily, macrophages in the full-blown disseminated infection. Studies in a valid disseminated endothelial cell target model indicate that CD8 T lymphocytes play an important role. Earlier studies using the invalid peritoneal infection model suggest that antibodies to the 56 kDa protein provide protection against only the homologous strain, cross protection is T cell dependent, and gamma interferon likely plays an important role. The 47 kDa and ScaA proteins, which are conserved among strains, stimulate partial protection. The critical gaps in knowledge include determining the basis for insufficient immunological memory triggered by natural infection, defining the contributions of T lymphocyte subsets, NK cells, dendritic cells, and various cytokines and chemokines to vaccine-induced immunity, the orientiacidal mechanisms particularly in infected endothelial cells, and the prevalence, mechanisms, and consequences of persistent Orientia infection.

The approach toward vaccine development should utilize the valid disseminated endothelial cell infection model, bioinformatics identification of potential conserved vaccine antigens, especially subdominant surface and secreted proteins, and determination of which novel adjuvants enhance long-lived protective memory T and B cells. The goal is to do better than nature by stimulating sterilizing, sustained cross-protection against all strains of O. tsutsugamushi.
Rickettsia felis burden in the tropics

E. Angelakis
Université de la Méditerranée, Marseilles, France

Abstract: Rickettsia felis bacterium has been observed since the early twentieth century in the cat flea. It was grown for the first time in my laboratory on cell Xenopus then insect cells particularly Aedes albopictus cells. It grows only at temperature under 30°C. First described in California, the bacterium is present in the whole world. For a long time it was considered a rare disease associated with fleas. In fact, in recent years, Rickettsia felis was found as the most frequently identified bacteria in patients with fever in tropical countries after malaria. These data were confirmed in West Africa and East Africa by different teams. Rickettsia felis has also been detected in tropical and tropical areas of South America, Asia and Oceania. Rickettsia felis and is the most common rickettsial currently in the world and very frequently associated with fever in the tropics and cough but no rash. In contrast controls without fever, can cause at a lower but significant level, the presence of Rickettsia felis DNA. So these circulations of Rickettsia felis in the blood that are not always associated with fever. Possible vectors in tropical areas may be mosquitoes in Africa. Rickettsia felis has the same epidemiological distribution as malaria. Rickettsia felis was found in Anopheles species and Aedes albopictus. A mouse experimental model was established showing that Rickettsia felis could be vectorized by Anopheles gambiae. Rickettsia felis, finally, recently, was found in book lice in the dust, which further complicates the epidemiological cycle of this bacterium. R. felis may be the most common bacteria emerging
Malaria: Past, present and future

N. White
Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand

Abstract: Malaria has always exerted a heavy toll on mankind. At the turn of the 20th century millions died each year in India alone. No other infectious disease has had more impact on the human genome, particularly in tropical regions. In the past 150 years malaria has been first controlled and then eliminated in Europe, North America and Russia. This was achieved mainly by a dual attack on the malaria vector—the anopheline mosquito, and the malaria parasite in the human host. The successes in temperate regions led to a global eradication effort endorsed by the World Health Assembly in 1955. The campaign was armed with an effective insecticide, DDT, and an excellent new antimalarial drug, chloroquine. However by 1969 it was acknowledged that the ambitious goal of global eradication could not be achieved. Over the next three decades many of the successes of the eradication effort were reversed and malaria resurfaced across the tropical world. The resurgence was associated with resistance to the available insecticides and to the available antimalarial drugs. The tide has turned again over the past 15 years with substantial increases in international support for malaria control activities, widescale deployment of insecticide treated mosquito nets, and the belated introduction of highly effective artemisinin combination treatments for uncomplicated malaria and artesunate for severe malaria. Global malaria mortality and morbidity have fallen substantially. Malaria eradication is now back on the agenda. The challenges now are how to maintain the political and financial support for malaria control and elimination as case numbers fall, to reach those areas where control activities are still weak, to address seriously control of P. vivax, and to overcome two looming familiar threats; insecticide and drug resistance. Resistance to pyrethroids is increasing and resistance to artemisinin in P. falciparum has emerged in South-East Asia, and now extends to the border of India. Artemisinin resistance has not been contained, and combination partner drug resistance has predictably followed. Spread of resistance to Africa would be disastrous. A moderately effective vaccine has been developed and new drugs are in the pipeline, but they will not generally available for years. The future is uncertain.
Flavivirus encephalitis and other neurological syndromes (Japanese encephalitis, WNV, Tick borne encephalitis, Dengue, Zika virus)

T. Solomon
University of Liverpool, Liverpool, United Kingdom

Abstract: Flaviviruses are some of the most important causes of encephalitis, and other neurological syndromes globally, and have an ability to spread to new areas causing large outbreaks.

Some are zoonotic, transmitted from animals to humans via mosquitoes (e.g. Japanese encephalitis virus – JEV, and West Nile virus – WNV) or ticks, (Tick-borne encephalitis virus – TBEV). For other flaviviruses humans are the natural hosts; these include dengue virus (DENV), and Zika virus (ZIKV).

The clinical epidemiology of neurological disease caused by flaviviruses varies. JEV is numerically the most important cause of encephalitis with up to 70,000 cases annually across Asia. Almost all those living in rural Asia become infected during childhood, but only a small proportion develops neurological disease. Clinical features include a non-specific febrile illness, aseptic meningitis, febrile seizures, encephalitis, with Parkinsonian movement disorders, and myelitis, causing a poliomyelitis-like flaccid paralysis. There is no specific treatment, but good supportive care is essential. Recognition and control of JE has been improved in recent years through better surveillance, improved diagnostics, on disability and disease burden and greater use of vaccines.

Being a mosquito-borne zoonotic Flavivirus, WNV is broadly similar to JEV. Its arrival and spread across the Americas in the last 15 years has taught us a great deal about the emergence of such viruses among populations of animals and humans that have not been exposed previously: disease tends to be seen in the elderly and sick.

TBEV is seen in cooler parts of Asia and Europe where ticks predominate. Humans tend to become exposed to infected ticks in wooded areas through tourism or work. The disease is well controlled in countries with strong vaccination programmes.

For dengue and Zika virus humans are the natural hosts, and so most patients present with a febrile syndrome, which may include a rash. However the neurological manifestations of dengue, including encephalitis, have been recognised increasingly over the last twenty years. The neurological associations of Zika virus infection are beginning to be recognised with the ongoing large outbreaks in South America.
Enterovirus encephalitis including Enterovirus 71 and D68

K. T. Wong
University of Malaysia, Kuala Lumpur, Malaysia

Abstract: Enteroviruses are small RNA viruses that belong to several species groups (A to H and J) in the genus Enterovirus and family Picornaviridae. Central nervous system (CNS) involvement in enterovirus infections is well known although it is a relatively rare complication. Several neurological syndromes have been described including aseptic meningitis, acute flaccid paralysis (myelitis), and the more serious encephalitis. Perhaps the best known neurotropic enterovirus for more than a century is the poliovirus, although other enteroviruses have also been associated with neurological syndromes. Except perhaps for poliovirus and enterovirus A71 (EV-A71), many reports were anecdotal and causative links yet to be firmly established, partly because of the difficulty of demonstrating virus in the cerebrospinal fluid or CNS tissues.

Based on poliovirus studies, enteroviral neuroinvasion had been long thought to be via haematogenous and peripheral nerve routes. Recent evidence from transgenic mouse models has confirmed poliovirus neuroinvasion by peripheral nerves. Human and animal studies have provided good evidence that EV-A71 may enter the CNS via spinal and cranial motor nerves by retrograde axonal transport but other neural pathways other than the motor pathway may help spread virus within the CNS. Brain MRI scans in echovirus 7, coxsackievirus A16, EV-A71 and enterovirus D68 (EV-D68) encephalitides often show similar lesions in the anterior horns of the spinal cord, dorsal brainstem and cerebellar dentate nucleus. If confirmed by autopsy and other studies, these findings could suggest a common pathway for enteroviral neuroinvasion via peripheral motor nerves.

The neuron in the CNS is the main viral target so neuronal viral cytolysis/necrosis is probably responsible for CNS injury for most enteroviruses. However, other mechanisms of cell injury such as apoptosis and immunopathogenesis may have a role and should be investigated. With better molecular techniques and MRI facilities, the diagnosis of enterovirus encephalitis should improve in the future. A greater understanding of the pathology and neuropathogenesis of non-poliovirus encephalitides is important with the imminent worldwide eradication of poliovirus, and the emergence of enteroviruses such as EV-A71 and EV-D68, which capable of causing epidemic encephalitides.
Acute encephalitis syndrome of unknown etiology: The NIMHANS experience

A. Desai
National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India

Abstract: Acute Encephalitis Syndrome (AES) is a major public health concern in India. Large outbreaks of AES affecting particularly children, occur annually in the country post monsoon from July to November. The National Vector Borne Disease Control Programme in India set up country wide surveillance for AES through sentinel sites with a focus on detecting Japanese encephalitis (JEV). Although JEV is the major cause of AES in India (ranging from 5-35%), the etiology in a large number of cases however remains unidentified.

Over the past 3 decades, a major thrust area at NIMHANS is to identify AES pathogens other than JEV. Our studies in collaboration with the University of Liverpool at Ballary, demonstrated Chikungunya virus, Enterovirus 75 and Parvovirus B4 as etiological agents of AES besides JEV. In addition, as a referral lab of the WHO-SEARO JE network (2006-10), we detected Dengue, West Nile and bacterial pathogens as causative agents of AES. More recently, under the co-operative agreement with CDC, we proposed and validated an algorithmic approach to determine the etiology of 1253 cases of AES in four major affected states- Uttar Pradesh, Assam, West Bengal and Karnataka. In the algorithm, serum and/or CSF samples collected from AES cases were first tested to detect JEV IgM antibodies. All JEV IgM negative serum samples were further tested for presence of Scrub Typhus IgM. Dengue Virus IgM and West Nile Virus IgM using commercially available kits, while CSF samples were subjected for detection of bacterial/viral nucleic acids for Streptococcus pneumonia, N. meningitidis, H. influenzae, Herpes simplex virus Type 1 (HSV), Enteroviruses and Chikungunya virus in that order of priority.

Out of the 1253 patients tested, paired CSF and serum samples were obtained from 639 patients (51%), only CSF from 352 (28%) and only serum from 262 cases (21%). Adult cases of AES predominated in Assam (210/409, 51.34%) whereas pediatric cases were seen in Uttar Pradesh. Overall, the algorithm enabled identification of etiology in 497/1253 cases (39.66%). JEV was the commonest etiology identified (260/1253, 21%) while, non-JE causative pathogens was identified in 237/1253 (19%) of the samples tested. Scrub typhus IgM (26%), Dengue IgM (5%) and West Nile virus IgM (1.8%) was detected using serum samples while S. pneumoniae (1.65%), H. influenzae (0.73%), HSV (0.62%) and Enterovirus (0.16%) was detected in the CSF using molecular tests.
Rabies encephalitis

A. Jackson
University of Manitoba, Winnipeg, MB, Canada

Abstract: Rabies is an acute infection of the nervous system in human and animals caused by rabies virus. Transmission usually occurs via a bite of an infected animal; transmission via aerosols and by tissue or organ transplantation are rare. Worldwide, endemic dog rabies is responsible for the vast majority of human cases, particularly in Asia and Africa. There are about 60,000 fatal human cases annually, and almost half are in children. Dog rabies can become well controlled by mass vaccination of dogs, which has proved to be very successful in Latin America. However, dog rabies remains uncontrolled in Asia and Africa. Rabies can be very effectively prevented after recognized exposures in humans by wound cleansing and active and passive immunization with rabies vaccine and rabies immune globulin, respectively. Human rabies has characteristic clinical features, including hydrophobia, and there are both encephalitic and paralytic forms of disease with progressive illness to death. Antemortem diagnostic laboratory tests include detection of rabies virus RNA (by reverse transcription - polymerase chain reaction amplification) in saliva or skin biopsies, rabies virus antigen detection in skin biopsies, and/or detection of neutralizing anti-rabies virus antibodies in serum and cerebrospinal fluid. When patients are treated aggressively in critical care units, there often are cardiac and/or respiratory complications and progression to multisystem organ dysfunction. Rabies is virtually always fatal and most survivors have received one or more doses of rabies vaccine prior to the onset of their clinical illness. There is no established effective therapy for rabies. The Milwaukee protocol, which includes therapeutic coma, lacks a clear scientific rationale and has proven to be ineffective and should no longer be used for the management of human rabies. Our understanding of basic mechanisms involved in the pathogenesis of rabies are quite limited and have proven to be an important barrier for the development of novel therapeutic approaches for the disease. There is recent evidence that rabies virus induces mitochondrial dysfunction in infected cells, which results in oxidative stress due to generation of reactive oxygen species and neuronal injury. This advance may lead to new approaches to the therapy of rabies.
MALDI-TOF
A. Chakrabarti
PGIMER, Chandigarh, India

Abstract: Among different mass spectrometry, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS) has become popular in infectious disease management, infection control and antimicrobial stewardship especially in the field of bacterial and fungal diseases, due to its simple sample pre-treatment, rapid identification of microorganism, and future scope of detecting biomarkers in infectious diseases, antimicrobial susceptibility testing, epidemiological typing, microbial virulence factors and its use in the field of virology and parasitology as well. The technique has the potentiality for point-of-care diagnosis and screening of large number of samples simultaneously. Many laboratories across globe use this technique in routine microbiology laboratory due to its efficiency and cost-per-analysis point of view. It outcompetes the classical microbial identification methods. FDA approved both VITEK MS system (BioMérieux) and MALDI_TOF MS Biotyper (Bruker Daltonics) for microbial identification. The identification system requires pure culture (~10^8 microbial cells) of a single species bacteria, mycobacteria or fungi from liquid or solid media. The mixed microbial species are hard to identify unless the ratio between the species is not lower than 1:5. For Mycobacteria, Nocardia, and fungi a cell destruction or extraction step is required. The majority studies reported correct identification >95% isolates. However, for better identification, periodic update of database is essential. Optimization of the distinction of few species still remains problematic like E. coli and Shigella species. The other applications of MALDI that may have impact on management of infectious diseases include antimicrobial susceptibility testing and epidemiological typing. Antimicrobial susceptibility testing targets a) modification and degradation product of antimicrobial after exposure to microbe, b) proteomic changes in resistant versus susceptible microbial species, c) shift of protein peak after growth of microbe in presence of antimicrobials, d) semi-quantitative estimation of intracellular/extracellular antimicrobials. The techniques require further standardization before getting regulatory approval. In case of microbial typing, the technique compares unique isolate peaks, whereas the identification targets universally conserved peaks. Modification of MALDI-TOF like SELDI-TOF (Surface-enhanced laser desorption) or ESI-MS (Electron spray ionization) are currently explored for their clinical potential.
Microbial culturomics
E. Angelakis
Université de la Méditerranée, Marseilles, France

Abstract: Microbial culturomics is a new approach in the biological exploration strategies of the XXI century. By multiplying the isolation strategies, identify quickly by MALDI-TOF techniques and identify bacteria in non identified MALDI-TOF database, by sequencing the 16S rDNA gene. Comparing the culturomics on samples of digestive origin shows that it has a performance comparable to that of metagenomics with only 15% of bacteria found in common by metagenomics and the culturomics. In my lab we have tested more than 700 000 bacterial colonies which helped find more different bacteria species in our laboratory than in all other laboratories in all the world combined this strategy. This strategy was also applied to the skin, urinary and vaginal microbiota with preliminary work that shows results as extremely important to increase the known bacterial repertoire. The culturomics plays a very important role in identifying the repertoire of genes associated with mucosae and provides bacterial isolates for future experimental models, and future therapeutic strategies.
Point of care testing for global health

V. Gant
UCLH NHS Foundation Trust, London, United Kingdom

Abstract: “Faster, better, cheaper” is a much bandied term in the context of POCT. This talk will start by describing those technologies which either are beginning, or look to be, capable of really delivering such promises. The opportunities offered by modern wireless communications and IT in this space will also be discussed. The majority of the talk, however, will concentrate on the cloud behind the silver lining; specifically, the very real barriers posed by the “innovation gap” between a good idea and a tractable, realistic solution which needs to be provided by industry pull-through; and the often neglected but crucial relevance and challenges set by issues of clinical Governance, poverty, whole healthcare systems, and the all too commonly ignored concept of “clinical value” – the latter relating to making sure that whatever you measure in such a modern and elegant way actually benefits the patient.
Whole genome sequencing in diagnostic microbiology

T. Peto
University of Oxford, Oxford, United Kingdom

Abstract: (no abstract received from presenter)
Polio eradication: End game and beyond

T. J. John
Christian Medical College, Vellore, India

Abstract: In 2013, the target of polio eradication was broadened to include wild and vaccine polioviruses. In the "Polio Eradication and End Game Strategic Plan 2013-18" eradication refers to wild polioviruses (WPVs) and end game refers to managing all risks from vaccine polioviruses. WPVs can be eradicated using oral poliovaccine (OPV). Inactivated poliovaccine (IPV) is necessary to eradicate vaccine polioviruses. Attenuation meant drastic reductions in neuro-virulence and transmission efficiency. Vaccine viruses are genetically unstable and tend to de-attenuate during replication. One risk of predictable but low frequency is ‘vaccine-associated paralytic polio’ (VAPP) in the vaccinated or in those who get secondarily infected. Another risk of unpredictable frequency is the generation of highly transmissible neuro-virulent ‘vaccine-derived polioviruses’ (VDPV). Circulating VDPVs (cVDPVs) are wild-like, causing polio outbreaks unless interrupted from circulation. Vaccine viruses can cause chronic intestinal infection in persons with B cell immunodeficiency; during prolonged infection immunodeficiency-associated VDPV (iVDPV) emerges.
Since 2011, annually VAPP and cVDPV cases outnumber WPV cases – this is ethically untenable. So OPV must be discontinued. Immediately VAPP will stop. But IPV cover is essential for withdrawing OPV, since immunity gap in the community is the major risk-factor of emergence of cVDPVs. Unless that gap is covered by IPV, withdrawing OPV will surely lead to uncontrolled polio outbreaks due to cVDPVs.
WPV-2 was eradicated in 1999. Most cVDPV outbreaks and one-third VAPP are caused by type 2. So, type 2 vaccine virus will be withdrawn first. All OPV-using countries have introduced IPV in preparation of withdrawing vaccine type 2 in April 2016. Thereafter only bivalent OPV (bOPV) containing types 1 and 3 will be available globally. This exercise is also rehearsal for withdrawing bOPV after global eradication of WPV 1 and 3. Only IPV will continue in a polio eradicated world.
Haemophilus influenza type B (Hib) vaccines: A looming success. Lessons learned from the Hib initiative
R. Hajjeh
NCIRD/OID/CDC, Atlanta, GA, USA

Abstract: Adoption of new vaccines is critical to improve child health overall and reduce child mortality. However, new vaccine introduction has historically been delayed in developing countries due to multiple factors (lack of data, economic, logistical and awareness factors). Recently, the Global Alliance for Vaccines and Immunizations (GAVI) supported the Hib Initiative to accelerate the introduction of Hib vaccines in developing countries, which was very successful and led to introduction of Hib vaccine in all GAVI eligible countries, as well as many other countries around the world. The strategy adopted by the Hib Initiative addressed barriers for vaccine introduction by focusing on three areas: communications to increase awareness about disease and vaccine; research to answer key questions needed to support evidence-based decisions, and long term program sustainability; and coordination with various stakeholders at global, regional and country levels to ensure successful program implementation. The success of the Hib Initiative provided a boost to new vaccine introduction, and the lessons learned from this experience were very useful to support accelerated introduction of the newer vaccines, including pneumococcal, rotavirus and HPV vaccines.
Pneumococcal conjugate vaccines

S. K. Saha
Dhaka Shishu Hospital, Dhaka, Bangladesh

Abstract: (no abstract received from presenter)
Prevention of enteric infections: Spotlight on Asia

G. Kang
Christian Medical College, Vellore, India, Vellore, India

Abstract: (no abstract received from presenter)
Antibiotic use and global trends of gram negative resistance
C. Rodrigues
P. D. Hinduja National Hospital & Medical Research Centre, Mumbai, India

Abstract: (no abstract received from presenter)
Risk stratification: Identifying the right patient for the right treatment

M. Bassetti
Santa Maria Misericordia University Hospital, Udine, Italy

Abstract: (no abstract received from presenter)
Strategic options for the management of severe gram-negative infections

A. Shorr
MedStar Washington Hospital Center, Washington, DC, USA

Abstract: (no abstract received from presenter)
The role of antimicrobial stewardship in developing strategies for appropriate therapy
G. H. Karam
Louisiana State University School of Medicine, New Orleans, LA, USA

Abstract: (no abstract received from presenter)
Melioidosis endemicity in India
C. Mukhopadhyay
Kasurba Medical College, Manipal, India

Abstract: In the recent most melioidosis meeting in Manipal (1st South Asian Melioidosis Congress) in November, 2015, Dr. David Dance from University of Oxford told that ‘nearly 165,000 people is getting affected with melioidosis every year in the world, out of which 44% are from South Asian countries’, and further he added that ‘India has the highest burden, with more than 50% death, which are mostly undiagnosed’. It is predicted that Indian subcontinent is presently the ‘hot spot’ of the disease, which has most number of cases and deaths. After the bacterium was discovered by the Indian bacteriologist, CS Krishnaswami, in 1912, along with his physician colleague, A. Whitmore, it took almost 80 years (1991) to diagnose the first case of melioidosis in an Indian medical set up in Mumbai. Since then, only 50 cases have been published in last 25 years, which may merely be considered as the ‘tip of the iceberg’. During our last 10 years journey with melioidosis research, we have performed the first extensive seroprevalence study with 29% seropositivity rate, which proved beyond doubt the significant environmental exposure to B. pseudomallei in the soil and water. Nearly 200 patients with melioidosis were detected in last 10 years in our tertiary care hospital predominantly with pneumonia and high mortality and mostly during heavy rainfall. Our improved laboratory set up help us diagnose cases rapidly and more accurately, and serve as the reference center for melioidosis in this region. Humans acquire melioidosis following contact with B. pseudomallei in the environment. We have detected the presence of B. pseudomallei while performing soil surveillance in and around Udupi district with nearly 40% positivity rate. Our clinical isolates are found to be diverse from Australian and Southeast Asian strains, suggesting their pure Indian origin more strongly. To strengthen the melioidosis research in this subcontinent, Indian Melioidosis Research Forum is formed with scientists and researchers from all over the world, with a more focused case finding from eastern and north-eastern states of India.
Predicted distribution of B. pseudomallei and burden of melioidosis in South Asia and worldwide

D. Limmathurotsakul
Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Abstract: *Burkholderia pseudomallei*, a highly pathogenic bacterium that causes melioidosis, is commonly found in soil in Southeast Asia and Northern Australia. Melioidosis can be difficult to diagnose due to its diverse clinical manifestations and the inadequacy of conventional bacterial identification methods. The bacterium is intrinsically resistant to a wide range of antimicrobials, and treatment with ineffective antimicrobials may result in case fatality rates exceeding 70%. The global distribution of *B. pseudomallei* and burden of melioidosis, however, remain poorly understood.

A globally comprehensive database was compiled, comprising of 22,338 geo-located records of human and animal melioidosis and presence of environmental *B. pseudomallei* from reports published from 1910 to 2014. We then combined the data in a formal modelling framework to predict the global distribution of *B. pseudomallei* and estimate the burden of melioidosis.

We estimate there to be 165,000 (95% credible interval 68,000-412,000) human melioidosis cases per year worldwide, of which 89,000 (36,000-227,000) die. We predict that only 40% of all melioidosis cases occur in the East Asia and Pacific region, where melioidosis is considered highly endemic. By contrast, South Asia is predicted to bear 44% of the overall burden, because large populations live in areas contaminated with *B. pseudomallei*. Our estimates suggest that melioidosis is severely underreported in the 45 countries in which it is known to be endemic and that melioidosis is likely endemic in a further 34 countries which have never reported the disease.

The large numbers of estimated cases and fatalities emphasise that the disease warrants renewed attention from public health officials and policy makers.
Why is melioidosis difficult to treat? - Insights into pathogenesis

J. Wiersinga
University of Amsterdam, Amsterdam, Netherlands

Abstract: Largely due to its recognition as a biological threat agent, current knowledge on melioidosis, caused by the Gram-negative bacterium *Burkholderia pseudomallei*, has increased tremendously in the last decade. In this talk, recent insights will be given on our understanding on the molecular characterization of *B. pseudomallei* and the immunology of melioidosis.

The genome of *B. pseudomallei* is composed of two chromosomes of which the largest part represents the *B. pseudomallei* core genome, whereas the remaining accessory genome has been associated with bacterial virulence. Virulence factors, most notably quorum sensing, type III secretion system, lipopolysaccharide and other surface polysaccharides, flagella and various factors essential for the intracellular life cycle of *B. pseudomallei*, have been further characterized. These so called microorganism associated molecular patterns (MAMPs) are recognized by pattern recognition receptors (PRRs) such as Toll-like receptors and NOD-like receptors (NLRs). The neutrophils play a critical in host defense, which is initiated by the TLRs. The proinflammatory immune response – including the activation of coagulation – is further ignited by the release of various damage associated molecular patterns (DAMPs) such as calprotectin and the nucleosomes which are also recognized by PRRs.

Severe melioidosis can probably be seen as the clinical manifestation of a PRR mediated dysregulation of the immune response to invading *B. pseudomallei*. *B. pseudomallei* employs numerous tactics to evade the immune response. Studies on host–pathogen interactions in melioidosis have identified a whole range of potential new treatment targets which will be discussed.
Challenges in diagnosis and management of melioidosis

D. A. B. Dance
LOMWRU, Vientiane, Lao, People's Democratic Republic of

Abstract: For many years it has been clear that melioidosis is endemic in parts of SE Asia and northern Australia, but over the past 25 years, the melioidosis iceberg has been emerging. Within known endemic areas, cases are being recognized with increasing frequency. New endemic areas are also being identified, particularly in Africa and the Americas, but also in Asia. In Laos, for example, the first case of melioidosis was diagnosed as recently as 1999, but since then more than 900 cases of culture-positive melioidosis have been diagnosed in a single laboratory, although this is just the tip of a national iceberg. Worldwide, the disease undoubtedly remains under-diagnosed, especially in the Indian sub-continent. The two main barriers to the diagnosis of the disease, which has its biggest impact on the rural poor, are access to high quality diagnostics, and the lack of awareness and familiarity of clinical and laboratory staff. Clinical diagnosis is difficult due to the protean manifestations of the disease. Where microbiology laboratories exist, the mainstay of diagnosis remains culture. The organism is easy to grow as long as the site of infection can be sampled, but laboratory technicians unfamiliar with the organism may discard it as a contaminant. An important clue is resistance to aminoglycosides and colistin combined with susceptibility to co-amoxiclav, although regional variants have recently been described. Latex agglutination or lateral flow tests are useful for screening suspect isolates, and the latter may be used for rapid diagnosis directly on clinical samples. Molecular tests such as PCR have not yet found a role in routine diagnosis. Available serological tests also lack sensitivity and specificity.

Current treatment regimens, comprising an initial parenteral phase with either ceftazidime or a carbapenem followed by a prolonged oral eradication phase with co-trimoxazole or co-amoxiclav, are based on strong evidence from a series of clinical trials conducted in Thailand. Several questions remain unanswered, however, such as the optimal duration of each phase and the role of adjunctive treatment.

Even with optimal antibiotic therapy the mortality in developing countries remains disappointingly high.
Tuberculosis: Challenges and Solutions for the 21st Century

S. Swaminathan
National Institute for Research in Tuberculosis (ICMR), Chennai, India

Abstract: (no abstract received from presenter)
The healthy human antibiotic resistome: a multi-body habitat analysis

M. Mitreva
McDonnell Genome Institute, St. Louis, MO, USA

Abstract: The human body habitats are home to an array of micro-organisms, and within these microbial ecosystems there is an exchange of genetic material, including antibiotic resistance genes. Recent metagenomic studies revealed that the human gut microbiota is a reservoir of antibiotic resistant genes (the gut resistome). However, little is known about the diversity and abundances of antibiotic resistance genes in other body habitats and how that compares to the gut resistome. By leveraging the most comprehensive human microbiome dataset of healthy adults generated by the human microbiome project, we characterize the human microbiome resistome from four body habitats including gut (stool), oral, anterior nares and vagina. The human resistome was profiled using a metagenomic shotgun sequencing alignment-based approach. By determining the resistome size per individual we found resistance genes distribute distinctly by body sites with certain body habitats being a better reservoirs then others. Furthermore, while resistance classes were incoming among body habitats (e.g. tetracyclin), the specific resistance genes per class were different (e.g. tetM in oral vs tetQ in gut). The profiles of resistance genes (in the body sites with universally present resistance genes) are more similar for the same subjects over time than between subjects at the same time of sampling. Finally, association analysis with sex, age and geography showed certain significant correlation for habitat specific resistance genes. These findings illustrate that the healthy human microbiota in general, beyond the gut microbiota, is a reservoir for antibiotic resistance genes. This reservoir may serve as a mobile resistance gene pool that facilitates the transmission of antibiotic resistance genes.
Abstract: Through analytical advances, the complexity of the human microbiome has recently become apparent. The emerging data have shed light on the microorganisms living in intimate relationship with each cell in the body, and on how much of a person’s daily function and health depends on this symbiosis. Fecal microbiota transplantation (FMT), also called bacteriotherapy, refers to the infusion of a fecal suspension from one individual into the gastrointestinal tract of another person, most often performed to cure diseases caused by microbial dysbiosis. FMT is by no means a new therapeutic modality, and was described as early as the fifth century. Nevertheless, until recently, only few peer-reviewed case reports could be found in the medical literature. In the past 3 years, stool has emerged as a biologically active, complex mixture of living organisms with great therapeutic potential for a number of diseases, most notably recurrent Clostridium difficile infection (CDI). Many case series and a number of clinical trials have repeatedly shown high cure rates, of up to 93%, in patients with recurrent CDI, compared with 30-40% cure obtained with standard antimicrobial treatment. FMT can be delivered via enema, colonoscopy, nasoduodenal tube, nasogastric tube and orally, as encapsulated FMT. An overview will be given about the current knowledge with regard to efficacy and safety of different delivery methods, focusing on oral therapy as the most convenient and cost-effective route. The development of the FMT capsule will be described as will our experience providing FMT to over 200 patients as part of clinical trials or routine care, including long-term follow up data. Few FMT-related adverse events have been reported to date, and most were related to the delivery mechanism. The potential use of FMT for other indications will be briefly explored, including inflammatory bowel diseases, functional bowel disorders, de-colonization of resistant pathogens and, through modification of the gut-brain axis, neuropsychiatric disorders.
Neonatal microbiota in health and disease

P. Panigrahi
University of Nebraska Medical Center, Omaha, NE, USA

Abstract: Bacteria populated the earth two billion years prior to emergence of eukaryotic life. Now, some 400-500 species are estimated to inhabit the human mucosal surfaces, bulk of which reside in the intestinal tract. Traditionally, a newborn gut was considered sterile, but new evidence indicate presence of bacteria in the fetus and meconium. Mode of delivery, feeding type, the environment, and caregivers provide the initial bacterial exposure to the newborn to help develop a healthy colonization pattern. There is ample evidence in favor of simple problems such as feeding intolerance to very severe diseases such as necrotizing enterocolitis resulting in part due to disruption of normal microbiota. However, there is paucity of data on a “true” healthy microbial pattern in neonates. Similarly, most of the work done on neonatal microbiome is from the west and a comparative comparison of microbiota has not been done in babies from different parts of the world. Apart from acting against pathogens and maintaining homeostasis in infectious, inflammatory, and autoimmune diseases, the intestinal microbiota has now been a focus of attention in their role in vaccine response. Maturation of mucosal immune system as a result of colonization by bacteria has been known for some time, and new research in humans and animals provides clear evidence of a bacterial role in the development of both innate and adaptive immune response in the mammalian host. The type, number, and timing of exposure of mucosal and dendritic cells to bacteria and bacterial products and induction of specific T helper and T-regulatory components of the immune system have been examined with some details in different disease models. We will discuss these and other factors currently known to play a role and their mechanism in modulating the infant immune response. Recent results from an Indian probiotic trial in neonatal sepsis using live bacteria in the first week of life will be presented in light of its mucosal effects in blockage of bacterial translocation and possible extra-intestinal impacts via modulation of innate immunity.
Beneficial modulation of the gut microbiota

P. Cotter
Teagasc Food Research Centre and APC Microbiome Institute, Cork, Ireland

Abstract: As the scientific community continues to develop an ever-greater understanding of the composition and function of the human gut microbiota, and the role of specific microbial populations in health and disease, attention has turned to the tools that are at our disposal with respect to altering these microbes in a beneficial way. The options available include the use of diet, probiotics/prebiotics, antimicrobials and, potentially, exercise. Here, our recent investigations of the relationship between protein, bacteriocin producing probiotics and exercise and the gut microbiota and, in turn, health will be described.
Abstract: Vaccines are now available to combat rotavirus, the most common cause of severe, dehydrating diarrhea among children worldwide. As of January 2016, 80 countries have introduced rotavirus vaccines into their routine immunization programs. High and middle income countries were the early introducers of rotavirus vaccines and in these countries, vaccines have reduced all-cause diarrhea and rotavirus hospitalizations by 17%-55% and 49-92%, respectively, and all-cause diarrhea deaths by 22%-50% in some settings. Additionally, indirect protection of children age-ineligible for rotavirus vaccine has also been observed in some high and middle-income countries. Rotavirus vaccine introductions in low income countries have been increasing in recent years and early data from these settings are promising. Vaccine effectiveness is comparable to the efficacy observed in clinical trials and the impact in high disease burden settings has been dramatic. As rotavirus vaccines continue to rollout in low income countries, the full range of health benefits in these settings can be documented.
Norovirus infection and vaccine development: Where are we?

M. O’Ryan
University of Chile, Santiago, Chile

Abstract: Noroviruses are currently recognized as the leading cause of acute gastroenteritis outbreaks associated with contaminated food and/or water consumption in industrialized countries and second to rotavirus as cause of childhood gastroenteritis. Individuals are infected many times throughout their lifetime, most of which are asymptomatic infections with fewer episodes of moderate to severely symptomatic infections which are particularly significant in young children living in resource-deprived countries. Symptomatic norovirus infections are in general less severe than rotavirus infections in children which do not preclude that severe norovirus infections characterized by intense vomiting, watery diarrhea and fever leading to shock and death occur worldwide. Near 200,000 norovirus-associated deaths are estimated to occur every year in children. Norovirus of the genogroup GII.4 have largely predominated throughout the past years and prevention may be possible through vaccination using virus-like particles. A Phase I challenge study using an intramuscular bivalent GI.1/GII.4 vaccine in adults demonstrated significant protection and Phase II trials in children are planned for 2017.
The outcomes of cryptosporidial infections in Indian children

G. Kang
Christian Medical College, Vellore, India

Abstract: Cryptosporidium is an apicomplexan protozoan parasite that has gained attention in the past two decades as a clinically important human pathogen. The recent Global Enteric Multicenter Study (GEMS) reported Cryptosporidium spp. as one of the four top pathogens causing moderate to severe diarrhoea in children. In India alone, we estimated cryptosporidiosis to cause 3.9 to 7.1 million diarrhoeal episodes, 66.4 to 249 thousand hospitalizations and 5.8 to 14.6 thousand deaths in children under the age of two years. A large proportion of children, especially those living in resource-limited settings, are asymptomatically infected.

The impact of cryptosporidiosis is not limited to the diarrhoeal episode alone but has been associated with long term sequelae, with several studies suggesting that both asymptomatic and symptomatic cryptosporidial infections have a significant adverse effect on nutritional status, cognitive development, increased overall diarrhoeal burden and mortality in children. Although there are studies showing high cryptosporidial disease burden in developing countries, resulting in immediate and prolonged morbidity, the epidemiology of cryptosporidial infections in humans is not clearly understood. Moreover, there is a dearth of longitudinal data on the course of infection in the absence of overt diarrhoeal disease. A clear understanding of the natural history of cryptosporidiosis and correlates of protection are essential in developing effective, efficient and sustainable disease control and preventive measures. In intensive active surveillance of a cohort of children from birth till three years of age to study the natural history of cryptosporidiosis in a semi-urban slum area in southern India, we have shown early childhood exposure and a high rate of asymptomatic infection. The proportion of re-infected children was high and clustering was observed in children for both infection and diarrhoea. Protection against cryptosporidial infection increased with the order of infection but was only 69% after four infections. C. hominis was the predominant Cryptosporidium species, and there was no evidence of species-specific protection. Clustering of infection is suggestive of host susceptibility. Multiple re-infections conferred some degree of protection against subsequent infection.

These studies demonstrate the power of harnessing the synergistic benefits of a birth cohort study design in a community setting and efficient molecular approaches to detect cryptosporidial infections, to enhance understanding of a common but under-recognised pathogen.
Molecular diagnostics and the aetiology of diarrhea in low-income countries

J. Platts-Mills
Division of Infectious Diseases and International Health, Charlottesville, VA, USA

Abstract: Studies of childhood diarrhea in developing countries have traditionally employed a wide range of diagnostic modalities including culture, microscopy, and enzyme immunoassay. Molecular diagnostics offer a substantial increase in sensitivity, however they also increase the background rate of pathogen detection. A quantitative analytic approach can help identify the subset of clinically significant molecular detections. In this symposium talk, we will present estimates of of pathogen-specific attributable fractions of diarrhea from ongoing re-analyses of two multisite studies of childhood diarrhea (GEMS and MAL-ED). Compared to prior burden estimates from these studies, this approach reveals a substantial increase in the burden of diarrhea due to pathogens for which conventional diagnostics were not sufficiently sensitive, in particular Shigella, ST-ETEC, and adenovirus 40/41. Burden estimates for other pathogens, including rotavirus and Cryptosporidium, were not significantly changed. After rotavirus, Shigella was associated with the highest burden of moderate-to-severe non-bloody diarrhea, which suggests that current guidelines limiting the role of antibiotics to bloody diarrhea in children in these settings need to be re-evaluated. These findings also have significant implications for the prioritization of pathogen-specific interventions aimed at reducing the burden of diarrheal disease in children in these settings.
Dengue, Chikungunya and Zika Virus: Global emergence
K. G. Luz
Hospital Giselda Trigueiro, Natal, Brazil

Abstract: (no abstract received from presenter)
Pathogenesis of severe dengue infection

G. N. Malavige
University of Sri Jayawardenapura, Nugegoda, Sri Lanka

Abstract: The pathogenesis of severe dengue (SD) is thought to be due to the complex interplay between the virus, host genes and the host immune response. As vascular leak, which is the hallmark of SD, occurs following the resolution of the viraemia, it was thought that an inappropriate immune response to the virus, was the main cause of SD. However, recent data shows that dengue NS1 alone activates monocytes through the TLR4 receptor, inducing inflammatory cytokine production and that NS1 was involved in vascular leak in acute dengue. We too have found that dengue NS1 stimulates IL-10 production from monocytes, which in turn could lead to suppression of dengue virus-specific T cell responses and thereby contribute to disease severity. In our studies, which have investigated the kinetics of changes in inflammatory mediators, the degree of viraemia and the onset and extent of vascular leak, have shown that inflammatory mediators are significantly elevated in patients with SD, around day 4 to 5 of illness. Levels of both IL-10 and IL-17 and other cytokines were significantly elevated in patients with SD when compared to milder dengue, before the onset of vascular leak.

Our previous studies had shown that platelet activating factor (PAF) was an important mediator of vascular leak. We found that although the dengue virus (DENV) or dengue immune serum did not induce PAF production by monocytes, lipopolysaccharide (LPS) acted synergistically with the DEN, in the production of PAF. Since LPS levels in serum have been found to be significantly elevated in SD, LPS could further contribute to disease pathogenesis and vascular leak.

Mast cells are an important source of PAF and have shown to be important in disease pathogenesis in dengue mice models. We found that mediators such as tryptase and secretory phospholipase, which are produced exclusively by mast cells, are significantly elevated in patients with DHF, during early infection. Therefore, in summary, the events that lead to severe dengue appear to occur before the onset of vascular leak and the role of mast cells and viral proteins in the pathogenesis of SD should be further investigated.
Management of severe dengue
Y. S. Leo
Communicable Disease Centre, Tan Tock Seng Hospital, Singapore, Singapore

Abstract: Dengue is an important human arboviral disease caused by infection of four antigenically related strains of dengue virus (DENV 1-4) belonging to the Flaviviridae family. Despite extensive worldwide efforts, it remains a major public health concern with 55% of the world’s population estimated to be at risk for dengue. Infection by any of the four dengue serotypes can cause a wide spectrum of disease manifestations that ranges from mild, self-limiting febrile dengue fever to severe, life-threatening disease. The pathophysiological hallmark that determines disease severity is the degree of plasma leakage, bleeding and single or multi-organ involvement. In recent years, there were several clinical trials using re-purposed pharmaceutical agents to treat dengue, however none has shown significant usefulness for its recommendation for routine use. Lacking the anti-viral agents, management of dengue is largely supportive in nature. Ability to recognise infection early and early signs of disease progression remain key in instituting early and appropriate interventions, preventing disease progression or late presentation of disease where treatment options are limited and outcomes are poor. Patients with severe dengue should be admitted to a hospital with access to intensive care facilities. Judicious intravenous fluid replacement is critical to balance the 2 stages between plasma leakage and fluid re-absorption during recovery phase. Dengue is a dynamic disease particularly so during the critical phase where plasma volume changes rapidly, close and frequent monitoring of hematocrit is critical to guide fluid replacement. Concealed bleeding may pose a clinical challenge and in instance blood transfusion may be needed. Dengue mortality can be reduced with system priming to recognise the disease and systematic treatment approach.
Zika virus: What you need to know

T. Yuill¹, R. Hajjeh², K. G. Luz³

¹Madison, WI, USA, ²NCIRD/OID/CDC, Atlanta, GA, USA, ³Hospital Giselda Trigueiro, Natal, Brazil

Abstract: (no abstract received from presenter)
Leptospirosis

D. Diament
Instituto de Infectologia Emilio Ribas, Sao Paulo, Brazil

Abstract: Leptospirosis is present worldwide and is especially important in developing countries, where sanitation is precarious. Sporadic cases are linked to contact with urine-contaminated water. In tropical countries, urban outbreaks can occur after floods in rainy season. Mild non-lethal anicteric forms comprise most cases and can be easily confused with flu, dengue fever, other mild viral illnesses and P. vivax malaria. About 5 to 10% of cases develop severe sepsis-like disease or meningitis during outbreaks. The serious illness form, also known as Weil’s Disease, courses with jaundice, shock, renal failure, coagulopathy and other organ dysfunctions, leading to prolonged hospitalization in intensive care facilities and death, with high healthcare costs. Differential diagnosis includes bacterial sepsis, hepatitis, yellow fever, Hantavirus disease, P. falciparum malaria and other severe febrile illnesses. Highly sensitive and specific rapid diagnosis tests are commercially lacking. Antibodies or antigen detection by enzyme-linked assays and nucleic acid detection by PCR in blood or other body fluids are promising. Mechanisms of disease are little known, but evidence points out to systemic inflammatory response syndrome-like pathophysiology in severe cases. Spirochete cell wall proteins, lipopolysaccharide, enzymes like phospholipase and other bacterial toxic products produce tissue damage and activate inflammatory response locally and systemically, through toll-like receptors on antigen-presenting cells, triggering cytokine secretion by innate and adaptive immune cells, resulting in inflammatory and immune responses. Some patients evolve with shock, coagulopathy, organ failure and death. Which regulatory mechanism leads to severe disease is not exactly known. Lethality varies widely in severe cases, reaching 50% in some reports, depending on diagnosis and treatment institution speed, level of care and other factors. Better comprehension of disease immunopathogeny can lead to adequate treatment and prevention.
Leprosy: Is it a disease to be neglected?
J. Muliyil
Christian Medical College, Vellore, Vellore, India

Abstract: On 31st December 2005 we realized that India had reached the goal of Eliminating Leprosy. This was quite pleasing since we had failed to reach the goal in 2000, as originally scheduled. This was also quite surprising for a country which had an annual new case detection rate of more than 4 per 10,000 population. Leprosy with its long incubation period and sub-clinical carriage did not appear to be a disease whose incidence can be reduced by treating clinical cases. This presentation is aimed at providing insights into the circumstance leading to elimination of leprosy and its implications.
Parasitic infections and allergies

P. Cooper
St. George's University of London, London, United Kingdom

Abstract: The hygiene hypothesis has been proposed to explain temporal trends of increasing allergy prevalence in high-income countries and in urbanizing populations in low-income countries (LICs). Improvements in hygiene and reductions in exposures to childhood infectious diseases are considered to cause increased allergy through a failure to educate appropriately the developing immune system leading to inadequate regulation of allergic inflammation. Parasite infections are extremely common in poor populations in LICs and a high prevalence of parasites, particularly helminth parasites, has been put forward to explain the low prevalence of allergy in rural populations of LICs. Data from epidemiological studies in populations infected with helminth parasites have provided strong evidence that exposures to helminth infections attenuate atopy and Th2 inflammatory responses directed against aeroallergens. Further, helminth exposures appear to modify the effects of atopy on allergic diseases (i.e. asthma, rhinitis, and eczema). However, exposures to some parasites with a life cycle phase of pulmonary migration may increase the risk of wheeze. For example, half the cases of wheeze in a rural case-control study were attributable to evidence of allergic sensitization to ascariasis, while two thirds of acute bronchospasm in an urban setting was attributable to house dust mite IgE. Helminths may, therefore, be the primary target of allergic responses in traditional rural populations and such responses may be subject to immune regulation leading to a milder clinical course of allergic diseases. In contrast, in urbanizing populations where the introduction of sanitation may lead to the gradual disappearance of helminth infections, aeroallergens may emerge as the primary allergic sensitizers, and because such responses may be subject to less rigorous regulation, could cause more severe disease. Prospective studies from birth in populations undergoing the process of urbanization are helping to define the role of exposures to helminth parasites and other childhood parasitic infections in the changing epidemiology of allergic disease in LICs.
Infectious disease pathology in India: Interactive cases

R. Gopalakrishnan
Apollo Hospital, Chennai, India

Abstract: India is in a unique position in that Indian clinicians and pathologists encounter both diseases endemic to other tropical and developing countries, as well as healthcare and immunosuppression associated infections more typical of developed countries. This interactive session will discuss several cases that illustrate the varied clinical presentations of infectious diseases, their differential diagnosis and correlate the clinical with the pathological findings in these patients.
Hepatitis C infection in people who inject drugs
T. Azim
icddr,b, Dhaka, Bangladesh

Abstract: Hepatitis C virus (HCV) is a major global public health problem. Worldwide, ~184 million people are infected, with a higher prevalence in developing countries compared to developed countries in North America and Europe. However, vulnerable populations (e.g., people who inject drugs (PWID), Aboriginal people, and incarcerated individuals) account for >80% of new infections and most of the onward transmission. In Bangladesh, PWID account for the vast majority of HCV infections.
Sources of data on HCV in Bangladesh in key populations at risk of HIV are available through various sources. The last national HIV surveillance conducted in Bangladesh in 2011 showed that in six cities >50% of PWID had antibodies to HCV; in the capital city of Dhaka, HCV prevalence among PWID was 39.6%. Information from 965 clients attending the HIV testing and counselling unit of icddr,b in 2011 where HCV antibodies were also tested also confirmed that the highest rate was in PWID (37.1%) followed by clients of FSW (1.6%) and less than 1% in others. Geographically, populations in Dhaka, especially old Dhaka, appear to be especially vulnerable to blood-borne infections such as HCV and HIV. In a study conducted in 2015 among 84 HIV positive PWID in old Dhaka, 61% were also positive for anti-HCV antibody. However, harm reduction services have been active in Bangladesh and the needle syringe program is among the best in South Asia. The prevalence of HCV has significantly declined in PWID in Dhaka since 1998 which appears to be a direct result of these services. Hepatitis C virus shows considerable sequence variability in its genome and has at least 6 genotypes which respond differently to available therapeutics. In Bangladesh, RNA from 81 samples obtained through different studies at different times were amplified for genotyping; 3a was the most prevalent (59.3%) followed by 3b (32.1%), 1b (4.9%), 1a (2.5%) and 3g (1.2%). Newer, short-course, and well-tolerated therapies have become available and it is being suggested that “Treatment as Prevention” be undertaken as a strategy in PWID to reduce onward HCV transmission. Such a strategy could become part of a comprehensive HCV disease elimination strategy.
Abstract: Significant progress has been made in treatment of hepatitis C (HCV) infection since the virus was discovered over 26 years ago. After introduction of directly acting agents (DAAs), the treatment for hepatitis C has significantly improved both in efficacy and tolerability. Clinical trials using combinations of DAAs have shown excellent sustained viral response rates (SVRs) in patients with all HCV genotypes. Hepatitis C has now become a curable disease from a chronic disease, and complications such as liver cirrhosis and hepatocellular carcinoma (HCC) are preventable. Given the safety and efficacy, treatment of HCV can move to the realm of primary care physicians. However, with availability of multiple DAAs in the market and several more on the pipeline, it has become more complex to decide which combination therapy would be more appropriate for individual patients. Additionally, despite an abundance of choices, the cost of drugs has become a major hindrance to access for many patients. This presentation will provide an overview and update on treatment of hepatitis C infection.
HIV and hepatitis C co-infection
T. TBD

Abstract: Infection with HIV and HCV contributes substantially to the global burden of disease, with an estimated 4-5 million people living with both infections. The natural history of HIV and HCV is significantly impacted by the coexistence of the other virus. Increases in all-cause, AIDS-related, and liver-related morbidity, hospitalization, and mortality are noted, with accelerated liver disease progression and high rates of end-stage liver disease, even in those receiving combination antiretroviral therapy (cART) Given greater access to cART, the number of global deaths related to HIV is falling. In contrast, the number of HCV-related liver deaths is rising. Fortunately advances in the development of directly acting antiviral (DAA) agents for the treatment of HCV now mean that highly effective, all oral regimens with low toxicity can be use to achieve sustained virological response (SVR) in the majority of HIV-HCV co-infected individuals. However high cost and limited access to these drugs currently prevent their widespread use, especially in low and middle income countries. This paper will review the epidemiological data on prevalence of HIV-HCV globally and discuss the natural history of co-infection. Most recent data on trials of DAA combination therapy in HIV positive people will be presented and issues relevant to this population including drug-drug interactions reviewed. Finally barriers to care and treatment relevant to global settings will be discussed.
Hepatitis E vaccine - where are we today?
P. Abraham
Christian Medical College, Vellore, India

Abstract: Outbreaks and sporadic cases of hepatitis E occur globally with large epidemics occurring in resource-limited regions where there is over-crowding, unsanitary conditions and poor health services including refugee camps and internally displaced populations. The World Health Organization (WHO) estimates that the virus infects 20 million people each year of which 3 million are acute hepatitis cases and 56,600 die. Fulminant hepatic failure is reported in those infected in the third trimester of pregnancy in some regions. Hepatitis E virus (HEV) infection can lead to hepatitis decompensation in those with pre-existing liver disease. Chronic HEV infection has been reported in solid organ transplant patients and those on immuno-suppression. There are four known genotypes of HEV. The most recent candidate vaccines have been two recombinant HEV vaccines. The first of these vaccines was based on a 56-kDa baculovirus-expressed ORF2 protein produced in Spodoptera frugiperda cells, developed at the National Institutes of Health, later licensed to GlaxoSmithKline. A phase II clinical trial was conducted in 1,794 young male military recruits in Nepal who received three doses 20µg of the alum-adjuvanted vaccine or placebo. Vaccinees were followed up to 2.2 years. The vaccine showed a 95% efficacy after the third dose. This vaccine study was limited by the fact that it was tested on almost exclusively young males, it did not measure the HEV infection rate and that antibody titers declined by the end of the study. The second vaccine was developed by researchers at Xiamen University in China, using a new recombinant HEV protein expressed in Escherichia coli. This vaccine, HEV 239 (Hecolin), was tested in a randomized, controlled trial involving 112,604 healthy participants aged between 16-65 years in Jiangsu Province, where HEV genotypes 3 and 4 are more prevalent. In those who received all three doses, 87% maintained antibodies and remained protected against HEV for up to 4.5 years. Its efficacy against HEV genotypes 1 and 2, in pregnant women and those younger than 16 years and older than 65 years are yet to be assessed. The vaccine is licensed for use in China. Though not yet prequalified by the WHO, the WHO is ready to assist national health authorities and regulators in a rapid assessment of this vaccine. Today, the real challenge will be to get an HEV vaccine to those who need it the most, at an affordable price.
Antimicrobial resistance: From problem to policy to action
S. Davies
London, United Kingdom

Abstract: Professor Dame Sally Davies, Chief Medical Officer for England, will set out why Antimicrobial Resistance (AMR) has become a Global Health Security issue. She will explain how, through our collective action, AMR has become a significant health issue across the globe and the impact on health if we do not take collective action to conserve the antimicrobials that we have, and encourage the development of new antimicrobials. Dame Sally will highlight the need for cross-government engagement in the fight against AMR – it cannot be seen as a health issue in isolation, but needs a ‘one-health’ approach. Finally, Dame Sally will consider the challenges that we face globally, the international action to date and important next steps.
Fungal infections after transplant

S. Swaminathan
Smrth Pediatric Care, Chennai, India

Abstract: The number and complexity of tissues being transplanted worldwide has increased, which has been made possible by more centers and well trained teams being involved, and better availability of organs. Increased understanding of the working of the immune system, and more choices in drugs has ensured greater graft survival with fewer long term complications. Simultaneously, advances in infection control, and targeted use of prophylactic agents has resulted in improved overall survival due to reduction in infections. However, this has resulted in the rise in relative importance of fungal infections as a cause of morbidity and mortality in transplant recipients. There have been many advances in this field, and this starts with risk reduction. Better understanding on the time line of fungal infections have helped us design enhanced infection control measures like HEPA filter in stem cell recipients, patient education on avoidance of high risk situations, a commitment to de-escalate immune suppression and use of targeted antifungal prophylaxis. In spite of such interventions, fungal infections continue to play a role. Early identification of patients who are at risk for invasive fungal infection can ensure use of pre-emptive therapy in selected cases. Better diagnostic modalities including radiology like high resolution computed tomograms of the chest, earlier invasive procedures including bronchoscopy and biopsy coupled with serological studies like beta d-glucan, and galactomannan have shortened the time to diagnosis of fungal infections. Simultaneously, advances in fungal identification, both culture and molecular techniques have helped the clinician use the most appropriate antifungal agent. We also have an expanding armamentarium of drugs, both new drugs in existing classes and a new class of antifungal agents, to best suit the individual patient. There is still scope for significant improvement in areas, which include evaluation of new markers which could hasten time to diagnosis, and new agents which can tackle some of the more difficult or resistant fungi.
Neutropenic sepsis

F. Menichetti
Pisa Hospital, Pisa, Italy

Abstract: Chemotherapy-induced neutropenia is the leading cause for bacterial and fungal infections in patients with haematological malignancies. The drop of neutrophils count below 1000 cells/cmm increase the risk of febrile episodes (TC > 38°C) and infectious complications but most of the bacteremic episodes are documented when neutrophils count is below 100/cmm (severe neutropenia). The duration of neutropenia also play a pivotal role in determining the risk of infection: prolonged neutropenia is defined by a duration of 3 weeks. Among 100 febrile episodes occurring during neutropenia 40% are FUO, 20% are clinically documented, 20% are microbiologically documented and 20% are bacteremia. Gram-positive cocci (CNS, St. aureus, streptococci, enterococci) represent around 50% of the blood isolates and gram-negative bacilli (Ps. aeruginosa, enterobacteriaceae) are documented in the same rate. Recently, an increasing rate of MDR gram-negative bacilli (i.e. K.pneumoniae KPC-producing and other carbapenem-resistant gram-negative bugs) are responsible for local epidemic clusters. Empiric antibiotic therapy is recommended in patient with febrile neutropenia: blood cultures (at least 2 sets) should be taken immediately and therapy started in 1 hour (febrile neutropenia is a medical emergency). Monotherapy with a betalactam antibiotic with anti-pseudomonal activity (meropenem, piperacillin/tazobactam) is usually started, adding an anti gram-positive agent (vancomycin, daptomycin) in case of a documented gram-positive bacteremia or in patient with local sign of CVC infection (“escalation” strategy). A de-escalation strategy is preferred in patient presenting with severe sepsis or septic shock and in the setting of a cluster of MDR gram-negative bacilli. Combination therapy is started (betalactam, aminoglycoside, antistaphylococcal agent) then de-escalated on the basis of microbiological documentation and/or clinical response. In case of KPC-producing K. pneumoniae epidemic a combination of colistin, tygecicline and gentamicin should be considered; some clinicians suggest the use of high-dose meropenem (although many of the isolates shows a MIC >128 mg/l). It is noteworthy that the use of rectal swab to identify colonized patients may be important for the infection control procedures (patient isolation) and to predict the subsequent sepsis. In neutropenic patients with fever not responding to 3 or 4 days of antibiotic therapy the start of an empiric antifungal therapy (echinocandin, amphotericin B) should be considered. Serological markers (betaglucan, mannan/anti-mannan etc.) may be useful to select patients at higher risk of yeast infection; galactomannan is otherwise useful to suspect Aspergillus infection.
Infectious complications of biologic therapeutics

S. Opal
Brown University, Providence, RI, USA

Abstract: An expanding array of new biologics are entering clinical practice to supplement existing therapies in the management of neoplastic diseases, organ transplantation, rheumatic diseases and numerous other inflammatory disease states. These biologics include monoclonal antibodies, soluble cytokine receptor constructs, growth factors and recombinant proteins. Their use have revolutionized treatment for some severe forms of rheumatoid arthritis, multiple sclerosis (MS) and inflammatory bowel disease where biologics have now become the standard of care. Such agents are not without risk as a number of common infections and at times rather unusual infections are being recognized with increasing frequency following the institution of biologics. Opportunistic infections are particularly a concern in patients receiving combination therapy with multiple biologics in addition to standard immunosuppressive agents such as corticosteroids, anti-metabolites and calcineurin inhibitors.

Because of their frequency and severity, the infections of greatest importance following a biologic are tuberculosis, opportunistic and endemic mycoses (histoplasmosis and coccidioidomycosis), and high risk viral infections (HIV, hepatitis B and C, adenoviruses and the JC virus that causes progressive multifocal leukoencephalopathy (PML). While these infections should receive the most attention, an array of pathogens ranging from viruses (herpes viruses, paramyxoviruses), bacteria (e.g. listeriosis, mycobacterial infections, skin and soft tissue pathogens, respiratory infections), numerous opportunistic fungi, and parasitic organisms including toxoplasmosis, pneumocystosis, and strongyloidiasis should also be considered. The greater the intensity, duration and combinations of biologics all increase the risk of secondary infection. Many biologics have prolonged immunosuppressive effects, thereby limiting cost and improving convenience, but this long pharmacodynamic effect leads to infection risk for prolonged periods up to years after stopping the treatment. A number of these infections can be detected in latent forms allowing for prophylaxis or avoidance of some biologics such as screening for PML by serology before using natalizumab (alpha-4 integrin monoclonal antibody), or screening for latent TB before using TNF inhibitors.
Cytomegalovirus

P. Ljungman
Karolinska Institute, Huddinge, Sweden

Abstract: Cytomegalovirus (CMV) remains an important pathogen in transplant patients. Sensitive and rapid turnaround quantitative PCR based monitoring coupled with the availability of effective antiviral therapy has reduced the overall burden of CMV disease after transplantation. However, in hematopoietic stem cell transplant (HSCT) patients, the increasing use of new donor and stem cell sources present new challenges in the prevention and treatment of CMV. Gastrointestinal disease is now the most common end-organ manifestation of CMV infection after HSCT, whereas pneumonia remains associated with high mortality. In addition, indirect effects of CMV infection continue to have both positive and negative effects on outcomes after HSCT. Antivirals with novel mechanisms of action and improved toxicity profiles compared to those currently available are in late phase clinical trials. Also CMV vaccines are in development. Despite these advances, CMV is likely to remain a significant pathogen in transplant recipients.
New antibiotics: What do we need?

D. Morgan
University of Maryland School of Medicine and Centers for Disease Dynamics, Economics and Policy, Baltimore, MD, USA

Abstract: Lack of effective antimicrobial therapy for multidrug-resistant organisms (MDROs) has been a growing concern particularly due to spread of extended-spectrum beta lactamase (ESBL) and carbapenem resistant Enteriobacteriaceae (CRE). Better therapeutics for MDROs are needed. Common MDROs include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), ESBL and CRE. Gram-positive organisms such as MRSA and VRE are stable or declining in frequency while gram-negative ESBLs and CREs are increasing. Recent antibiotics generally focus on MRSA and gram-positive MDROs with few new agents effective against gram-negative organisms. Outside of common healthcare-associated MDROs, Gonococcus has become highly antibiotic-resistant in many parts of the world. Furthermore, most therapy for MDROs is intravenous and associated with a high rate of adverse effects and burden of disease related to long courses of treatment. New antibiotics are needed with novel mechanisms of action against MDRO organisms, fewer side effects, less impact on the microbiome and easier, non intravenous delivery. Studies of new drugs need to focus on rational use with minimal duration, easiest form of delivery and clear recognition of effects on the microbiome. Use of new antibiotics must be appropriate and avoid overuse. Choosing Wisely and the growth of Antimicrobial Stewardship may help appropriate use.

Finally, a new model of infectious disease management is developing based around the microbiome. Manipulation of the microbiome may become a mainstay for treatment of many diseases. Currently, fecal transplants for C. difficile are the only approach to microbiome manipulation proven to work. Other uses may include decolonization of MDROs from the gastrointestinal tract. Future microbiome manipulations may include targeted microbiome changes via capsules to the GI tract and possible inoculations to the skin or mucosal surfaces. Development of ways to manipulate the microbiome could improve treatment of infectious disease without producing antibiotic resistance. Development of antimicrobials active against ESBLs, and CREs that are safe and easy to use is needed. Longer range antimicrobial therapies will likely involve microbiome manipulation.
The antibiotic pipeline: What can we expect?

**U. Theuretzbacher**
CEFAIA, Vienna, Austria

**Abstract:** Antibiotic resistance is widespread. Despite the recognized and growing need for new antibiotics, today most large pharmaceutical companies have dropped active antibacterial drug discovery programmes. While antibiotics are regarded as non-profitable compared to other fields, small companies—mostly backed by promising academic discoveries—are stepping in to drive research and early clinical development in the antibiotics field. In the 1980s and 90s the antibiotic pipelines were satisfying the need for improved antibiotics against the prevalent resistant strains at that time. Currently, extensively- or pan-resistant Gram-negative bacteria require novel antibiotics without co- and cross-resistance to known drug classes. A few research&development programs based on classical antibacterial compounds against Gram-negative bacteria that bind to new targets or have a new mode of action are in the early research phase and their potential is difficult to assess. Due to such thin discovery pipelines, attitudes have changed and antibacterial approaches outside the mainstream are increasingly pursued and publicly funded. These alternative methodologies range from peptides and peptidomimetics to antibodies, prophylactic and therapeutic vaccines, adjunctive therapies, bacteriophage cocktails. The value of such approaches as well as the regulatory pathways are not clear yet. Potentiating strategies have seen a resurgence in recent years and are focused on blocking specific resistance mechanisms such as beta-lactamases, resistance-regulating determinants, preventing transfer of resistance plasmids or on protecting the microbiome, disrupting biofilms, targeting dormant bacteria, blocking virulence factors, or supporting the immune system. In response to relaxed regulatory requirements and economic incentives, recent years have seen a trend towards reviving old drugs (e.g. fosfomycin, fusidic acid, minocycline, aztreonam), modifying old drugs (e.g. colistin) or potentiating old drugs (e.g. combination of approved drugs, ß-lactamase-inhibitor combinations). These approaches will not solve our major problems with resistant bacteria but may buy some time.
Incentivizing antibiotic innovation

C. Årdal
Norwegian Institute of Public Health, Oslo, Norway

Abstract: Antibiotic resistance can develop quickly. The CDC demonstrated in 2013 that the first reported cases of bacterial resistance occurred in less than three years after market introduction of six key antibiotics. Yet antibiotic innovation is progressing at a more sedate pace, with only seven new classes of antibiotics launched between 2000 and 2014 (Laxminarayan 2014). One reason for this mismatch is that the pharmaceutical industry is not incentivized to develop new antibiotics. Existing, generic antibiotics are inexpensive and still generally effective. New classes of antibiotics are often necessary for only a small number of patients or as an insurance mechanism for potential future outbreaks, making the return on the sizeable investments in research and development insignificant or negative. These poor returns encourage the pharmaceutical industry to focus their efforts elsewhere. Yet resistance continues to emerge, and if we wait until a major outbreak occurs, given the long lead-times for developing a new antibiotic, it will be too late. New incentives are necessary to stimulate greater antibiotic innovation, and they must be linked to the sustainable and appropriate use of the resulting antibiotic. Otherwise resistance may develop faster. New incentives need to reward developers for their knowledge generation, not the number of treatments sold. They also need to ensure that patients receive the necessary antibiotic, regardless of income status. These are fundamental changes to the current reward system for pharmaceutical innovation. The EU-financed Innovative Medicines Initiative project, Driving reinvestment in R&D for antibiotics and advocating their responsible use (DRIVE-AB), is tasked with identifying new, sustainable economic models as well as recommendations for a viable path forward to greater antibiotic innovation.
Basic improvement methods in stewardship

A. H. Holmes
Imperial College London and Imperial College Healthcare NHS trust, London, United Kingdom

Abstract: Pragmatic strategies to improve antibiotic prescribing will be discussed in this session. Although a whole healthcare economy approach to antibiotic stewardship will be advocated, the particular focus will be within acute health care. Implementation and adoption will be considered along with improvement methods in stewardship. Supporting organisational models will also be reviewed and practical examples and case studies described. The real and potential challenges faced in delivering effective antibiotic stewardship and sustaining improvement will be discussed.
Update on HIV Prevention

K. Mayer
The Fenway Institute, Boston, MA, USA

Abstract: In recent years, definitive studies have demonstrated the efficacy of the use of antiretroviral medications for primary and secondary HIV prevention. The HPTN 052 trial enrolled 1,752 partners in HIV discordant couples in Africa, Asia and the Americas, and randomized the infected partner to receive immediate versus deferred antiretroviral therapy. HIV-infected participants who immediately initiated treatment were more than 96% less likely to transmit HIV to their partners compared to those in the delayed arm. The public health benefit of early treatment has been corroborated by population level studies correlating decreasing HIV incidence in several areas of southern Africa with access to early initiation of antiretrovirals. However, since the majority of people living with HIV globally are unaware of their infection, and less than 1/3 are virologically suppressed, new approaches to primary prevention for high risk seronegatives are also needed. Ten randomized, controlled trials of antiretroviral pre-exposure prophylaxis (PrEP) have been conducted, with studies in men who have sex with men, heterosexual discordant couples, and injection drug users finding that oral tenofovir-based regimens have been effective in decreasing HIV incidence. Several studies of PrEP in young African women have not demonstrated efficacy, while others have, with variable levels of medication adherence explaining most of the divergent findings. Tenofovir-emtricitabine taken orally for PrEP has been approved by regulators in the US and Africa, and is being considered for approval in several African and European countries. New approaches to chemoprophylaxis are under study, including the use of vaginal and rectal gels, vaginal rings, and injectable agents. Because antiretroviral PrEP does not protect against other sexually transmitted infections (STI), it must be given as part of a comprehensive sexual health package, which includes counseling and screening for treatable STI. Other interventions that can decrease HIV transmission include adult male circumcision of HIV-uninfected men, recreational drug treatment, including access to clean syringes and other drug paraphernalia, and opiate substitution therapy. The advent of new biomedically-based prevention interventions does not obviate the need for behavioral interventions, but suggests that counseling interventions should incorporate reinforcement of medication adherence, as well as risk reduction counseling.
The good, the bad and the beautiful: Anti-retroviral therapy considerations in children and adolescents

A. Shet
St. John’s Medical College, Bangalore, India

Abstract: HIV care for infants, children and adolescents has improved by leaps and bounds. Whereas the landscape two decades ago was bleak for children born with HIV who faced inevitable death, it is now filled with hope with the ever-increasing access to anti-retroviral therapy (ART) and care. Coupled with this progress is the success of prevention of mother-to-child transmission of HIV interventions, again with ART, resulting in fewer new infections in children. Yet, there is a long pathway to be traversed before we can achieve complete control of pediatric HIV.

Challenges: Being born with HIV or acquiring HIV in childhood can be devastating, even in the era of ART. Taking ART is a lifelong practice; the risk of long-term adverse effects is real and lasting, and children generally have to take ART for an average of 20 years longer than an adult. This could mean constant monitoring, and in many cases, life-threatening long-term consequences. Adolescence is a time when adherence to any treatment or norms established earlier is questioned, and HIV care suffers the same fate. Rebellion and poor adherence to ART results in risk of drug resistance and treatment failure. Perinatally infected children may face mental challenges, including learning disabilities and behavioral disorders. Integrated with the social support offered for these challenges, one also needs to maintain an honest and respectful discussion with children about growing up with HIV, including their sexual and reproductive health.

A hopeful future: The ambitious “90-90-90” goal launched by UNAIDS in 2014 focuses not just on the 90% of the HIV-infected population that they aim to diagnose and treat, but also on the 90% of all treated who will be virologically suppressed. This shift in our focus from mere volume of care, to actual quality of care in terms of retention and suppression, are key to optimal HIV outcomes. Nelson Mandela once said, “There can be no keener revelation of a society’s soul than the way it treats its children.” The know-how and tools that are available in today’s world offer the global community the very real and beautiful possibility of controlling pediatric HIV.
Manifestations and management of IRIS

G. Meintjes
University of Cape Town, Cape Town, South Africa

Abstract: In many resource-limited settings a substantial proportion of HIV-infected patients still commence antiretroviral therapy (ART) with advanced HIV-related immunosuppression with low CD4+ T-lymphocyte counts and active opportunistic infections. Such patients are at high risk for developing the immune reconstitution inflammatory syndrome (IRIS) in the first weeks to months of ART as immune responses to opportunistic infection antigens are rapidly restored resulting in inflammatory reactions directed at antigens of the opportunistic infection. This may result in hyper-inflammatory new presentations of opportunistic infections or paradoxical deterioration in patients already on treatment for the opportunistic infection. IRIS is most commonly described in association with mycobacterial, fungal and viral infections. Tuberculosis-associated IRIS (TB-IRIS) is the most significant form of the condition encountered in settings where TB endemic. In a recent meta-analysis, we found that TB-IRIS is reported in 18% (95%CI= 16-21%) of patients starting ART while on TB treatment. Major risk factors for the condition are a low CD4 count, high HIV viral load, disseminated TB and short interval between starting TB treatment and ART. A key determining factor thus appears to be antigen load. Innate and adaptive components of the immune system have been shown to contribute. A gene transcriptional signature characterised by innate immune signaling genes distinguished patients who developed TB-IRIS from those who did not, and was evident within a few days of starting ART and prior to symptoms. TB-IRIS is characterized by high concentrations of cytokines in peripheral blood, with elevated interleukin-6 identified consistently across studies. Common clinical presentations are worsening pulmonary infiltrates, enlarging lymph nodes and abscess formation. Central nervous system involvement (e.g. meningeal inflammation, enlarging tuberculomas) may be life-threatening. The average duration of the condition is 2-3 months, but a small proportion of cases may have manifestations lasting > 1 year. We demonstrated in a previous clinical trial that prednisone (starting at 1.5mg/kg/day) reduced hospitalization and improved symptoms in patients with TB-IRIS. We are currently evaluating prednisone for prevention of TB-IRIS in high-risk patients with TB starting ART in a randomized placebo-controlled trial (PredART trial: https://www.predart.org/site/index).

Cryptococcal IRIS typically presents with recurrent meningitis in the first months of ART, often with associated raised intracranial pressure. No clinical trials have been conducted, but management usually involves re-initiation of induction antifungal therapy until relapse is excluded, therapeutic lumbar punctures and in severe cases corticosteroids.

A priority in IRIS research is identifying key inflammatory pathways that trigger the condition that could be targeted with more specific immunotherapy to prevent and/or treat the condition.
The long-term impact of antiretroviral therapy in resource-limited settings

N. Kumarasamy
YRG CARE Medical Centre, Chennai, India

Abstract: With the advent of antiretroviral therapy (ART), HIV has shifted to a chronic manageable condition, even in resource-limited settings. Now, the long-term effects of being on ART and living with HIV are emerging. These include the adverse effects of long-term ART and morbidity due to non AIDS complications such as cardiovascular, hepatic, renal, metabolic and neurocognitive disease, cancers and ageing as well as complications due to hepatitis B and C co-infection. Although first and second-line antiretrovirals are available in resource-limited settings, new antiretrovirals are urgently needed in order to sustain HIV as a chronic manageable condition. Several clinical trials are underway to eradicate HIV from reservoirs among patients who are on long-term ART and virologically suppressed, leading to the hope of eventual eradication of this virus.
Active case finding of kala-azar

P. Das
Rajendra Memorial Research Institute, Patna, India

Abstract: (no abstract received from presenter)
Abstract: Visceral leishmaniasis is the most severe form of leishmaniasis, and if untreated, it is fatal. Although pentavalent antimony (Sb⁵⁺) is most widely used drug for its treatment, but in the state of Bihar in India and in Nepal moderate to severe resistance to Sb⁵⁺ led to it being abandoned in the Indian subcontinent. Governments of India, Nepal and Bangladesh launched an elimination initiative for visceral leishmaniasis (VL) in 2005 and oral miltefosine was selected for treatment. Prolonged regimen of almost one month, frequent gastrointestinal adverse events and teratogenic potential are major hurdles of the miltefosine treatment leading to poor compliance. Further, long half life of miltefosine makes it vulnerable for drug resistance. Recently two important breakthroughs in the treatment of VL provide new perspective in the control of VL in Indian subcontinent. In a randomized controlled study over 300 parasitologically confirmed patients were treated with single dose of 10 mg/kg of liposomal amphotericin B (AmBisome, L-AmB). The cure rate was 95.7% which was comparable to the comparator conventional amphotericin B (96.3%). In another phase 3 study which closely followed the single dose study multiple combinations of the three available drug, L-AmB, miltefosine and paromomycin were administered between 8-11 days. In this open labelled, randomized, controlled, non-inferiority trial in Bihar, India, single injection of 5 mg/kg L-AmB and 7-day miltefosine; L-AmB and 10-day paromomycin; miltefosine and paromomycin for 10 days were compared with the conventional treatment. The efficacy rates for all patients enrolled (intent to treat, ITT) were: amphotericin B 93.0%; L-AmB and miltefosine 97.5%; L-AmB and paromomycin 97.5%; miltefosine and paromomycin 98.7% (95.06-99.78). Combination therapies were well tolerated and had fewer adverse events than standard treatment. These studies provide newer vistas in the treatment of VL. Their early implementation will provide a tremendous boost to the Elimination programme.
Post kala-azar dermal leishmaniasis: Burden, diagnosis and treatment challenges
V. Ramesh
Safdarjung Hospital, New Delhi, India

Abstract: Post-kala-azar dermal leishmaniasis (PKDL), a sequel to kala-azar mainly caused by *Leishmania donovani* is endemic in the eastern part of India and the adjoining countries of Bangladesh and Nepal. The importance of tracking this infection is vital for the eradication of kala-azar. It is important to note that PKDL can occur as long as 20 to 30 years after the episode of visceral infection. The impact of adequate therapy of kala-azar on the occurrence of PKDL remains unclear. The diverse clinical manifestations of PKDL continue to evade clinicians. Unfortunately the recognition and classification of this dermatosis remains unsatisfactory. Traditional methods like slit-skin smear and histopathology supplemented by history are not sensitive since Leishman- Donovan bodies may not be demonstrable in a significant number. Immunohistochemical and culture facilities are infrequently available and need expertise. Recent studies have resorted to the use of rk39 strip test and PCR/qPCR to confirm the diagnosis. However the routine availability of these tests needs much improvement even in the endemic areas. Awareness of PKDL in non-endemic areas is to be increased as kala-azar has also been reported from some of these places. Little has been done to devise good therapeutic regimens to treat PKDL. The antimony era proved very bad with gradually increasing doses of parenteral antimony leading to a state where complications outran benefit. Further the development of antimony resistance finally put an end to this era. Oral miltefosine made a breakthrough in the beginning of this century and is currently the recommended drug for this condition. The development of resistance and high incidence of gastrointestinal side-effects following increased or prolonged dosage are major deterrents. Trials are being conducted with liposomal amphotericin to optimize the dose and duration in PKDL. The greatest problems confronting clinicians in the use of these two drugs, miltefosine and liposomal amphotericin, is the availability, cost and hospitalization in case of the latter. Combination therapy is a powerful tool that has still to be explored. This critical juncture when kala-azar appears to be on the wane signals the need for better drugs and diagnostic facilities to effectively keep PKDL under control.
Combination treatment for visceral leishmaniasis patients co-infected with human immunodeficiency virus in India

S. Burza
Medecins Sans Frontieres, London, United Kingdom

Abstract: There are considerable numbers of patients co-infected with Human Immunodeficiency Virus (HIV) and Visceral Leishmaniasis (VL) in the VL-endemic areas of Bihar, India. These patients are at higher risk of relapse and death, but there are still no evidence-based guidelines on how to treat them. In this study, we report on treatment outcomes of co-infected patients up to 18 months following treatment with a combination regimen.

This retrospective analysis included all patients with confirmed HIV-VL co-infection receiving combination treatment for VL at an MSF treatment centre between July 2012 and September 2014. Patients were treated with 30 mg/kg body weight intravenous liposomal amphotericin B (AmBisome®) divided as six equal dose infusions combined with 14 days of 100 mg/day oral miltefosine (Impavido®). All but eight patients started or were continued on antiretroviral therapy (ART). Kaplan-Meier and proportional hazard models were used to estimate cumulative incidence of death, relapse, poor outcome (relapse and/or death) and associated risk factors over an 18-month period following completion of treatment.

102 patients (76% males, 57% with known HIV-infection, 54% with a prior episode of VL) were followed-up for a median of 11 months (IQR:4-18). Median CD4-count at VL-diagnosis was 169 cells/µL (IQR:88-230). Overall tolerance to treatment was excellent. Sixteen patients died of whom 2 before completion of treatment and 2 others after a VL relapse. Another 6 patients had a VL relapse during the follow-up period. Cumulative incidence of all-cause mortality and VL relapse at 6, 12 and 18 months was 11.7%, 14.5%, 16.6% and 2.5%, 6.0%,13.9% respectively. Cumulative incidence of poor outcome at 6, 12 and 18 months was 13.9%, 18.4% and 27.2% respectively. Not initiating ART and concurrent tuberculosis were independent risk factors for mortality and poor outcome. No factors were associated with relapse.

In this study, combination therapy appeared to be well tolerated, safe and effective and may be considered as an option for treatment of VL in HIV co-infected patients. Extended follow-up and multidisciplinary management is critical. Evidence from randomized clinical trials or larger prospective studies are essential to establish optimal treatment regimens.
The health of refugees and displaced persons in South Sudan

J. Wamala
Ministry of Health, Juba, South Sudan

Abstract: (no abstract received)
Managing health and infections in refugees: Turkey's experience
H. Leblebicioglu
Ondokuz Mayis University Medical School, Samsun, Turkey

Abstract: Turkey is located adjacent to the regions of war and crisis. After the outbreak of conflicts in Syria on March 2011, over 4.5 million people have been forced to leave their country and over 2,200,000 of them took refuge in Turkey. Turkish government has implemented "open-door policy" and shouldered a tremendous load collaborating with non-governmental organizations and spent nearly $8 billion for caring of refugee population. Refugees were first met at border crossing points, registered and given identity cards that document the status of "temporary protection". A symptom-based screening (not a standard protocol) was implemented for urgent health problems during registration and children were included in the national vaccination program comprising oral polio, measles (MMR), TdaP-Hib-IPV (quintet vaccine), hepatitis-B and conjugated pneumococcus.

As of January 4, 2016; 267,476 refugees are placed in 25 separate accommodation centers in ten different cities and remaining majority of refugees live out of the camps. Although health and education facilities are better in the camps, those non-camp residents also have free access to primary care and even secondary or tertiary-care if address-based registry was made and complied to the referral chain. Mop-up vaccination campaigns are launched for non-camp residents scattered in large cities and the coverage has extended above 90 percent for polio and measles. Healthcare capacity for refugees/asylum seekers was re-established by recent regulations on the basis of "Law on foreigners and international protection" that has entered into force on 11 April 2014. According to the current legislation; medical requirements of Syrian refugees including medicine, dentures, eyeglasses, hearing aids and similar medical materials are provided, treatment costs are to be billed to the Governor of the relevant province.

A significant number of the refugees suffer physical and psychological traumas of the war while infections are not among the leading health problems. According to the records of Ministry of Health; 5505 cases of cutaneous leismaniasis and 558 cases of tuberculosis were detected and treated (in and out of the camps) as of October 2015. Tuberculosis was screened in 10,689 refugees and the prevalence was found to be similar to the Turkish population (18.7/100,000). Screening was terminated. No case of malaria was detected in the blood smears of over 100,000 people. A significant increase was detected in cases of measles, particularly in southeastern region where the camps are located. This caused a shift in national vaccination program and the booster of MMR vaccine was withdrawn from the first year of primary school to the preschool period.

Breakdown of healthcare infrastructure, shortage of medical personnel, medical supply and drugs, limited access to clean water and problems with garbage disposal had lead to outbreaks of hepatitis A, typhoid fever and cholera in Syria. Increasing number of cutaneous leishmaniasis cases in Turkey and Lebanon, tuberculosis in Lebanon and Jordan among refugees was reported. Overall due to the lack of infrastructure of health care system in Syria, increasing number of refugees and overcrowded camps with suboptimal sanitation conditions in Lebanon and Iraq, these emerging and re-emerging pathogens not only threat the refugees but also effect the citizens of Middle East countries and even Europe. Therefore there is an urgent need of international collaboration between United Unions, European Union, governments, WHO, CDC, ECDC, humanitarian organizations, funding bodies and pharmaceutical companies to cope with infectious diseases, humanitarian crisis and recover health care and public health system in Syria.
Rapid diagnostic point of care tests in resource limited settings

J. Kafkova
St. Raphael Clinic, Nairobi, Kenya

Abstract: One of the definitions of diagnostic point of care testing is provision of laboratory testing at or near the site of patient care. It has the potential to minimise the time to obtain the result of the test, which expedites the diagnosis and initiation of the treatment especially in resource-limited settings where health care infrastructure is weak and access to quality and timely medical care represents a challenge. It is estimated, that introduction of rapid, laboratory-independent diagnostic tests for four diseases (syphilis, malaria, tuberculosis and bacterial pneumonia) in developing countries could prevent more than 1.2 million deaths annually. In resource-limited settings, laboratory medicine is still one of the most neglected pillars of the health care. In such settings, primary health care services largely depend on diagnostic point of care testing; therefore the benefits need to overweight the costs. To optimise the diagnostic point-of-care, there is a need for strict evaluation focused on relevant clinical outcomes and operational costs and these evaluations differ from the conventional tests. However, there is no consistent, standardized approach to assess the point-of-care testing technologies in resource-limited settings. Diagnostic point-of-care testing possesses significant importance in infections like TB or HIV, because it eliminates the long turn-around times and delays and the resulting loss of patients from the testing and therapy pathway. An ideal rapid diagnostic point-of-care test used in resource-limited settings should fulfil the following criteria: allowing a quick clinical decision, can be used by a health care worker (possibly by a nonprofessional), affordable, rapid, acceptable test efficacy, and cost effectiveness.
Infectious diseases in refugees and migrants during the European Migrant Crisis 2015

V. Krcmery
St. Elizabeth University College of Health and Social Sciences, Bratislava, Slovakia

Abstract: Migrant Crisis in Europe 2015 had two major routes, Balkan route via Greece, Hungary, Austria to Germany and African route with mainly economic refugees and migrants via Mediterranean Malta Lampedusa, Sicily to continental Italy, France, Spain and UK. Here we present first data on migrant health of the Balkan route from September to October 2015. About 316,000 political and humanitarian refugees, 95% from Syria, Iraq and Afghanistan passed through checkpoint Hegyeshalom, Nickelsdorf 50 km east from Vienna and 10 km from Bratislava, between September 6th and October 20th. Most of them were healthy young people with children, about 10 percent sick per transport, in 97 trains from Zakanyi Croatian Boundary or Röszke, HU-Serbian Boundary to Hegyeshalom, Nickelsdorf HU, AT checkpoint. Sick patients reported themselves to the symptomatic field health center with 8-12 HC Tropic team staff serving in 5 languages. In RTI patients, nasal/tonsil swabs was taken to Mueller Hinton agar and transported to National reference Laboratory for ATB resistance, Nitra, SK.

No major tropical diseases were noted, no case of malaria or leishmaniasis was detected. Even less cases of emerging ID including HIV and tuberculosis were detected as well. Majority of ID included pneumonia upper respiratory tract infections, skin and soft tissue infections, scabies, few cases (<3%) of diarrhoea but no case of cholera have been observed in described period. Among acute cases, diabetic coma, myocardial infarction, hypertension crisis and has been noted. From 155 positive results from bacteriology from migrants, only 2 MRSA strains and 3 penicillin resistant pneumococci were obtained, the rest was commensal bacterial flora and Candida albicans.

Balkan route in refugee crisis in 2016 in Europe from Syria, Iraq does not represent major health threat to continental EU, only few cases of transmissible diseases were noted and an absence of tropical diseases, multiresistant pathogens and no outbreaks were observed within first 2 months of exodus. Only few MRSA and penicillin resistant strains from patients from upper and lower respiratory tract infections were isolated. Spectrum of diagnoses was similar to surrounding Slovak, Hungarian and Austrian population of that EU region.
Abstract: We live in a world with the constant threat of emerging viral infections. In the last two decades, we have seen the highly publicised emergence of the Nipah Virus, SARS, MERS, the re-emergence of Ebola and the H1N1 2009 pandemic influenza together with a host of other emerging and re-emerging viruses including Zika, Chikungunya, Dengue. As clinicians, we are the front line of response to these threats and the key to the response has to be good surveillance and clinical management. High quality clinical microbiology support is critical as is both “shoe-leather” and molecular epidemiology. Only after the diagnosis has been clearly established and the epidemiology clarified, can quality clinical trials be considered for therapeutics and vaccines although the development could begin as soon as a novel pathogen is identified. We have learned many lessons from the responses both local and global to these new viral threats. One important one is the role of risk communication both among staff and the public. This is often ignored at our own peril as the responses of the community often have a disproportionate role in our work in controlling these infectious threats. Despite the billions of dollars poured into the prevention and control of these infections, most are without effective vaccines or therapeutics. There are also a number of emerging issues in pathogenesis and virulence which have yet to be answered. The task ahead is daunting but with good international collaboration, we have the opportunity to make a significant difference in the next emerging viral threat while not ignoring the current smouldering epidemics and endemic infections around us.
Intensive care considerations in epidemics

P. A. Tambyah
National University Health System, Singapore, Singapore

Abstract: Intensive care units are often the focus of epidemics – these include novel emerging pathogens as well as endemic multi-resistant organisms or even less common environmental pathogens or common hospital acquired infections. The reasons for this are simple – patient in the intensive care units are vulnerable – many are immunocompromised either by their underlying diseases or because of the therapeutic agents used to treat their cancers or rheumatological conditions. They also have numerous invasive medical devices which can put them at risk of device associated infections and many outbreaks have been documented in intensive care units all across the world from breaks in infection control in the management of patients with invasive medical devices. In addition, many patients with severe acute emerging infections such as SARS, MERS or novel strains of influenza will present to intensive care units. These pose a challenge to intensivists and all the staff in intensive care units who have to ensure that the best medical care is provided to these patients without them becoming the foci of outbreaks within the intensive care units themselves. The World Health Organization’s Core Competencies for Infection Control are a good starting point for developing our own guidelines for infection control in our intensive care units to ensure that epidemics of infectious diseases are not allowed to spread in our ICUs and to provide the best possible clinical outcomes for our patients.
Epidemiology of sepsis in low- and middle-income countries

V. Ramasubramanian
Apollo Hospitals, Chennai, India

Abstract: The burden of sepsis is high in low and middle income countries. This often results in a high mortality along with associated increase in hospital stay, morbidity and health-care related expenses. High costs of medical care related to sepsis often lead to termination of hospitalisation and discharge, apparently, against medical advice in these countries, where cost of medical treatment is usually borne by the individuals themselves. But those who can afford medical care often prefer to stay much longer and complete the entire treatment schedule in hospitals, as the infrastructure to ensure continuity of medical care is lacking in society.

There is, however, little data available on the epidemiology of sepsis in low and middle income countries. Studies are small and observational, mainly from patients admitted to corporate hospitals. These studies indicate that the burden of infections of suspected sepsis are either undifferentiated acute febrile illnesses related to tropical infections or gram negative infections related to urosepsis, skin and soft tissue infections or pneumonia. Data from prospective large scale studies are lacking.

One should also appreciate the fact that the epidemiology of sepsis in low and middle income countries is closely intertwined with the issue of antimicrobial resistance. Studies have also shown that there is a correlation between the warmer temperatures and the incidence of gram negative infections.

Finally, the problem of diagnosing sepsis and differentiating it from systemic inflammatory response is a major challenge in the developing world. Unless diagnostic modalities are improved, a true picture of the epidemiology of sepsis will be a mirage.
Antibiotic use in the ICU

J. Cohen
Brighton & Sussex Medical School, Brighton, United Kingdom

Abstract: (no abstract received from presenter)
New therapeutics for sepsis

S. Opal
Brown University, Providence, RI, USA

Abstract: A new generation of sepsis therapeutics is in development to promote clearance of microbial pathogens or their mediators and regulate the deleterious elements of the systemic host response in sepsis/septic shock. These investigations are undertaken with the realization that prior efforts to improve outcomes in sepsis have flawed either by: (1) failing to account for the intrinsic complexity of sepsis pathophysiology; or (2) assuming that septic patients would respond in a uniform and predictable manner to the experimental therapy. Clearly the definition for sepsis as an infection with systemic inflammatory response syndrome does not define a patient population that consistently and predictably reproduces the same outcome with novel sepsis therapeutics. The current sepsis treatments in clinical development are targeting a specific subpopulation of septic patients likely to respond to the invention. They studies generally rely upon some type of laboratory biomarker to predict with greater accuracy the likelihood of responsiveness to the specific therapeutic agent under evaluation. Novel therapeutics now under clinical evaluation are targeting one of the following: the pathogen or microbial mediators (hemofilters); epithelial barrier support strategies (protease inhibitors, growth factors); endothelial barrier protectors (angiopoietin-1/Tie 2, anti-complement antibodies, thrombomodulin, etc.); immune reconstitution agents (anti PDL1 antibody, thymosin-1, GM-CSF), or other targets (gelsolin, pro-protein convertases, HMGB-1 antibodies, and pro-resolving agents). In this era of precision medicine it is now possible to define a responsive patient population to a specific agent with much better accuracy. This biomarker-based strategy is now being put to the test in current clinical trials in sepsis with new therapeutic agents.
The surveillance for enteric fever in Asia project (SEAP): Estimating the community burden of enteric fever

D. Garrett
Sabin Vaccine Institute, Washington, DC, USA

Abstract: Background: The Surveillance for Enteric Fever in Asia Project (SEAP) is a phased multi-country, multi-site surveillance study designed to characterize the burden of enteric fever in selected settings in Bangladesh, Nepal, and Pakistan.

Objectives: SEAP Phase I is aimed to assess health facilities with potential to participate in phase II, and to inform the design of phase II. SEAP Phase II objectives are to use the study sites identified in phase I to characterize the burden of enteric fever in selected Asian settings, including clinical manifestations, severity of illness, long-term sequelae of illness, antimicrobial resistance patterns of enteric fever isolates, and cost of illness.

Methods: SEAP Phase I was a 2-year retrospective review of existing data. SEAP Phase II is a prospective study combining hospital-based and laboratory surveillance with healthcare utilization survey to estimate disease burden. Phase II will also include long-term follow-up of all blood culture confirmed cases to assess long-term sequelae, an economic evaluation to characterize the economic burden of enteric fever, and the description of the antimicrobial sensitivity profile. All positive specimens collected will be included in a bank of Salmonella bacterial strains isolated during the study period.

Results of Phase I: In Bangladesh, Salmonella typhi and S. paratyphi accounted for 29% and 5% of all blood cultures in children enrolled in the ongoing Invasive Bacterial Vaccine Preventable Diseases Surveillance. Forty-five percent were female. Fever, diarrhea, nausea/vomiting and abdominal pain were present in 100%, 30%, 29% and 10% of patients, respectively. In Pakistan, 81% and 29% of all microbiologically-confirmed enteric fever cases, were S. typhi and S. paratyphi, respectively. Thirty-six percent were female. Fever, diarrhea, nausea/vomiting and abdominal pain were present in 97%, 26%, 40% and 21% of patients, respectively.

Conclusion: Results of SEAP Phase I demonstrate the continued burden of typhoid fever illness in participating countries, and highlight the need for SEAP Phase II, a well-designed prospective study based on input of committed stakeholders to better quantify true burden of illness and severity. Ultimately, results of SEAP Phase II will inform policy recommendations for vaccine use, and facilitate the assessment of the impact of interventions.
Development status of typhoid conjugate vaccines globally

S. Sahastrabuddhe
International Vaccine Institute, Seoul, Korea, Republic of

Abstract: *Salmonella* Typhi, the bacteria that causes Typhoid fever, is one of the first bacterium cultured and isolated. This scourge still affects many children and adults mainly in the poor communities in the developing countries. There are currently two moderately efficacious typhoid vaccines that are licensed in many countries and one of them has been prequalified by WHO, but there are limitations to these vaccines in terms of storage conditions, age of administration and need for revaccination because of limited efficacy. There are new vaccine candidates in the pipeline using conjugation technology or recombinant DNA technology. Two of these conjugate vaccines are available in India and although the data is still unclear about their effectiveness, they should be utilized to better control the disease. In this presentation, we will get updates on the current status of vaccine development for various typhoid conjugate vaccines and ways forward.
Strategies on containing and treating drug resistant typhoid in low and middle-income countries

A. Arjyal
Oxford University Clinical Research Unit, Lalitpur, Nepal

Abstract: Multiple strategies for the patient and clinician, and for the population and policymakers should be urgently schemed to counter drug resistant enteric fever in LMICs. The usual patient-clinician interface, a single meeting at the point of care, with one or two follow-ups afterwards, should be extended both retrospectively and prospectively. Retrospectively, with a careful screening and documentation of putative exposures in the probable incubation period, and prospectively, with a post-treatment tracing of close contacts for features of illness and monitoring of the patient for relapse or treatment failure. Where blood-culture is available, pairing of clinical data with susceptibility data should be carried out. All this information should be notified to an empowered local public health body so that preventive measures may be instituted promptly. Clinicians and other team-members involved must be rewarded for prevention and control efforts. Promulgation of current diagnosis and treatment guidelines, readily accessible and implementable with local resources, should be carried out routinely. This should be based on a constant pipeline of treatment studies, preferably randomised controlled trials, conducted in an area with a similar susceptibility pattern. As an example, the fluoroquinolones, drugs of choice until quite recently, shouldn’t be used in most of South Asia, where there is a widespread circulation of fully resistant strains, and agencies such as the WHO should promptly endorse a fact as such. Notification and guideline access should exploit the widespread availability of web resources and mobile communications.

The development of rapid diagnostic tests must be prioritized and the way must be paved for the discovery and production of newer antimicrobials and rediscovery and reuse of older agents hitherto no longer in use. Awareness about antibiotics should be increased and stringent controls over antibiotic use should be exercised. Vaccination, even if it be with the existing Vi polysaccharide, despite its limited efficacy or high market prices, can be carried out selectively in populations, age groups or geographic areas at a high risk of disease. The provision of hygiene, sanitation and safe drinking water may need tremendous investments in infrastructure and can be very difficult to attain in a short span of time. Until such a time, given the high costs of resistant disease to the individual and society, the additional strategic steps to contain it outlined above are definitely worth the extra endeavours.
Global typhoid policy recommendations
A. Zaidi
Bill & Melinda Gates Foundation, Seattle, WA, USA

Abstract: The burden of typhoid is significant and occurs largely in children, with the highest rates occurring in children under 5 years of age living in poor urban environments in South Asia and sub-Saharan Africa. Water scarcity, climate change, and rapid uncontrolled urbanization in low and low-middle income countries may mitigate any improvements in water, sanitation and hygiene infrastructure historically seen with socio-economic development, and lead to conditions favoring more typhoid transmission in the future. In addition, the alarming increases in antibiotic resistance and the emergence of a globally pervasive and dominant multi-drug resistant strain (H58) seriously limits the oral therapeutic options available and has the potential to drive increased burden and case fatality. Despite the substantial burden and the high probability that effective typhoid conjugate vaccines (TCVs) will be available in the near future, there has been a lack of global momentum for achieving typhoid control. In order to align the global community towards concerted action on typhoid, an aggressive goal for global typhoid control, and an action plan is needed. We believe aggressive typhoid control is achievable through an integrated approach including improving surveillance systems to accurately measure disease burden, accelerating the introduction of TCVs in endemic areas, and incorporating water, sanitation, and hygiene systems improvements. The adoption of the Sustainable Development Goals presents an opportunity to drive this multi-sectoral approach, addressing the interconnected issues of poverty, clean water and sanitation, urbanization, and health. This is a high leverage opportunity for the global community to drive an intensive typhoid control strategy and impact this significant public health problem.
Protecting the healthcare worker around the world

R. Gallagher
Royal College of Nursing, London, United Kingdom

Abstract: The protection of healthcare workers is central to the success and delivery of health and social care and public health strategies globally. Healthcare workers are positioned at the interface between the patient (or population) and interventions to improve health and can be exposed to different risks depending on their role and health setting including biological (micro-organisms), chemical, physical and radiological. The level of risk may also vary from country to country. Healthcare workers are expensive to educate and train and the chronic global shortage of doctors, nurses and midwives is exacerbated when staff are lost through avoidable exposure to risks that damage their health and potential ability to work. The costs of making reasonable adjustments to retain employees who develop health conditions or disabilities is acknowledged to be lower than costs of recruiting and training new staff (Faculty of Public Health 2006). This presentation will explore a range of risks that exists in different care settings where lessons and learning has been identified. Scientific and professional organisations both share responsibilities and accountability for success in protecting healthcare workers and need to work together to achieve this aim. This presentation will share learning and the experience of the Royal College of Nursing (a UK based professional nursing organisation) and its relationships with European and wider global stakeholders through its work to improve the protection and safety of healthcare workers. The success of campaigns to highlight risks of sharps injuries and subsequent introduction of legislation will be specifically explored.
Technologies for hospital disinfection and textiles for bioburden reduction

G. Bearman
Virginia Commonwealth University, Richmond, VA, USA

Abstract: Reduction of microbial contamination of the hospital environment is a challenge yet has potential impacts on infection prevention efforts. This lecture will explore the potential role of new technologies to limit bioburden on inanimate surfaces and healthcare worker uniforms. The literature on new technologies such as antimicrobial textiles, hydrogen peroxide and UV light-based decontamination systems for cleaning of hospital rooms will be explored. Knowledge gaps on cleaning of hospital surfaces are summarized and the application of these technologies as part of a horizontal infection prevention platform will be discussed.
The impact of education on reducing Ebola virus disease transmission in healthcare facilities

S. Mehtar
Stellenbosch University, Cape Town, South Africa

Abstract: Background: The largest Ebola outbreak in history occurred between Dec 2013 and October 2015, in Sierra Leone, Liberia and Guinea- a total of 28640 cases with 11 315 deaths (39.5%) were recorded. Amongst healthcare workers (HCW) , a total of 881 cases with 531 deaths was recorded until the end of Dec 2015. The strategic plans included strengthening of healthcare systems, infection control (IC) training of as many (HCW) as possible, and establishing a national IC programme.

Training: ICAN is the largest IPC organisation in Africa with a high level expertise in IPC. In collaboration with the WHO and CDC, ICAN delivered the main IC training in Sierra Leone. A one week Basic IPC course on containing Ebola was prepared. The course was structured to provide formal lectures but mainly to engage the students in problem solving, group discussion and peer-presentations to assess their ability to teach others.

Results: In total, 215 HCW were trained in three batches over 9 months with an overall pass rate of 93%. Challenges highlighted during the early days of the EVD outbreak was confusion, not only among the HCW but also the tutors; fear of the unknown and non-evidence based rituals were introduced and perpetuated- some, like spraying humans with chlorine, were dangerous. The impact of the training programme reflected in infection rates amongst HCW falling from February onwards.

Conclusion: An increase in IC supplies and a robust, evidence based training programme clarified safe IC practices and increased confidence in the workplace. Education was a major contributor to containing HCW EVD spread.
Protecting the health care worker during outbreaks – The case of viral hemorrhagic fever outbreaks

**H. De Clerck**
Médecins Sans Frontières (MSF), Antwerp, Belgium

**Abstract:** Médecins Sans Frontières (MSF) / Doctors Without Borders, an International Medical Humanitarian Non Governmental Organization, has an experience of 20 years in intervening in Viral Hemorrhagic Fever (VHF) Outbreaks (Marburg-, Ebola-, Lassa-fever-outbreaks). Healthcare providers caring for Ebola-, Marburg-, and, in a lesser extend, Lassa-patients, are, next to family and friends of patients, at highest risk of getting infected by those diseases, as they are most likely to come in contact with infectious blood and/or body fluids of VHF patients. This was sadly pointed out by the more than 880 Health Care Workers that got infected with Ebola-virus in the recent 2013-2015 Ebola-outbreak in West-Africa. More than 500 of them died. The protection of Health Care Staff is, considering all this, not surprisingly, a main concern during VHF outbreak interventions. In this talk MSF shares its experience in how to do so: from Personal Protection Equipment, over HR management and training and staff health policies to general intervention strategies. We’ll try to give an overview of all activities needed in order to guarantee, as much as possible, staff safety. We’ll as well discuss challenges, recent developments and future needs in the domain of Bio-safety and staff safety.
HIV and syphilis

K. Mayer
The Fenway Institute, Boston, MA, USA

Abstract: HIV-infected people are at increased risk for syphilis, partially because of their immunodeficiency, but particularly because of ease of transmission of syphilis in sexually active people. Unlike HIV, syphilis can readily be transmitted through insertive or receptive oral sex. HIV-infected individuals, particularly men who have sex with men with multiple partners and male or female sex workers tend to have higher rates of HIV, syphilis and co-infection than the general population in their respective communities worldwide. The presentation of syphilis may be highly diverse in HIV-infected patients, ranging from asymptomatic gummas, which may be obscured by their location (e.g. inside the vagina or rectum) to a wide array of maculopapular eruptions. Untreated syphilis can be particularly virulent in HIV-infected patients, resulting in neurosyphilis, which can result in sensory, cognitive, and/or ocular impairment, if left untreated in HIV-immunocompromised patients. Conventional diagnostic assays for syphilis based on antibodies to treponeme and non-treponeme antigens can be more difficult to interpret in HIV-infected, compared to uninfected, patients, remaining reactive (“serofast”) long after successful treatment has been completed. This poses a challenge to the clinician, since inadequately treated syphilis can result in neurosyphilis. The organism remains susceptible to penicillin in most cases, and in all settings except for acute primary infection, treatment with 2 successive weekly courses of intramuscular benzathine penicillin is indicated. Lumbar puncture should be done if neurosyphilis is suspected, since the treatment would require higher doses of intravenous penicillin, if diagnosed. Rare cases of macrolide-resistant syphilis have been reported, so second line treatment in penicillin allergic patients can consist of daily doxycycline for 3 weeks, if penicillin desensitization is not feasible. When HIV-infected patients are severely immunocompromised, the initiation of antiretroviral therapy can result in an immune reconstitution inflammatory syndrome if they have undiagnosed syphilis. Because of its high prevalence in HIV-infected patients, syphilis screening should be conducted quarterly in non-monogamous, sexually active HIV-infected patients.
Prostatitis: Challenges in diagnosis and treatment

K. G. Naber
Technical University of Munich, Munich, Germany

Abstract: Acute prostatitis is usually a bacterial infection caused by uropathogens and should be treated initially by broad-spectrum antimicrobials until the results from urine culture are available for a more tailored antibiotic therapy. Only about 10% will become a chronic prostatitis.

Chronic prostatitis-like symptoms in men may have multifactorial causes. Therefore, these patients should be investigated thoroughly for various possible pathologies. A chronic infection of the prostate may either be the cause or the consequence of such a disease and should be diagnosed properly or excluded. Uncritical use of antimicrobials is by no means justified, because antibiotic therapy may have adverse effects for the patient and/or collateral damage for the environment.

Besides detailed history and clinical evaluation, the investigation for a chronic infection of the prostate should only be performed after the patient has stopped any antibiotic therapy for at least 4 weeks. If the midstream urine of the patient does not indicate any urinary tract infection, a localization study should be performed.

Pathogens usually recognized as causing a chronic prostate infection are the same as the traditional uropathogens (TP), mainly *E. coli*, other *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and enterococci. But also non traditional pathogens (NTP) including Gram-positive bacteria, such as staphylococci and streptococci, and also ureaplasmas, mycoplasmas and especially *Chlamydia trachomatis* (Skerk 2008). A gonococcal prostatitis may be fairly rare and can be acute and chronic.

The fluoroquinolones are recommended as drugs of choice in chronic infection of the prostate, if the pathogens are susceptible, because of their favourable prostate pharmacokinetics, which are however different between the analogues. Clinical studies with levofloxacin have shown, that our conventional dosage regimens may have to be reconsidered in favour of higher dosages and probably shorter treatment durations. In case of STI in addition macrolides and tetracyclines may be included into the therapeutic armamentarium.

In chronic pelvic pain syndrome (CPPS) where infection cannot be found, phenotyping of the symptoms and a multimodal therapy may be considered since such a complex syndrome may have several underlying pathologies.
Global challenges of implementing human papillomavirus vaccines

H. Rees
University of the Witwatersrand, Johannesburg, South Africa

Abstract: Every year cervical cancer affects around 528000 women and causes 266000 deaths worldwide with 80% of deaths occurring in less developed countries with a concomitant 18-fold difference in mortality occurring between developed and developing countries. Cervical cancers is caused by the Human Papilloma Virus (HPV) with the oncogenic types 16 and 18 accounting for 70% of invasive disease. Other cancers associated with HPV infection include vaginal, vulvar, penile, oropharyngeal and anal cancers. In addition, HPV types 6 and 11 cause anogenital warts and recurrent respiratory papillomatosis. In 2009, the World Health Organisation issued the first position paper on HPV vaccines, revised in 2014, in which it supported HPV vaccine introduction into national immunization programmes where: i) prevention of cervical cancer and/or other HPV-related disease is a public health priority ii) the introduction is programmatically feasible and economically sustainable, and where iii) cost-effectiveness aspects have been duly considered. They recommended that the primary target population should be girls aged 9-13 years but that HPV vaccination of males is not recommended as a priority, especially in resource-constrained settings, as the available evidence indicates that the first priority should be for cervical cancer reduction by timely vaccination of young females and high coverage with each dose. In 2014 the recommendations for HPV vaccine changed form a three dose to a two-dose schedule.

In 2011 the Global Alliance on Vaccines and immunisation (GAVI), tasked with supporting the introduction of new vaccines into the world’s poorest countries, approved support of HPV vaccines introduction into GAVI eligible countries with the low negotiated price of US$ 4.50 per dose compared to US$ 100 in high-income countries. By 2015 GAVI plans to support the immunisation of approximately one million girls with HPV vaccines and by 2015 more than 30 million girls in less developed countries.

This presentation will explore the reach, successes and epidemiological impact of HPV vaccine introduction worldwide and will consider some of the challenges such as the introduction of school immunisation programmes, the immunisation of boys, and the controversy around HPV vaccine introduction in India.