HICO, Gyeongju, Korea, September 26-28, 2019

Speaker Presentations

September 26, 2019

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Wayne State University, USA |
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K-1. Control of seasonal and pandemic influenza

Benjamin J. Cowling
WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, The University of Hong Kong, Hong Kong, China

Influenza viruses cause considerable morbidity and mortality each year in seasonal epidemics. Influenza pandemics occur from time to time with the potential to cause even greater health and economic impact than typical annual epidemics. Controlling seasonal and pandemic influenza is therefore a public health priority. There are three main classes of interventions to control influenza, namely vaccines, therapeutics, and non-pharmaceutical interventions. In this presentation, I will discuss the evidence supporting their use.

Influenza have moderate effectiveness against seasonal influenza, and one factor that causes the effectiveness to vary from year to year is the degree of difference in the antigenic match between vaccine strains and circulating strains. Because most influenza vaccines are produced in chicken eggs, in a process that can take many months, it is thought that vaccines will not be available to control the next influenza pandemic at least in the earliest stages. Influenza antivirals have an important role to play in treating influenza, but are often reserved for patients with more severe disease or with a greater risk of disease progression, and are not generally used to control transmission in the community.

Thus, efforts to control the next pandemic will rely largely on non-pharmaceutical interventions (NPIs). Most influenza virus infections cause mild and self-limiting disease, with only a small fraction of cases requiring hospitalization, and influenza virus infections therefore spread mainly in the community. Influenza virus is thought to transmit predominantly via respiratory droplets but the size distribution of particles responsible for transmission remains unclear, and in particular there is a lack of consensus on the role of fine particle aerosols in transmission. There are major uncertainties in the effectiveness of simple personal protective measures against influenza, such as hand hygiene and face masks. Influenza virus infections are thought to spread mainly through close contact in the community (e.g. homes, workplaces, schools, public places, etc.), with more frequent and intense contact among children having a particularly important role in transmission. Social distancing measures aim to reduce the frequency of contact and increase physical distance between individuals, thereby reducing the risks of person-to-person transmission. School closures are a good example of a social distancing measure that can reduce influenza transmission in the community, although there are high social costs and ethical issues. A final group of NPIs is measures related to international travel, including entry and exit screening of travelers for infection, travel restrictions or reductions, and border closures.
Antibiotic resistance continues to be a major threat to public health worldwide. Current expenditures have been calculated to exceed $55 billion per year in the United States alone, and estimates predict that over ten million people will die worldwide by the year 2050 from antimicrobial resistance. The most worrisome pathogens that have the highest dangers are the multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) Gram-negative isolates. The most common mechanisms of Gram-negative resistance include beta-lactamase and antibiotic-modifying enzymes, loss of porins, overexpression of transmembrane efflux pumps, target mutations, ribosomal modification, and/or mutations in lipopolysaccharide structure. The Centers for Disease Control and Prevention (CDC) list carbapenem-resistant Enterobacteriaceae (CRE) as an urgent threat, and MDR Acinetobacter spp., MDR Pseudomonas aeruginosa, and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae as serious threats; specifically, these organisms account for an estimated 600, 500, 440, and 1,700 deaths per year, respectively, and these numbers are predicted to rise. Furthermore, the World Health Organization (WHO) lists these four organisms as their highest priority pathogens for research and development (R&D) of new antibiotics. Stepping up the battle against Gram-negative resistance will likely include a combination of strategies such as the application of antimicrobial stewardship (ASP), rapid diagnostic testing (RDT), timely administration of antimicrobials, combination therapy, vaccinations and the use of new novel agents including bacteriophage (phage) therapy. It is also vitally important that the antimicrobial pipeline continues to keep pace with the continuing changing antimicrobial resistance patterns emerging. ASP initiatives have been shown to decrease antibiotic consumption and lower the rates of antibiotic resistance. RDT can help shorten the window to organism identification and susceptibility results and thus can assist in antimicrobial de-escalation and provide support for decreasing the time to appropriate therapy. The main rationale behind utilizing combination antimicrobial therapy is to exploit possible synergy and decrease the emergence of resistance. The majority of vaccinations in our armamentarium provide activity against viruses; however, multiple vaccinations against Gram-negative pathogens are pending approval. Although a narrow pipeline of antimicrobials to target these problem Gram-negative organisms are in pre-clinical development, options that are currently available are extremely limited. The 10 x ‘20 initiative is a collaborative program to promote an antibiotic R&D operation to develop ten new antibiotics by the year 2020. Currently approved agents that are promising to help our fight against Gram-negative resistance include ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, plazomicin, and eravacycline. Despite these encouraging therapeutic agents, real-world data to implement these products on a widespread basis is not currently available. Other antimicrobials that are presently in the Gram-negative pipeline include cefiderocol, fosfomycin disodium, sulopenem, aztreonam/avibactam, cefepime/AT101, and LYS228. Bacteriophages are viruses that hijack the machinery within bacteria, replicate within the cell, lyse the organism, and release their offspring to re-initiate the process. Phage monotherapy has been shown to be potent against resistant Gram-negative bacteria. Even more promising is the utilization of phage-antibiotic combinations, as this approach has shown many positive interactions, including the stimulation of phage production, reductions in bacterial growth, enhanced biofilm degradation, and alterations in the emergence of bacterial resistance. Although these steps may assist in the ongoing fight against Gram-negative resistance, the public and healthcare community must work together to make these effective. The purpose of this presentation is to explain current trends in Gram-negative resistance and describe novel approaches to prevent and target Gram-negative infections.
This talk will discuss the use of molecular epidemiology methods to identify and track HIV networks. These methods use sequence data from standard HIV genotypes that are collected for HIV drug resistance testing. The sequences are then analyzed in real-time to infer ‘clusters’ of highly related HIV infections. These methods can identify ‘hot spots’ of HIV transmission, including the transmission of drug resistant HIV. The demographics, risks and clinical characteristics associated with people with HIV in the identified clusters can be used to efficiently target prevention efforts, like enhanced treatment adherence measures, to stop cluster growth.
The field of mycology continues to evolve. Changes in immunosuppression use result in new patterns of infection. Two of the leading opportunistic infections remain CMV and invasive fungal infection and their occurrence is related. New antifungal drugs are being studied which will have advantages in treatment of azole resistant fungal infections and these drugs are needed with the emergence of *Candida auris* and mould infections in transplant recipients. Increasing antifungal resistance mandates a strong stewardship response and rapid diagnostic tests are needed to direct therapy in this patient group. Genomics are another tool increasingly applied for epidemiology and infection prevention. The new frontiers for study in this vulnerable patient group are manipulating the microbiome and host immune response to prevent and treat infection. Expertise and collaboration across disciplines is needed to develop and implement these interventions in the immunocompromised population.

K-4. Emerging Fungal Threats

MA Slavin

*Peter MacCallum Cancer Centre, Royal Melbourne Hospital and National Centre for Infections in Cancer, Melbourne, Australia*
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O-1. Middle East Respiratory Syndrome: what we should learned from the 2015 Korea Outbreak

Myoung-don Oh
Professor, Dept. of Internal Medicine, Chief, Div of Infectious Diseases, JW Lee Center of Global Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

Middle East Respiratory Syndrome coronavirus (MERS-CoV) was first isolated from a patient with severe pneumonia in 2012. Since then, as of June 2019, 2449 cases of MERS-CoV infection were reported to WHO from 27 countries, with a case fatality ratio of 34.5%. The 2015 Korea outbreak of MERS-CoV involved 186 cases, including 38 fatalities. Nosocomial transmission occurred at 16 hospitals, and 4 largest clusters accounted for 82% of the total cases. The epidemic lasted for 2 months and the government quarantined 16,993 individuals for 14 days to control the outbreak. Economic loss was estimated as 8.5 billion US dollars.

The lessons we learned from the 2015 Korea outbreak of MERS are as follows. (1) A single, missed case may trigger a huge, nationwide outbreak. (2) The first line of defense against emerging infection is doctors in the community clinics/hospitals, and they should be well informed about emerging infectious diseases through continuing medical education. (3) Superspreading events may occur in healthcare settings, especially at emergency departments/ICUs, and therefore improving infection prevention and control practices in all health care facilities is required. (4) Early detection and isolation of cases is of critical importance. (5) Aggressive strategy for quarantine is necessary, especially when large number of individuals are exposed in the healthcare settings. (6) Droplet precautions should be added to the standard precautions when providing care to any febrile patients with respiratory symptoms.
The deployment of penicillin in the early 1940s spurred a huge search for antibiotic-producing fungi and streptomycetes. Around 1944 Giuseppe Brotzu, a public health doctor in Sardinia (Italy) began to think it strange that children who swam near a sewage outfall rarely caught typhoid despite the disease being prevalent on the island. He speculated that something killed bacteria entering the sea. Whether or not his hypothesis was correct will never be known, but he did isolate an antimicrobial-producing mould – *Cephalosporium acremonium* – from the outfall. Untroubled by the strictures of modern medicine (or even the ethics of the time) he used crude extracts of this to treat infections, with some apparent success. But Brotzu was no chemist and could take his discovery no further. Instead the mould culture was passed to the Oxford team who had developed penicillin. They found it produced 3 antibiotics – penicillin N, a toxic steroid and, in trace amounts - cephalosporin C.

It was almost 20 years after Brotzu’s discovery the first derivatives of this ‘natural cephalosporin’ finally - cephalothin and cephaloridine - finally reached the market. Thereafter, progress was swift. Compared with penicillins of the same era the early cephalosporins had a broader spectrum and were lesser vulnerable to β-lactamases. Even more important, the cephalosporin nucleus proved more manipulable that the penicillin, allowing successive ‘generations’ of molecules in which anti-gram-negative activity was progressively increased, with lower MICs and more species covered. Incorporation of a 7’ oxyimino-aminothiazolyl increased stability to the β-lactamases prevalent in the 1970s and 80s, and this structure is present in virtually every cephalosporin developed from the late 1970s onwards.

By the 1990s cephalosporins had become ‘standard of care’ for many infections. But this proved their undoing. Resistance proliferated, first by the selection of Enterobacteriaceae and *P. aeruginosa* mutants that hyperproduce AmpC cephalosporinases, then via the spread of extended-spectrum β-lactamases – particularly CTX-M types. Cephalosporins were also strongly implicated in disturbing the gut microbiome so as to select for *C. difficile* infection. As these problems proliferated and the century turned it seemed that the glory days of the cephalosporins were over; their roles were supplanted by penicillin β-lactamase inhibitor combinations and carbapenems.

But now we are seeing a renaissance, fuelled both by the remarkable range of modifications that can be made to the cephalosporin nucleus and by the strategy of combining cephalosporins with β-lactamase inhibitors – something that should have been done decades ago. New cephalosporins and cephalosporin combinations, now reaching the clinic offer new activity, with coverage against many problem bacteria.

Thus, ceftaroline and cefotibiprole are the first anti-MRSA-β-lactams. Cefotolozane/ tazobactam is the most active antipseudomonal β-lactam, overcoming efflux and AmpC mediated resistance in the species (though not that due to carbapenemases) as well as most ESBL-producing Enterobacteriaceae. Cefazidime/avibactam overcomes KPC and OXA-48-like carbapenemases in Enterobacteriaceae, as well as ESBLs and AmpC, though not metallo-carbapenemase. Finally, cefiderocol – which is accumulated via bacterial iron uptake systems, overwhelming bacterial defences – has low MICs for Enterobacteriaceae and non-fermenters with all carbapenemase types.

In short, there is considerable life left in the cephalosporins as they enter their fourth quarter century....
### September 27, 2019

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<td><strong>Biofilm formation and antimicrobial resistance in osteoarticular infection by staphylococci:</strong></td>
<td>Kyung-Hwa Park</td>
<td>Chonnam National University Hospital, Korea</td>
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Staphylococcus aureus is responsible for a raft of different infections, including bacteremia, infective endocarditis and osteomyelitis. These conditions are often hard to treat and frequently lead to chronic or recurrent infections despite high dose antibiotic therapy and a potent host immune response. The long-term persistence of S. aureus in host tissues is typically associated with genotypic and phenotypic changes that reduce bacterial virulence but enhance resistance to host defences and/or antibiotics. For example, small colony variants typically arise via mutations in genes that encode components of biosynthetic pathways and are resistant to, or tolerant of several different antibiotics. However, the factors that drive genotypic diversity and the mechanisms by which these altered phenotypes confer resistance to host defences and antibiotics are largely undetermined. Therefore, the objective of this work was to understand the host and bacterial factors that promote host adaptation and how the resulting phenotypes contribute to staphylococcal survival in the host, with a long-term objective of designing novel therapeutics that prevent these processes. One of the most important host defences against S. aureus is the neutrophil, which targets phagocytosed staphylococci with the oxidative burst, a mixture of reactive oxygen species. Our data show that the phagocytosed S. aureus suffer DNA damage leading to induction of the mutagenic SOS response as shown by recA reporter assays. Subsequent work using a panel of mutants identified specific DNA repair processes that were essential for survival of S. aureus during interactions with neutrophils and intraperitoneal infection in mice. In addition to enabling staphylococcal survival of host immune defences, the repair of oxidative DNA damage enhanced the emergence of small colony variants, via mutations within genes that encode components of the electron transport chain, via the action of the error prone polymerase UmuC, which is part of the SOS regulon. We subsequently found that one of the advantages of the SCV phenotype for S. aureus is high level resistance to killing by neutrophils, providing an explanation for the association of this phenotypic variant with long-term staphylococcal infections.

Recent years have provided evidence that bactericidal antibiotics trigger the production of reactive oxygen species in bacteria, which contributes to the killing activity of these drugs. Multiple distinct classes of antibiotics triggered SOS induction in S. aureus, although this varied in some cases depending on the staphylococcal strain and antibiotic class. For example, the aminoglycoside gentamicin did not trigger recA expression, whilst the bacteriostatic drug chloramphenicol did. Since the majority of antibiotics caused DNA damage in both strains investigated, we determined which repair processes were needed to survive exposure to the antibacterials. This revealed a crucial role for the same repair processes used by S. aureus to survive phagocytosis by neutrophils. Crucially, we also discovered that this repair pathway is required for induction of the mutagenic SOS response. Therefore, a single DNA repair pathway was discovered to promote staphylococcal survival during exposure to neutrophils, antibiotics and induction of the SOS response associated with host adaptation and acquisition of antibiotic resistance (Figure 1). Since inhibition of this DNA repair pathway would be expected to aid immune clearance of infection and promote antibiotic efficacy, we are currently developing small molecule inhibitors. Preliminary data suggest that we have generated a small molecule that potentiates the activity of the antibiotic ciprofloxacin, whilst reducing the SOS response. Ongoing work aims to assess whether this molecule also promotes immune-mediated killing of S. aureus and whether the efficacy of the molecules can be enhanced. In summary, staphylococcal DNA repair processes are central to both pathogen survival and host adaptaton by promoting resistance to host defences and antibiotics and triggering induction of the SOS response. Pharmacological inhibition of DNA repair could, therefore, provide a useful therapeutic approach in the era of widespread antibiotic resistance.
Several controversies and advances have arisen in the treatment of infections caused by Multidrug-Resistant \textit{Staphylococcus aureus} (MRSA). First, new antibiotics are available but are expensive and lack robust data to inform their use in the most needed clinical settings. Second, the use of combination antibiotics to treat MRSA remains controversial. Finally, standardized management strategies for MRSA, treatment algorithms to inform duration of treatment for Staphylococcal bloodstream infection, and new adjunct therapies for MRSA offer exciting advances in the management of this serious, common infection. This talk will summarize recent developments in the treatment of MRSA.
Antibiotic resistance continues to increase at alarming rates. According to the Center for Disease Control and Prevention, more than 2 million individuals in the US alone are infected with antibiotic resistant pathogens each year and these infections kill more than 23,000 individuals every year. There has been a void of novel antibiotic discoveries and over the last 30 years and an extreme shortage of new anti-infectives in the pipeline over the last two decades. While there is an urgent need to create new antimicrobials, there is also an urgency to prevent the further spread of antibiotic resistance and to preserve our remaining armamentarium of antimicrobials. One strategy for combating the emergence of resistance is the use of antibiotic combinations. Antibiotic combinations have the potential to improve the time of patient response, improve overall drug performance in the case of providing synergy and lower the target antibiotic exposure threshold needed to improve organism eradication. In addition, antibiotic combinations may facilitate lower daily antibiotic doses, the potential to de-escalate therapy and improve patient safety while lowering the potential for antibiotic resistance.

Methicillin-resistant Staphylococcus aureus (MRSA) continues to be one of the most important antibiotic resistant pathogens responsible for high rates of morbidity and mortality worldwide. Case fatality rates for MRSA bloodstream infections is high ranging from 15-45%. Treatment is often challenging due to MRSA’s remarkable ability to evade immunological defenses and antimicrobial killing. Vancomycin has been the mainstay of therapy for many years to treat invasive infections and is still considered the standard of care by many clinicians and experts. However, in recent years, confidence in the effectiveness of this antibiotic has changed due to the ever increasing reports of treatment failure that has been associated with the emergence of strains with reduced susceptibility to vancomycin. Additional characteristics that have been cited to contribute to reduced response to vancomycin include its slower bactericidal rate of killing, susceptibility to the inoculum effect and relatively poorer penetration into a variety of tissues. Daptomycin has gained popularity as a viable treatment option for patients who have failed or are intolerable of vancomycin therapy. While this antibiotic has been shown to have superior invitro activity against MRSA compared to vancomycin, there is limited clinical data to support a true advantage. In addition, the emergence of daptomycin non-susceptibility during therapy has been documented especially following vancomycin therapy. Therefore, combination therapy has been thought to be an important adjunctive treatment option to improve patient outcome and stem the tide of further antimicrobial resistance.

Previously, combinations with antibiotics like aminoglycosides and rifampin were very popular to add on to beta-lactams or vancomycin for the treatment of serious gram-positive infections. However, these regimens are no longer recommended due to increased toxicity concerns, harmful drug-drug interactions and lack of clinical data supporting improvement in patient care. Recently, there is data to support novel beta-lactam antibiotic combinations with vancomycin and daptomycin. These combination regimens appear to have the potential to improve patient outcome, may be safer and decrease the potential for antibiotic resistance. This lecture will discuss the proposed mechanisms behind these new and novel antibiotic combinations and present preliminary in vitro and clinical evidence of improved patient outcome.
Abstracts of the ICIC & ISAAR 2019 / Infection & Chemotherapy 2019 Sep;51 (Suppl 1):S1-S70

S1-4. Biofilm formation and antimicrobial resistance in osteoarticular infection by staphylococci:

Kyung-Hwa Park
Chonnam National University Hospital, Korea

Staphylococcus aureus and Staphylococcus epidermidis represents the leading cause of osteoarticular infections including orthopedic device related infection. This particular tropism and its ability to cause difficult-to-treat infections lie in the wide panel of staphylococcal virulence factors, which allow host colonization, tissue invasion and host immune system evasion.

With regard to osteoarticular infection, three phenotypic mechanisms provide a bacterial reservoir responsible for staphylococcal infection chronicity and relapse.

First, osteoarticular infections have associated with biofilm formation and antimicrobial evasions, which emphasize the need of infected tissue removal, especially in cases of orthopedic device associated infections. Biofilms are defined as surface-attached groups of microbial cells encased in an extracellular matrix. Biofilm development can be divided into several key steps including attachment, micro colony formation, biofilm maturation and dispersion; and in each step bacteria may recruit different components and molecules.

Second, implications of the ability of staphylococci to invade and persist within bone cells, especially osteoblasts has been suggested for years.

Lastly, bacterial phenotype switching to small-colony variant (SCVs) has been associated with persistence of osteoarticular infection. These mechanisms are connected with each other under stringent environmental conditions and result in resistance or tolerance to antimicrobial agents. The mechanism of biofilm-associated antimicrobial resistance seems to be multifactorial.

This talk will give an idea about clinical consideration of biofilm formation and antimicrobial resistance mechanism through demonstration of the tough case of orthopedic device related infection by S. aureus. Also, the new innovations in the treatment of biofilm related osteoarticular infections will be introduced.
### Symposium 2  Emerging infectious diseases/Global health

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S2-1. Vaccines for *Aedes* Mosquito-Transmitted Viruses

In-Kyu Yoon

*International Vaccine Institute (IVI)*

Over the past several decades, diseases transmitted by *Aedes* mosquitoes have spread rapidly as both the mosquito vectors and the viruses have expanded their geographic distributions. Population growth, uncontrolled urbanization and skyrocketing international travel have driven epidemics of *Aedes*-transmitted viruses, most notably dengue, yellow fever, Zika and chikungunya. Dengue is now endemic in more than 120 countries with over half the world’s population at risk. Estimates of approximately 400 million people infected with dengue virus and 100 million symptomatic cases each year vary with the frequency and magnitude of epidemic activity, but are likely conservative. Major dengue epidemics in large tropical urban centers result in significant morbidity and mortality, especially in resource-poor countries where they often create chaos and a breakdown in primary health care as hospitals and clinics become overloaded. Yellow fever outbreaks in South America and Africa highlight the continued risk of epidemic yellow fever to global public health, compounded by shortages of yellow fever vaccine supplies, necessitating the large-scale use of fractional-dose yellow fever vaccine. Zika and chikungunya have caused explosive epidemics in the Americas after recent introductions from Asia. Neurological complications from Zika virus infection led to the World Health Organization (WHO) declaring a public health emergency of international concern (PHEIC) in 2016. Co-circulation of different *Aedes*-transmitted viruses has potential consequences yet to be fully delineated. Fortunately, new tools including vaccines, therapeutics, and novel vector control methods are being developed to add to already existing prevention and control methods. None of these approaches will likely halt the spread of *Aedes*-transmitted diseases if used alone. For example, vaccines and vector control measures will likely need to complement each other by increasing population level immunity and decreasing transmission intensity, respectively, within the framework of a comprehensive implementation program. Furthermore, complexities in the performance of some of these tools may require additional implementation studies to determine their optimal use. The only licensed dengue vaccine, Sanofi Pasteur’s Dengvaxia®, is a tetravalent live attenuated recombinant vaccine which is effective only in individuals with prior dengue virus infection, and, in fact, increases the risk of severe dengue in some individuals without prior infection. Two other tetravalent live attenuated dengue vaccine candidates, TAK-003 sponsored by Takeda and Butantan-DV sponsored by Butantan, are now undergoing phase III efficacy trials to support possible future licensure. However, concerns remain that these live vaccines may have similar complexities as Dengvaxia®. New vector control tools have shown promise including *Wolbachia*-infected *Aedes* mosquitoes which are currently being rolled out in large field efficacy trials and/or implementation projects in several urban centers in Asia and Latin America. *Wolbachia*-infected *Aedes* mosquitoes have the theoretical advantage of potentially decreasing vector competence for several different viruses at the same time, including dengue, yellow fever, Zika and chikungunya. The prevention and control landscape for *Aedes*-transmitted viruses is changing rapidly and will certainly see new and impactful developments within the next few years.
S2-2. New microbes in humans, a new era

Didier Raoult

IHU Mediterranean Infection, France

The discovery of microbes has been achieved through optical microscopy, which allows to observe objects with a maximum size of 0.6 to 0.8 µm. This observation made it possible to define the microbes in the XIXth century. Viruses, on the other hand, were defined as elements that could cause diseases but were not visible under the microscope and could be filtered by 0.2 µm filters.

Subsequently, the definition of microbes was enriched by the definition of prokaryotes, (without a nucleus) and eukaryotic (with a nucleus) microbes. Later, Woese’s work on the ribosome led to the classification of the microbial world into three branches, bacteria and archaea (that are prokaryotes) and eukaryotes. This classification based on ribosomal RNA analysis remained stable for nearly 40 years.

However, the discovery of microbes visible under optic microscope and exhibiting the characteristics of viruses in the 21st century opened the field of giant viruses. The first were mimiviruses, which are visible under optic microscope, and which may contain more than 1000 genes and whose particle contains a DNA chromosome and RNA messengers, more than 500 proteins, and a translation apparatus almost complete for some of them, with the exception of the ribosome. Thus, giant viruses can be considered as microbes without ribosomes, constituting the other branch of life.

Since then, systematic sequencing and environmental analyzes have revealed the groups of prokaryotes that are not visible under an optical microscope, which would therefore not meet the definition of microbes. One of these groups seems to have a very distant but common origin with bacteria, commonly called candidatus phylogenetic radiation, that we call “mini-microbes”, which have a size that ranges between 250 and 450 µm. These mini-microbes are present in humans’ mouths and recently we have been able to show them in urine, blood and feces. These microbes are exosymbionts, for the moment, cultured only in the presence of another microbe and are, probably, a new microbial branch. Finally, mini-archaea have also been found in the environment, but not yet in humans to our knowledge. They, probably, also represent an independent branch.

It is likely that based on the ribosomal analyzes we will arrive at 5 distinct branches, and if we use other genes, better conserved than the ribosomal rDNA whose RNA polymerase allows to integrate the giant viruses, it is likely that we now have six distinct branches of the living world, of which a large part constitutes obligatory intra or extra cellular parasites. Their role in human pathology is for the moment uncertain given the almost total absence of studies on these emerging areas, as on that of archaea in humans whose first studies are just beginning to appear.
Recent decades have seen increasing outbreaks of emerging and re-emerging infectious diseases in many different regions of the world. While some of these will be identified by national and international surveillance systems, initial signals of potential outbreaks may be missed if local laboratory capacity is restricted in terms of resources and funding or if novel pathogens are not being routinely tracked. There is thus a need for alternative, innovative strategies for the surveillance and detection of emerging infectious diseases (EID).

GeoSentinel is an EID network originally created as a joint project between the International Society of Travel Medicine (ISTM) and the United States Centers for Disease Control and Prevention (US CDC). GeoSentinel has several major objectives including conducting surveillance for EIDs; rapidly sharing novel data on emerging infections with participating sites, internet information services (e.g. ProMED), and public health authorities (e.g. US CDC, European CDC, Public Health Agency of Canada); and analyzing, presenting, and publishing surveillance results collaboratively with CDC, GeoSentinel sites, and GeoSentinel’s two regional subnetworks, CanTravNet and EuroTravNet.

The GeoSentinel surveillance network provides robust data that defines the spectrum of illness and its relation to place of exposure for significant health risks facing travelers and migrants. There are currently 68 GeoSentinel sites in 29 countries and 221 Affiliate Members with a presence on every continent except Antarctica. The GeoSentinel database now contains about 300,000 patient records; these include 54% post-travel visits, 31% seen during travel, and 15% migrants.

GeoSentinel has successfully identified new outbreaks over the last two decades including leptospirosis in participants in the Borneo Ecochallenge (2000); sarcocystis in travelers to Tionan Island, Malaysia (2010); an outbreak of dengue fever in Angola (2013); schistosomiasis in vacationers in Corsica (2014); sentinel cases of Zika virus disease in Costa Rica (2016), and Vietnam (2016); yellow fever in areas of Brazil that were not thought to be at risk (2018); and chikungunya in travelers in southern Thailand (2019).

In summary, GeoSentinel is a vibrant unconventional global surveillance system that has made important contributions to the identification of EID outbreaks and trends in infectious disease epidemiology among travelers and migrants. In addition, GeoSentinel has the potential, through the development of a biobank of clinical samples, to collaborate with high level laboratories in academia and government to identify new pathogens responsible for respiratory, gastrointestinal, and systemic infections. GeoSentinel translates clinical and epidemiological data into meaningful evidence that is of critical importance to the containment of the global spread of infection.
International travel is a main force in disease emergence and spread worldwide. As a result, the number of imported infectious diseases is increasing in many parts of the world and they can spread rapidly throughout the world causing significant impact on world economy and health. For example, SARS, pandemic influenza, MERS, Ebola and many other infectious diseases had been spread new geographic area. Factors associated with vulnerability of countries to the importation and spread of infectious diseases include population density, international travel, animal reservoirs, healthcare and public health infrastructures. To proactively respond to various emerging infectious diseases, it is necessary to quickly identify which diseases are occurring and where they occurring. With the development of the Internet, it has become the basis for obtaining various information quickly and easily. There are several services including Promed, GPHIN, Medisys, Healthmap, CIDRAP, and WHO DON, provide information on infectious disease outbreaks around the world in different formats but it is impossible to manually monitor all the data collected there. Also in addition to the distance between the origin of outbreak and the relevant countries, the amount of human exchange has to be considered to estimate the risk of importing the disease. Information on air travel can help identify the origin of the importation and predict further geographic spread. Since it is difficult to evaluate or predict the possibility of the introduction of such diseases by simple disease information, recent attempts have been made to overcome limitations by incorporating various technologies such as machine learning and artificial intelligence. In this presentation,
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S3-1. How can WGS help in nosocomial outbreak investigations?

Stephan Harbarth

Geneva University Hospitals, Switzerland

Studying hospital outbreaks by using molecular tools, i.e. synthesizing the molecular epidemiology data to its appropriate clinical-epidemiologic context, is crucial in order to identify infection source, infer transmission dynamics, appropriately allocate prevention resources and implement control measures. Whole-genome sequencing (WGS) of pathogens has become the reference standard, as it is becoming more accessible and affordable. Consequently, sequencing of the full pathogen genome via WGS and major progress in fit-for-purpose genomic data analysis tools and interpretation is revolutionizing the field of outbreak investigations in hospitals. Metagenomics is an additional evolving field that might become commonly used in the future for outbreak investigations. Nevertheless, practitioners are frequently limited in terms of WGS or metagenomics, especially for local outbreak analyses, as a result of costs or logistical considerations, reduced or lack of locally available resources and/or expertise. As a result, traditional approaches, including pulsed-field gel electrophoresis and multilocus sequence typing, along with other typing methods, are still widely used. In my presentation, I will summarize current challenges, strengths and limitations of WGS for nosocomial outbreak investigations, using examples from the published literature as well as from our own experience in Geneva (Switzerland). In addition, I will attempt to provide recommendations (whenever applicable), to clinicians, hospital epidemiologists and microbiologists pertaining to the efficacy of the various typing methodologies available to study the molecular epidemiology of outbreaks caused by the most significant pathogens in nosocomial settings.
Over the past decade, there are abundant evidences in the scientific literature that contaminated environmental surfaces and noncritical patient care items play an important role in the transmission of several key health care-associated pathogens including methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, Acinetobacter, norovirus, and Clostridium difficile. Thus, surface disinfection of noncritical environmental surfaces and medical devices is one of the infection prevention strategies to prevent pathogen transmission. In this session, I will discuss an approach to facilitate effective surface cleaning and disinfection in health care facilities. These components are: creating evidence-based policies and procedures; selection of appropriate cleaning and disinfecting products; educating staff to include environmental services, patient equipment, and nursing; monitoring compliance (eg, thoroughness of cleaning, product use) with feedback (ie, just in time coaching); and implementing a “no touch” room decontamination technology and to ensure compliance for patients on contact and enteric precautions.
Carbapenem-resistant Enterobacteriaceae (CRE) including carbapenemase-producing Enterobacteriaceae (CPE) are now spread worldwide. In Korea, the number of CRE isolation is rapidly increasing, and impending endemicity is a concern. Therapeutic options include polymyxin, tigecycline, or the combination of them with carbapenem, which is currently the mainstay of treatment. In addition, various combination regimens with new carbapenemase inhibitors and other classes of antimicrobials are in the process of evaluation. To cope well with CRE/CPE, thorough infection control, such as active surveillance, early detection, strict contact precaution, cleaning the environment, and antibiotic stewardship is very important. In this lecture I would talk about the basics of CRE/CPE, and then I will cover the ideal principles of infection control for the CRE/CPE. In addition, I would also like to present some unexpected hardships that actually occur in the clinical settings.
S3-4. Surveillance of surgical site infection: present and future

Doo Ryeon Chung

Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine; Center for Infection Prevention and Control, Samsung Medical Center, Seoul, Republic of Korea

Surgical site infection (SSI) remains one of major surgical complications causing significant morbidity, mortality, and increased cost. Surveillance of SSI has been established as the core component for the prevention of SSI and recent studies have shown the positive impact on reducing rates of SSI. However, conventional SSI surveillance has been dependent upon comprehensive manual review of medical records which are labor-intensive and time-consuming. As the surveillance extended to a wide range of surgical procedures, the need for developing the surveillance methods to overcome these obstacles has increased.

Many hospitals worldwide use electronic medical records, and challenge has continued to develop the tools identifying the cases with specific clinical outcomes from the records using the various techniques such as electronic algorithms and machine learning. Recently, there have been increasing reports on successful development of SSI surveillance tools applying the electronic algorithms with prediction model. Although those are still at primitive levels to enable only semi-automated surveillance, it was possible to reduce the work burden on infection preventionists significantly. Rapidly advancing artificial intelligence technology is expected to make fully-automated systems for SSI surveillance possible in the near future.
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<td>Plenary Lecture 1</td>
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<td>Jae-Hoon Song&lt;br&gt;&lt;i&gt;Asia Pacific Foundation for Infectious Diseases, Korea&lt;/i&gt;</td>
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Progress in science and technology has led to breathtaking improvement in medicine in last century. It has transformed how we encounter our patients, make diagnoses, treat illnesses, and prevent diseases. However, no previous historical progress has been as fundamentally transformative as the one we are witnessing now. Novel digital technologies, which has already reshaped our daily living, are now beginning to change the way we understand diseases and practice medicine. Albeit the application of novel technologies has been concentrated on chronic diseases such as cancer, diabetes, or heart diseases, there have been several projects on infectious diseases worthy of note.

1. Web-based digital epidemiology

The electronic health record (EHR) system has been widely implemented during the last two decades, but detailed analysis of those vast collection of digitized data became possible with recent development in data management and computing power. As data from individual hospitals harbors significant limitations in volume and generalizability, large datasets from groups of hospitals, local government agencies, regulative bodies, and commercial firms have been used for research of infectious diseases, among innumerable fields. One step further, many groups are building collaborative efforts to collect large-scale, international, standardized collections of healthcare data. The Observational Health Data Sciences and Informatics (OHDSI, pronounced “Odyssey”) is one of the largest such programs. Use of more general concept of “big data,” collected from the internet and social networking services (SNS), has been implemented in the fields of epidemiology and outbreak responses. After the Google Flu Trends spearheaded the emergence of “digital epidemiology,” internet-based surveillance has been applied to monitor the activity of respiratory, and vector-borne infections. Digital resources for infectious disease detection include Pro-MED mail, GPHIN, HealthMap, MedISys, Argus, BioCaster, and EpiSPIDER. HealthMap is an example of such effort, which aggregates information from online news, eyewitness reports, and official reports for monitoring disease outbreak and emerging infectious diseases. Furthermore, ResistanceOpen project provides an online map of antimicrobial resistance, based on publicly available and user contributed resistance data. Big data can provide more expansive information when combined with large scale clinical and genomic data. Information provided by such data could give a valuable insight on the transmission dynamics of infectious diseases, helping find optimal intervention strategies to control them. One such project, PANGEA-HIV 2 is a consortium to identify individuals with higher risk of infection or infecting others using phylogenetic methods. Digital epidemiology using big data has clear advantages in middle- and low-income countries where resources for epidemiologic surveillance are insufficient. However, the closure of Google Flu Trends showed the pitfall of this approach alone, and “hybrid” systems that integrate traditional and digital surveillance have been proposed. Despite such setbacks, big data and digital epidemiology seem to have a promising role in precision public health.

2. Mobile-based surveillance

Mobile devices are virtually ubiquitous nowadays. mHealth, a term used for medical and public health measures using mobile devices, are being actively tried in the area of infectious diseases. Classical approach is the use of mobile devices as a channel for the dissemination of health-related information between general public and authorities. The possibility has been studied during the Ebola outbreak in Africa. Mobile phone apps have been used to educate people on transmission methods and common symptoms of Ebola, and to report suspected cases or absence thereof by local officers. Mobile devices can be also used to help patients with chronic conditions adhere to the treatment and respond appropriately to side-effects. Many studies have demonstrated a potential role of mHealth in care for people with HIV/AIDS. Twitter became an alternative data source because anyone with an internet connection can retrieve Twitter data. For instance, a study from 2014 showed that incorporating data from Twitter into CDC influenza-like illness models can reduce forecasting errors.

3. Point-of-care test

Recent technological progress enabled the production of diagnostic devices which are small enough to be carried to point-of-care (POC), return results within hours at most, does not require trained professionals, and are economically affordable. Such devices,
combined with mHealth, will provide POC microbiologic tests where traditional laboratory does not exist. Also, wearable devices have been applied to monitor various information ranging from vital signs to hand hygiene.

4. Artificial intelligence

Interest on machine learning (ML) and artificial intelligence has been predominantly concentrated on the interpretation of digitized information (e.g., radiologic imaging or retinal fundus photographs) and clinical decision-making. Regarding infectious diseases, there were studies which used ML to trigger a warning for patients with suspected sepsis or septic shock. Also, ML has been applied to predict risk of *Clostridium difficile* infection, reservoirs of zoonotic diseases, and clinical outcomes in Ebola virus disease infection. In a broader perspective, there have been studies to use ML for novel drug discovery and pharmacovigilance.

Novel digital technologies will transform medicine and public health in coming days. The field of infectious diseases are not an exception. Big data, digital epidemiology, mobile and ubiquitous devices, and machine learning will provide unforeseen depth of new insight to how we diagnose, treat, and prevent infectious diseases. However, various limitations and hurdles lie ahead. Initiatives and expertise from those who are at the frontline of battle against infectious diseases will be of critical importance.
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11:50 ~ 12:30 Plenary Lecture 2

P2-1 Paradigm shift in the diagnosis and treatment of tuberculosis
Jae-Joon Yim
Seoul National University College of Medicine, Korea
Globally, 10 million people developed tuberculosis (TB) in 2017. In addition, TB caused 1.3 million deaths among HIV-negative people and an additional 300 000 deaths among HIV-positive people. Early and accurate detection of TB is important for the timely initiation of treatment and prevention of TB transmission. Furthermore, early detection of drug resistance is crucial for early treatment of multi-drug resistant (MDR) TB. Conventional methods for the diagnosis of TB have limitations in terms of early as well as accurate detection. Acid-fast bacilli smears show short turnaround times and high specificity, but lower and variable sensitivity. Confirmation of mycobacterial culture takes a few weeks and conventional drug susceptibility tests based on culture takes another few weeks.

To overcome the shortcomings of culture-based TB diagnosis, several methods of molecular diagnosis, which could provide a rapid diagnosis of TB as well as drug susceptibility profiling, was introduced and being adopted more frequently. Among them, the Xpert MTB/RIF assay is being used most frequently. It is an automated, single-cartridge-based nucleic acid amplification test using reverse transcription-polymerase chain reaction detection of the TB-specific rpoB gene. Xpert MTB/RIF assay represents an important advance in the field of rapid molecular diagnosis of TB and drug resistance. The test enables simultaneous identification and detection of TB and rifampicin-resistance to be completed within 2 hours. As rifampicin-resistant M. tuberculosis is also likely to be resistant to isoniazid, the early detection of rifampicin resistance using Xpert MTB/RIF assay prompts the initiation of management of MDR-TB. For the molecular detection of resistance to 2nd line anti-TB drugs, line-probe assay (eg. MTBDRsl assay) is available and the newer version of Xpert MTB/RIF assay (‘ultra’) has been tested. In addition, rapid, reliable, and increasingly affordable whole-genome sequencing of TB bacilli is becoming an option of diagnosis of drug resistance and source investigation of TB outbreak.

For the treatment of TB, several repurposed drugs (eg, fluoroquinolones, linezolid) and newly developed anti-TB drugs (eg, bedaquiline, delamanid) became available. To shorten the treatment duration of drug-susceptible pulmonary TB, several 4-month regimens adopting fluoroquinolones instead of isoniazid or ethambutol have been tried. Unfortunately, none of those 4-month treatment regimens showed non-inferiority to the current 6-month regimen. A recent phase 2 trial using linezolid instead of ethambutol failed to show higher rates of culture conversion at 8 weeks of treatment. Several trials testing shorter regimens with high dose rifamycins or new drugs including pretomanid are ongoing.

Meanwhile, efforts have been made to shorten treatment for MDR-TB. In 2010, a relapse-free cure rate of 87.9% among 206 patients treated with a 9-month regimen of gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout the treatment period supplemented with prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of 4 months was reported. These results were replicated in a larger clinical trial (‘STREAM Stage 1’) and the regimen was endorsed by WHO. However, this shorter regimen includes too many drugs, as many as seven, and still includes an injectable agent (kanamycin) for the first 4–6 months. Additionally, the number of candidates for this shorter treatment, i.e., patients without resistance to all drugs included in the regimen, could be limited. Based on the proven efficacy of these new anti-TB drugs, several clinical trials using 6–12-month regimens for MDR-TB treatment without an injectable (eg, MDR-END, NeXT, Nix-TB) are on-going.
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<td><em>Tan Tock Seng Hospital, Singapore</em></td>
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Antibiotics have transformed the practice of medicine, making once lethal infections readily treatable and making other medical advances, like cancer chemotherapy and organ transplants, possible. The prompt initiation of antibiotics to treat infections has been proven to reduce morbidity and save lives. However, 20-50% of all antibiotics prescribed in U.S. acute care hospitals are either unnecessary or inappropriate. Like all medications, antibiotics have serious side effects, including adverse drug reactions and *Clostridium difficile* infection (CDI). Patients who are unnecessarily exposed to antibiotics are placed at risk for serious adverse events with no clinical benefit. The misuse of antibiotics has also contributed to the growing problem of antibiotic resistance, which has become one of the most serious and growing threats to public health. Unlike other medications, the potential for spread of resistant organisms means that the misuse of antibiotics can adversely impact the health of patients who are not even exposed to them. The Centers for Disease Control and Prevention (CDC) estimates more than two million people are infected with antibiotic-resistant organisms, resulting in approximately 23,000 deaths annually.

Improving the use of antibiotics is an important patient safety and public health issue as well as a national and global priority. In the United States national action plan for addressing antimicrobial resistance calls for improving antibiotic use through antibiotic stewardship. A key challenges to the broad implementation of stewardship programs in US hospitals, and other healthcare settings, has been the lack of a clear definition for what exactly constitutes a stewardship program. Guidance was needed that could be implemented in any healthcare setting and monitored at the local and national level.

To address this challenge, the CDC developed the Core Elements of Hospital Antibiotic Stewardship Programs in 2014. This document listed seven key components and actions that were associated with successful stewardship programs. Also starting in 2014, the CDC began assessing implementation of these seven core elements through a national survey completed by almost all acute care hospitals in the country. From 2014 to 2017, the percent of US hospitals indicating that they have implemented all of the core elements has risen from 41% to 76%. The favorable response to the hospital core elements has led CDC to develop similar core elements documents for long term care facilities, nursing homes and resource limited settings, as well as an implementation guide for small hospitals.

This lecture will review the development, dissemination and implementation of the core elements, with a focus on the hospital core elements. It will discuss both challenges to and opportunities for expanding and improving implementation. Finally, plans for updating the 2014 hospital core elements will be discussed.
S4-2. Management of MRSA bacteremia with antimicrobial stewardship program

Tetsuya Yagi
Nagoya University Hospital, Japan

MRSA bacteremia is a serious infection and can be lethal disease without appropriate therapy. The management of MRSA bacteremia would be one of the important targets of antimicrobial stewardship program (ASP) which focuses not only on dosing and selection of antimicrobial agents, but also appropriate use of clinical microbiological examination and therapies other than antibiotic therapy. Therapeutic outcome of MRSA bacteremia depends on the timing of the institution of appropriate antimicrobial therapy. Application of MALDI-TOF MS or simultaneous multi-items detection for strain identification directly from positive blood culture samples may be useful for institution of early appropriate therapy. Evaluation of entry of MRSA or infection focus of secondary MRSA bacteremia is essential for the choice of antibiotics and source control. Detection of distant metastatic lesions is important determinant for adequate duration of therapy. ASP for MRSA bacteremia in our hospital is based on the 24-hours, 365-days support for blood culture examination so as not to delay the process of the positive samples.

On the other hand, AST at the hospital of my outside work (once a week) is lead by pharmacists, and I support them with weekly consultation. For MRSA bacteremia, we developed a bundle consisting of six elements, early institution of anti-MRSA drugs, source control, dose-adjustment using TDM, recheck of blood culture examination, echocardiography, appropriate duration of therapy. After implementation of the bundle, compliance with the elements of the bundle was greatly improved, and 30-day mortality and in-hospital mortality were significantly reduced to be almost half of the pre-intervention period. Multivariate analysis showed sepsis and intervention (introduction of MRSA bacteremia bundle) were two statistically significant factors to influence on the mortality in MRSA bacteremia.
To combat antimicrobial resistance in hospitals, antimicrobial stewardship program plays a synergistic role with infection prevention and control. Antimicrobial stewardship promotes the optimal use of antibiotics by optimising dosing, route and duration. In this lecture, I will focus on recent evidence base informing practice in the dosing, route and duration of antibiotic use in treating serious bacterial infections. In vitro and in vivo pharmacologic models support prolonged infusion of beta-lactams in target attainment rate. However, randomised clinical trials have so far failed to validate these observations conclusively. Recent observational data supported the role of oral antibiotics in gram negative bacteraemia. However not all oral antibiotics are equal; the role of oral beta-lactams is more controversial. Increasing high-level evidence has reduced the duration of antibiotics in a range of serious bacterial infections, including gram negative bacteraemia. Combination antibiotics are an often proposed strategy for treating highly resistant gram negative bacterial infections. Yet recent evidence including meta-analysis and randomised clinical trials have failed to support its role in MRSA, Pseudomonas and extensively drug resistant gram negative infections.
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<td>S5-1</td>
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<td>“One Health” strategy to control and prevention of zoonotic influenza threats in humans</td>
<td>Woo Joo Kim</td>
<td>Korea University College of Medicine, Korea</td>
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<td>S5-2</td>
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<td>One health: Animal and Influenza Virus Interfaces</td>
<td>Youn-Jeong Lee</td>
<td>Animal and Plant Quarantine Agency, Korea</td>
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<td>S5-3</td>
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<td>One health: the Hong Kong experience with influenza</td>
<td>Benjamin Cowling</td>
<td>The University of Hong Kong, Hong Kong, China</td>
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Influenza virus infection has been the cause of significant morbidity and mortality in humans through history. Particularly influenza A virus (IAV) causes annual epidemics and infrequent pandemics. IAV is a zoonotic pathogen that is responsible for subclinical or clinical infections in broad host ranges, including wild water-birds, poultry, mammalian animals and humans, etc. IAV infections in human have been limited only to H1, H2, and H3 subtypes. Since the outbreak of H5N1 avian influenza (AI) human infections in Hong Kong in 1997, the episodes of human infections by novel avian or swine influenza viruses have been reported increasingly around the world. H5Ny and H7Ny AI viruses infections among livestock and human populations have occurred in China and Southeast Asian countries since 2003. H1Ny variant swine influenza virus infections have emerged in pig fairs in the United States since 2001. Enzootic AI outbreaks have resulted in huge economic impacts in agricultural sectors. While there is no sustained human to human transmission of zoonotic influenza viruses until now, the emergence and spread of novel animal influenza virus infections in humans is a major concern because of their pandemic potential. With rapid population growth, the rise in poultry and pig breeding, weak farm and animal market biosecurity, and changes in human behaviors, there have been increased risks in the inter-species transmission of animal influenza viruses from wild water-birds to poultry and humans. Lessons learned from experiences of AI outbreaks in agriculture and public health sectors emphasize the One Health (OH) approach to prevent and control of epizootics in poultry and transmissions to humans. Effective OH approach towards zoonotic influenza control and prevention needs to strengthen the intimate collaborations between human, animal and environmental health. This lecture discusses the current situations of animal influenza infections in humans, risk factors and viral determinants for cross-species transmission at the human-animal interface, and the “One Health” strategy for the control and prevention of zoonotic, novel IAV threats.
S5-2. One health: Animal and Influenza Virus Interfaces

Youn-Jeong Lee
Avian Influenza Research and Diagnostic Division, Animal and Plant Quarantine Agency (APQA), Korea

Influenza type A viruses are one of the most important agents, which can cause disease in human and animal. Animal influenza viruses can be classified as avian influenza, swine influenza, or other types of influenza viruses depending on their host origin. Wildfowl and shorebirds are thought as natural reservoir of influenza type A viruses. Avian influenza viruses that cause severe disease in poultry are called highly pathogenic avian influenza (HPAI). The cumulative number of HPAI outbreaks in domestic poultry was over 15,467 cases in 68 countries since 2005. The H5 and H7N9 avian influenza viruses persist in some poultry populations and they have caused human infection, sporadically.

Human infection with H5N1 avian influenza virus was firstly reported in Hong Kong in 1997. The Goose/Guangdong (Gs/Gd) lineage of H5 viruses have spread from Asia to Europe, Africa and North America, and have become endemic in poultry populations in some countries. The cases of inter-countries and inter-continental transmission of H5Nx viruses by wild bird migration have been reported since 2005. The cumulative number of confirmed human cases for avian influenza A(H5N1) was 455 deaths among 861 infected cases in 17 countries during 2003-2019. The Gs/Gd lineage of H5 virus constantly evolves by mutation and reassortment with the emergence of new clade and new subtypes (H5Nx; H5N1, H5N2, H5N3, H5N5, H5N6, H5N8, H5N9).

South Korea also had been affected several times by H5Nx influenza virus since 2003. During 2003-2011, there were four HPAI outbreaks by H5N1 virus. The longest epizootics by clade 2.3.4.4.A H5N8 virus had been occurred during 2014-early 2016. The largest epizootic was caused by clade 2.3.4.4.C H5N6 and clade 2.3.4.4.B H5N8 virus in 16/17 winter season. The last epizootic was occurred in 17/18 winter season by clade 2.3.4.4.B H5N6 virus. From the most cases in each HPAI epizootics in South Korea, genetically closed viruses had been isolated in migratory birds and domestic poultry. It means that the migratory birds were the main source of virus introduction into Korea. Although there was a lot of damage of poultry industry, there was no human infection case in Korea. Korean veterinary authorities have struggled to eradicate HPAI in poultry. The control measures for HPAI are rapid diagnosis, elimination of infected poultry, movement restriction, enhanced surveillance and increasing of biosecurity.

In 2013, human infections with H7N9 virus were firstly reported in China. Since then, the virus has spread in poultry of whole country and a total of 615 deaths among 1,567 confirmed human cases have been reported. In China, a H7 vaccine was applied in poultry since September 2017. Although H7 vaccination reduced H7N9 infection case in poultry and human, the risk still exists. Recently, there is new report that some H7N9 and H7N2 viruses, isolated from poultry in China, exhibit the increased virulence and expanded host range to ducks. In Korea, the veterinary authorities have been conducted active surveillance in wild birds, domestic poultry and quarantine process for the monitoring Chinese H7N9.

Enhanced active surveillance in animal sectors, including wild birds and domestic poultry, and the effective control measures of influenza outbreaks in poultry sectors can reduce the public health risk.
While human influenza viruses cause a considerable disease burden in our communities each year, avian and swine influenza viruses also cause disease burden in animals, and can pose zoonotic threats to humans. Under the one health framework, control of avian and swine influenza is important. Hong Kong experienced the first outbreak of highly-pathogenic avian influenza A(H5N1) in 1997, with 18 infections of which 6 were fatal. Highly pathogenic influenza A(H5N1) has gone on to cause almost 1000 documented human cases worldwide. Other avian influenza viruses have also spread to humans, including most notably influenza A(H7N9) between 2013 and 2017 in mainland China.

Hong Kong has taken a proactive approach to controlling avian influenza, with a number of measures implemented in farms, wholesale markets and retail markets. These measures have led to major reductions in animal outbreaks, and in the human risk of infection as proxied by influenza A(H9N2) detections in the markets. In the longer term, central slaughtering facilities would be the best way to reduce human risk of zoonotic influenza. A number of the measures adopted in Hong Kong have been implemented in mainland China as a response to the outbreaks of influenza A(H7N9).
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Yae-Jean Kim  
*Samsung Medical Center, Korea* |
| **S6-2**      | Approach and Management of Perinatal Herpes Virus Infection  
David Kimberlin  
*University of Alabama at Birmingham, USA* |
| **S6-3**      | Risk and Consequences of Congenital Zika Virus Infection  
Tawee Chotpitayasunondh  
*Queen Sirikit National Institute of Child Health, Thailand* |
Cytomegalovirus (CMV) is the most frequent cause of congenital infection worldwide, with an estimated incidence in developing countries of 0.6-0.7% of all live births. The burden of disease of congenital CMV infection is significant in the society because it is the leading non-genetic cause of sensorineural hearing loss and an important cause of neurodevelopmental disabilities in children. Recent study suggested that antiviral therapy with 6 months of oral valganciclovir in symptomatic infants, improved hearing and neurodevelopmental outcomes. However, preventive approaches such as use of CMV hyperimmune globulin and development of a maternal vaccine have not shown consistently successful results. Despite its clinical significance, many neonates with congenital CMV infection do not get diagnosed in time because the majority of infected neonates are asymptomatic at the time of birth. Therefore, prenatal detection of newborns at high risk for congenital CMV infection is important. Researchers are trying to find a proper biomarker and best newborn screening method in the field. With efforts, diagnostic, preventive and therapeutic strategies in infants with congenital CMV are evolving. However, there are still needs for the global efforts to increase the awareness among general public, health care providers and health care policy makers.
Approximately 85% of neonatal herpes simplex virus (HSV) cases are perinatally acquired. While disease incidence varies across the world, in the United States the incidence of neonatal HSV has increased to approximately 1 in every 1,900 live births. Diagnostic assessments obtained from neonates suspected of having HSV infection have increasingly utilized molecular technologies, sometimes with strong investigative support of such moves and sometimes because molecular diagnostics have supplanted traditional tissue culture methodologies. Therapeutic advances in the management of neonatal HSV infections have dramatically changed the likelihood that a patient will survive their acute infection. Mortality rates in disseminated HSV disease have decreased from 85% in the pre-antiviral era to 29% today. Mortality rates in neonatal HSV infections involving the central nervous system disease (CNS disease) have been equally dramatic, decreasing from 50% in the pre-antiviral era to 4% today. Improvements in neurologic morbidity have been achieved with use of long-term oral acyclovir suppressive therapy following management of the acute infection. The diagnosis and management of neonatal HSV will be addressed in this session.

S6-2. Approach and Management of Perinatal Herpes Virus Infection

David Kimberlin

University of Alabama at Birmingham, USA
Zika virus (ZIKV) is one member of the Family Flaviviridae, mostly transmitted by biting of infected Aedes mosquitoes. This virus was first isolated from a rhesus monkey in Zika forest, Uganda on 1947 but first human infection were diagnosed on 1952 in Uganda and Tanzania. But the largest human outbreak occurred on 2015-2016 in South, Central and North America. Brazil was hardest hit by widespread spread of ZIKV outbreak and had reported newborn babies with microcephaly including other central nervous system malformation which potentially associated to ZIKV. Since then, ZIKV infection have been reported around the world especially from Southeast Asia, Oceania, and parts of Africa. One observational study on 2016-2017 in Thailand found that 21.4% was confirmed ZIKV among symptomatic patients. Study suggest that ZIKV has been circulated at a low but sustained level for at least 16 years as an endemic transmission.

Maternal ZIKV infection has been associated with varying degree of fetal, neonatal and infant abnormality outcomes. A congenital Zika syndrome (CZS) has been characterized with microcephaly, brain calcification, abnormal hearing and vision, psychomotor delay, brain stem dysfunction with sucking and swallowing difficulty, seizure, extremities contractures and hypertonia. The risk of microcephaly range from 1% to 15% in confirmed prenatal ZIKV infection. Neurological anomalies including neurodevelopment abnormalities, learning disability which may be late presentation in affected newborn with normal head size or “look-normal” at neonatal period. The greatest risk for CNS damage has been proposed to be maternal infection in the first trimester or 14-17 weeks of gestation. In one largest study of 183 infants which definite or probable diagnosis of CZS with microcephaly had occurred mostly in first trimester 77%, second trimester 18% and third trimester 5%. Pregnancy with ZIKV infection before 7-8 weeks of gestation are at risk of miscarriage of the fetus. The other CNS anomalies of fetus without microcephaly may develop in maternal ZIKV infection after 30 weeks of gestation. The precise mechanism of congenital transmission remain unknown but studies indicate that the placenta and fetal nervous tissues are at risk for ZIKV infection via transplacental transmission.

Infant born to ZIKV infection mother should be clinically and laboratory follow up for at least 2 years for the proper management. The definite diagnosis of ZIKV infection especially CZS is solely base on laboratory findings. The gold standard for confirm diagnosis is positive PCR for ZIKV from body fluid specimens while immunological test (IgG or Ig M) have some limitation because of cross reaction with other flaviviruses. But Zika IgM positive in newborn baby blood can be diagnosed as CZS even though PCR for Zika in urine or blood were negative.

Pregnant women need to have access to relevant health care system, including contraception, diagnostics and pregnancy-termination services if legally approved. The affected young infants need to have multidisciplinary long term care and support for the better quality of life. Health care provider should identify the timing of the infection during pregnancy which effect on the risk of fetal abnormality in case of symptomatic illness but it is unclear whether asymptomatic poses a risk to the fetus. At present, there is no vaccine for prevention, no antivirals for treatment of ZIKV infection. Preventing mosquito bites are more important by clothes covering, insect repellent, sleep in the mosquito nets and destroying the breeding place. Safe sex for 3-6 months after returning from Zika area is important for sexual transmission of this virus.

Conclusion : National surveillance of ZIKV infection among pregnant women , newborn with microcephaly and /or other neurological abnormality will help to better care and management of this maternofetal and neonatal infection. The biomedical and clinical research are necessary for better understanding of new knowledge in providing the appropriate strategies for vaccine development, therapeutic modality. Establishment of prospective cohorts in identifying the risk and consequences of congenital / neonatal Zika syndrome is essential.
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<td>Global Epidemiology and Clinical Impact of Carbapenem-resistant <em>Acinetobacter</em> Species</td>
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<td><em>National Taiwan University Hospital, Taipei, Chinese Taipei</em></td>
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<td>Global epidemiology and clinical impact of carbapenemase-producing Enterobacteriaceae</td>
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<td>David Livermore</td>
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<td>Prognosis of patients with bacterial bloodstream infection in an aspect of causative pathogens: from the first one-year report of Kor-GLASS</td>
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<td>S7-4</td>
<td>Treatment of Carbapenem-resistant Gram-negative</td>
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Acinetobacter baumannii, a member of A. calcoaceticus-Acinetobacter baumannii complex, has risen to prominence particularly because of its ability to cause infections in immunocompromised patients and has become one of the most difficult pathogens to treat. This organism is now a predominant pathogen in many hospitals worldwide as it has acquired resistance genes to virtually all antimicrobial agents capable of treating Gram-negative bacteria. The only conventional remaining treatment options are the carbapenems. In the last decade, carbapenem-resistant A. baumannii (CR-AB) isolates have emerged as important nosocomial pathogens globally. In 2017, the World Health Organization ranked CR-AB among the first catalog of antibiotic-resistant pathogens with "critical priority" because the healthcare-acquired CR-AB strains pose a tremendous threat to human health. A. baumannii possesses an inherent class D β-lactamase gene (blaOXA-51-like) that can have the ability to confer carbapenem resistance. Additionally, mechanisms of carbapenem resistance have emerged due to the importation of the distantly related class D β-lactamase genes blaOXA-23 and blaOXA-58 by mobile promoters carried on ISAba elements. Of the presently available antimicrobials, the most active agents against CR-AB in vitro are polymyxin B or colistin, and tigecycline. Previously in vitro investigations showed that some combination schemes have potential in vitro efficacy against CR-AB isolates, including imipenem or meropenem plus sulbactam or colistin, rifampin plus colistin, and tigecycline in conjunction with colistin. Currently, several novel agents, e.g. cefepime- zidebactam, cefiderocol, and eravacycline, hold promise in the treatment of infections by CR-AB.
For 20 years after the launch of imipenem in 1985, carbapenemase-producing Enterobacteriaceae remained extremely rare and carbapenems became the ‘go to’ antibiotics for infections due to Enterobacteriaceae resistant to cephalosporins, fluoroquinolones and aminoglycosides.

Subsequently the situation worsened dramatically. Klebsiella spp. with VIM carbapenemases caused the first major national problem, spreading in Greece around 2005. This harbinger of coming trouble was followed by proliferations of KPC, OXA-48-like and NDM carbapenemases, to the point where several countries – Italy, Greece, Romania, India, Brazil – now record carbapenem resistance in >25% of K. pneumoniae, which is the most frequent host for acquired carbapenemase genes.

Acquired carbapenemases retain strong regional links: KPC types are the predominant types in the Americas, Greece (where they substantially supplanted VIM types) and China. OXA-48-like carbapenemase dominate in most of the rest of Europe, Turkey (where they originated) and the Middle East (excluding Israel). NDM dominates in the Indian subcontinent, Global travel, medical tourism and migration are eroding these associations to some degree, e.g. with substantial import of NDM into the UK, Canada and the Middle East, but they remain strong.

KPC carbapenemases are strongly associated with the nosocomial spread of K. pneumoniae ST258 and related clones carrying these enzymes, though there has also been recent and disturbing spread to hyper-virulent strains, often of ST11. Problems with other carbapenemase, besides KPC types, are more often associated with the spread of encoding plasmids among multiple bacterial strains, which complicates tracking by hospital epidemiologists and infection control staff. Classical OXA-48 is often carried by 50/70 kb IncL/M plasmids whereas the genes for NDM enzymes have spread among diverse plasmids, which – at least in India – are spreading in the community as well as in hospitals.

The clinical impact of carbapenemase producers has been substantial. Infection control to prevent their spread has been successful at a national level notably in Israel and – to a degree – in the UK, but adds cost and reduces bed efficiency. Isolates with OXA-48 carbapenemase often have only low-level carbapenem resistance, allowing unnoticed stealth spread.

Where infections with carbapenemase-producing Enterobacteriaceae do occur they have forced the use of colistin, an old antibiotic with significant toxicity and very uncertain pharmacodynamics. In severe infection colistin is probably best used in combination, but useful partners are few, given the multi-resistance of many carbapenemase producers and those that are most reliably active in vitro (tigecycline and fosfomycin) carry their own uncertainties. This situation is gradually improving as new diazabicyclooctane- and boronate-based β-lactamase inhibitor combinations become available, with growing data to support the view that these achieve better outcomes than colistin and its combinations at least in the case of isolates with KPC and (for ceftazidime/avibactam) OXA-48 carbapenemases.

S7-2. Global epidemiology and clinical impact of carbapenemase-producing Enterobacteriaceae

David M Livermore
Norwich Medical School, University of East Anglia, NORWICH NR4 7TT, UK
S7-3. Prognosis of patients with bacterial bloodstream infection in an aspect of causative pathogens: from the first one-year report of Kor-GLASS

Eun-Jeong YOON, Dokyun KIM, Changseung Liu, Young UH, Jeong Hwan SHIN, Kyeong Seob SHIN, Young Ah KIM, Jong Hee SHIN, and Seok Hoon JEONG

Department of Laboratory Medicine and Research Institute of Bacterial Resistance, Yonsei University College of Medicine, Seoul, South Korea; Department of Laboratory Medicine, Yonsei University Wonju College of Medicine, Wonju, South Korea; Department of Laboratory Medicine and Paik Institute for Clinical Research, Inje University College of Medicine, Busan, South Korea; Department of Laboratory Medicine, Chonnam National University College of Medicine, Cheongju, South Korea; Department of Laboratory Medicine, National Health Insurance Service Ilsan Hospital, Goyang, South Korea; Department of Laboratory Medicine, Chonnam National University Medical School, Gwangju, South Korea

As a part of National Action Plan in 2016 on antimicrobial resistance, a newly established national AMR surveillance system, Kor-GLASS, which is compatible with the Global Antimicrobial Resistance Surveillance System (GLASS) platform proposed by the World Health Organization (WHO), was launched and initiated in May 2016. The system is a prospective cohort study based on the collection of non-duplicate clinical isolates and data by specimen from sentinel hospitals. During the 1-year period between May 2016 and April 2017, six sentinel hospitals sampled 67,803 patients for blood culture and a total of 3,523 (5.2%) target pathogens were recovered. The predominant bacterial species was Escherichia coli (n = 1,536, 43.6%), followed by Klebsiella pneumoniae (n = 597, 16.9%) and Staphylococcus aureus (n = 584, 16.6%), Acinetobacter spp. (n = 229, 6.5%), composed of 188 Acinetobacter baumannii and 41 non-baumannii Acinetobacter spp., Enterococcus faecalis (n = 217, 6.2%), Enterococcus faecium (n = 161, 4.6%), and Pseudomonas aeruginosa (n = 127, 3.6%). Salmonella spp. (n = 44, 1.2%) and Streptococcus pneumoniae (n = 28, 0.8%) were rarely recovered. By eliminating the day-0 death, 30-day mortality was observed in patients with BSIs caused by 9.5% (141/1492) of E. coli, 16.8% (96/572) of K. pneumoniae, 15.3% (87/567) of S. aureus, 42.5% (77/181) of A. baumannii, 14.2% (17/120) of P. aeruginosa, 27.6% (40/145) of Ent. faecium, and 14.1% (22/156) of Ent. faecalis. Mortality dynamics were presented a power-law tendency curve of cumulative survival over six weeks after the BSI onset caused by E. coli, A. baumannii, Ent. faecalis, K. pneumoniae, and S. aureus, while those by Ent. faecium presented steep increase of mortality in the fourth week after the BSI onset and a continued tedious mortality, and those by P. aeruginosa presented sharp increase of mortality in the fifth week of the BSI onset, resulting in 20.0% (24/120) of 42-day mortality. The Sequential Organ Failure Assessment (SOFA) score that was calculated using the collected raw data for the day of initial blood culture indicated that the patients with BSIs caused by A. baumannii was in worst conditions (5.9 ± 3.5) and those by K. pneumoniae (4.9 ± 3.6), Ent. faecium (4.5 ± 3.5), Ent. faecalis (4.4 ± 3.8), and S. aureus (4.4 ± 3.8) were followed, while the patients with BSIs caused either by P. aeruginosa (3.9 ± 3.2) or by E. coli (3.6 ± 3.0) had relatively less SOFA scores. The BSIs caused by Ent. faecium and A. baumannii were mostly hospital-originated, 80.0% (116/145) and 88.4%, (117/181), respectively, and more than half of the patients with BSIs caused by A. baumannii (64.6%, 117/181) were hospitalized in intensive care units. Cefotaxime resistance was observed in 35.1% (523/1472) of E. coli and in 28.7% (164/572) of K. pneumoniae, carbapenem resistance in 23.3% (28/120) of P. aeruginosa and in 88.4% (160/181) of A. baumannii, vancomycin resistance in 0.6% (1/156) of Ent. faecalis and in 30.3% (44/145) of Ent. faecium, and cefoxitin resistance was found in 53.4% (303/567) of S. aureus. Antimicrobial resistance and associated failure of the empirical antimicrobial therapy was associated with the mortal of the patients with bacterial BSIs. In addition, strain types, i.e. ST131 H30Rfx for E. coli, w250 capsular type for K. pneumoniae, ST191 for A. baumannii, and CC5 MRSA for S. aureus were identified as risk factors for 30-day mortality, and resistance determinants, i.e. group 1 CTX-M extended-spectrum beta-lactamases for E. coli, OXA-23 for A. baumannii, and OprD deficiency for P. aeruginosa, and virulence factors, i.e. colibactin for K. pneumoniae and TSST-1 for S. aureus, were also the risk factors of 30-day mortality for the patients with BSIs. The cohort study aiming the antimicrobial resistance surveillance gave a clear snapshot for bacterial BSIs occurred in general hospitals in South Korea and highlighted the importance of national monitoring system for the antimicrobial resistance on the infection-causative pathogens helping the clinicians for an adequate antimicrobial therapy for better outcome of the patients.
MDR and XDR Gram-negative are serious causes of healthcare-associated infections worldwide. The common presentations of these particular pathogens include hospital-acquired pneumonia and bloodstream infection. MDR- and XDR infections have become more difficult to treat with the emergence of isolates resistant to commonly available prescribed antibiotics (e.g., carbapenem). This results in poor prognosis, high treatment failure and significantly increased mortality. Currently, a consensus recommendation for the optimal treatment of these infections has not been established. Several antimicrobials have been used to treat MDR- and XDR as well as carbapenem-resistant Gram negative infections, including colistin, sulbactam and tigecycline as monotherapy or combination therapy as well as the introduction of new antibiotic classes. In this session, I will discuss the approaches for treatment of carbapenem-resistant Gram-negatives as well as limitations of each approach.
### September 28, 2019

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<td>09:00</td>
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<td><strong>New approaches for fungal infections in immune-compromised host</strong></td>
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<td>S8-1</td>
<td>Fungal Epidemiology and Emerging Resistance in Asia</td>
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<td>Jong Hee Shin, Chonnam National University Medical School, Korea</td>
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<td>ICU &amp; Flu: New Risk Factors for Invasive Aspergillosis</td>
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<td>Wei-Lun Liu, Fu Jen Catholic University Hospital, Chinese Taipei</td>
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<td>S8-3</td>
<td>Talaromycosis and mucormycosis: challenges and opportunities</td>
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<td>Patrick Woo, The University of Hong Kong, Hong Kong, China</td>
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<td>S8-4</td>
<td>New diagnostic and therapeutic strategies for invasive fungal infection</td>
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<td>Monica Slavin, Peter MacCallum Cancer Centre, Australia</td>
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The epidemiology of invasive fungal infections has changed greatly over the past few decades; however, *Candida* and *Aspergillus* remain the main fungal pathogens. Several surveillance programs have documented the emergence of azole resistance among *Aspergillus fumigatus* and other *Aspergillus* species worldwide. Azole-resistant *A. fumigatus* strains with mutations in the Cyp51A gene and its promoter have been identified in several Asian countries. *Candida albicans* now represents less than 50% of all candidemic cases in Asia, where fluconazole resistance has been observed among bloodstream isolates of the most common non-*albicans Candida* species such as *Candida tropicalis* and *Candida parapsilosis*. *Candida auris* is an emerging fungal pathogen worldwide. *Candida auris* isolates are grouped into distinct clades: South Asian, East Asian, African, and South American. A recent report in Korea has revealed the unique nature of the East Asian clade of *C. auris. Invasive aspergillosis (IA) is a life-threatening opportunistic infection that has been best described in hematology patients. Increases in IA incidence may be partly associated with the increase in galactomannan testing over the past decade. In recent years, however, serum galactomannan-negative IA has increasingly been observed in populations other than hematology patients. Acquired azole resistance has emerged in *A. fumigatus*; its most common mechanism involves the modification of Cyp51A and its promoter (TR34/L98H and TR46/Y121F/T289A), which have been found in environmental and clinical isolates from many countries. This mechanism is thought to be related to the use of fungicides in agriculture. Strains containing these mutations have been identified in several Asian countries, including China, Taiwan, Thailand, Japan, and Korea. *Candida tropicalis* is the most common non-*albicans Candida* species causing fungemia in Asia, except for Korea and Japan. Global surveillance data have shown that the highest rates of fluconazole resistance among *C. tropicalis* bloodstream isolates occur in Asian countries. The emergence and clonal spread of fluconazole-resistant *C. parapsilosis* bloodstream isolates harboring a Y132F mutation in Erg11 have been reported in Korean hospitals. Echinocandin resistance was found to be distinctly uncommon among isolates of *C. albicans*, *C. parapsilosis*, and *C. tropicalis*, and most prominent among *Candida glabrata* isolates worldwide. Increased echinocandin resistance in *C. glabrata* is often accompanied by azole resistance, resulting in multidrug-resistant strains. Reports from some centers in Asia indicate increasing *C. glabrata* rates among bloodstream isolates. The global emergence of *C. auris* raises several serious concerns for public health due to high rates of antifungal drug resistance, organism misidentification, and high transmissibility among hospitalized patients, leading to nosocomial outbreaks and significant patient mortality. *Candida auris* infections have been reported in at least 30 countries on six continents, including Asian countries such as Korea, Japan, China, Singapore, Malaysia, and Taiwan. A recent report showed lower rates of antifungal susceptibility, lower Erg11 mutation rates in association with fluconazole resistance, and unique genotypes in *C. auris* isolates from Korea (East Asian clade) compared with those from the other three clades (South Asian, African, and South American). During 2006–2018, *C. auris* isolates were recovered yearly from ear specimens (mostly) or blood (rarely) in Korea; isolates from both blood and ear cultures were genetically similar. However, apparent nosocomial clusters of fungemia have not yet been detected.
Recent advances in medical technologies have increased the survival rate of severely ill patients admitted to intensive care units (ICU). This heterogeneous patient population is highly susceptible to invasive fungal infections. Invasive pulmonary aspergillosis (IPA) is an opportunistic infection that occurs predominantly among severely immunocompromised patients with hematological malignancies, most notably during prolonged neutropenia, but also in those who have undergone allogeneic stem cell transplantation or solid organ transplantation. However, IPA is emerging in non-neutropenic critically ill patients with predisposing conditions, such as corticosteroid treatment, chronic obstructive pulmonary disease and other chronic airway abnormality, solid cancer with or without treatment and HIV infection. Decompensated cirrhosis has been described as a risk factor for IA, and impaired phagocytosis has been proposed as a possible reason for heightened risk in these groups. Diabetes has been observed as another risk factor for IA, possibly due to impaired innate and acquired immunity caused by hyperglycemia.

Severe influenza infections are usually defined as patients requiring ICU admission. IPA has been increasingly reported that may occur in the setting of severe influenza even among immunocompetent hosts. More recently, influenza was identified as an independent risk factor for IPA and is associated with high mortality. Why patients with severe influenza are at risk for IPA is not yet clear. The influenza virus alters the bronchial mucosa, resulting in epithelial disruption and mucociliary clearance dysfunction, which may facilitate the invasion of Aspergillus. Another hypothesis proposed to explain a depressed immune response in the apparently immunocompetent patient with severe influenza relates to the biphasic response in which the initial hyperinflammatory phase is followed by immunoparalysis phase. This latter process is characterized by neutrophil deactivation, and may place the patient at risk for developing opportunistic infections, such as IPA. Immunosuppression has been described as a late stage of the biphasic response to sepsis and multiple organ dysfunction syndrome.

IPA contribute significantly to morbidity and mortality in critically ill patients. Diagnosis is challenging because the signs and symptoms are non-specific, and initiation of additional diagnostic examinations is often delayed because clinical suspicion is low. Definitions of invasive fungal infections suggested by the European organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) are difficult to apply for identifying IPA in ICU patients. For the ICU setting, an algorithm (AspICU algorithm) was described by Blot and colleagues to distinguish invasive pulmonary aspergillosis from Aspergillus colonization in patients who are critically ill. The Aspergillus galactomannan (GM) test is a commercially available diagnostic tool detecting Aspergillus antigen in serum, bronchoalveolar lavage (BAL) fluid, or cerebrospinal fluid. Serum GM levels in non-neutropenic patients appear to be inaccurate, but GM detection in BAL fluid is a useful tool in establishing the diagnosis of IPA in non-neutropenic critically ill patients.

Studies on patients with IPA have similarly shown excessive rates of inappropriate initial therapy and even higher mortality than infections caused by bacterial pathogens in the ICU setting. The importance of prompt identification of IPA through a combination of risk factor analysis and diagnostic assays has been demonstrated to be a key factor affecting IPA-related mortality.
Talaromyces (Penicillium) marneffei is the most important pathogenic thermally dimorphic fungus causing systemic mycosis in Southeast Asia. T. marneffei infection is endemic in tropical regions, especially Thailand, Vietnam, northeastern India, Southern China, Hong Kong, Taiwan, Laos, Malaysia, Myanmar, Cambodia, and Laos. Bamboo rats (Rhizomys sp. and Cannomys sp.) and soil from their burrows are considered to be important enzootic and environmental reservoirs of T. marneffei, respectively. Historically, T. marneffei infection in human has been considered to be exclusively associated with HIV infection. In some regions such as Hong Kong and southern China, T. marneffei infection has long been considered as one of the top three AIDS-defining opportunistic infections, alongside tuberculosis and cryptococcosis. In recent years, a decline in the incidence of T. marneffei infection among HIV-infected patients was seen in regions with access to highly active antiretroviral therapy and other control measures for HIV. In contrast, T. marneffei infection has been increasingly reported among non-HIV-infected patients with impaired cell-mediated immunity since the 1990’s. Their comorbidities included primary adult-onset immunodeficiency due to anti-interferon-gamma autoantibodies and secondary immunosuppressive conditions including other autoimmune diseases, solid organ and hematopoietic stem cell transplantations, T lymphocyte-depleting immunosuppressive drugs, and novel anti-cancer targeted therapies such as anti-CD20 monoclonal antibodies and kinase inhibitors. Moreover, improved immunological diagnostics identified more primary immunodeficiency syndromes associated with T. marneffei infection in children.

Sinopulmonary and rhinocerebral mucormycosis has been increasingly reported in patients with hematological malignancies and bone marrow transplantation, but intestinal mucormycosis remains very rare. A few years ago, we investigated an outbreak of intestinal infection due to RHizopus microsporus in 12 patients on treatment for hematological malignancies over a period of 6 months in a teaching hospital. The intake of allopurinol during hospitalization (P<0.001) and commercially packaged ready-to-eat food items in the preceding 2 weeks (P<0.001) were found to be independently significant risk factors for the development of intestinal mucormycosis. A total of 709 specimens, including 378 environmental and air samples, 181 food samples and 150 drug samples, were taken for fungal culture. Among them, 16 samples of allopurinol tablets, 3 pre-packaged ready-to-eat food items and 1 pair of wooden chopsticks, were positive for RHizopus microsporus, which were confirmed by ITS sequencing. The mean viable fungal counts of allopurinol obtained from wards and pharmacy were $4.22 \times 10^3$ and $3.24 \times 10^2$ cfu/g of tablet respectively, much higher than the mean count of $2 \times 10^2$ cfu/g of food. Phylogenetic analysis showed multiple clones from isolates of contaminated allopurinol tablets and ready-to-eat food of which some were identical to patients’ isolates, and with one isolate in the corn starch used as excipient for manufacturing this drug. The primary source of the contaminating fungus was likely to be the corn starch used in the manufacturing of allopurinol tablets or ready-to-eat food. RHizopus microsporus was thermo-tolerant and could multiply even at 50°C. The long holding time of the intermediates during the manufacturing process of allopurinol has amplified the fungal load. Microbiological monitoring of drugs manufactured for highly immunosuppressed patients should be performed.
S8-4. New diagnostic and therapeutic strategies for invasive fungal infection

Slavin MA

Peter MacCallum Cancer Centre, Melbourne, Australia

Invasive fungal infections remain a major and lethal complication of the immunocompromised. Fungi which are either inherently drug-resistant such as *Lomentopora prolificans, Fusarium* spp or *Candida auris* or have selected azole- or echinocandin- resistance are emerging globally. Further, drug-drug interactions and toxicity limit the utility of current drugs. Rapid diagnostics and new antifungal agents are urgently required. These challenges have resulted in the development of rapid diagnostic approaches for resistance testing such as molecular and genomic resistance testing. Standardisation of aspergillus PCR performance now means that it can now be incorporated into EORTC/MSG definitions of infection whilst Candida PCR is becoming more widely used and Mucormycosis PCR is under evaluation. Beyond serological based tests, imaging modalities are also improving.

New agents targeting the antifungal cells wall are most developed and examples such as rezafungin (CD101) will be discussed. New agents acting on fungal cell membrane metabolic pathways are being studied including inhibitors of the glycoxylate cycle and pyrimidine synthesis exemplified by the dihydroorotate dehydrogenase inhibitor olorofim (F901318). The potential of inhibiting cell signalling pathways, which control cellular differentiation, mating and filamentous growth such as mitogen-activated protein kinases (MAPK), is being explored. Although conserved between fungi and human cells upstream signalling differences occur. Calcium signalling pathways and transcription factors that regulate gene expression and are important to multiple cellular functions may also be drug targets. Additionally the role of new anti-cancer agents with epigenetic effects such as histone deacetylase (HDAC) inhibitors in combination with antifungal agents is being assessed. Additionally the role of immunotherapy harnessing cytotoxic T-cells or Dectin-1 chimeric antigen receptor (CAR) T-cells is progressing. How the microbiome may be manipulated to prevent or treat fungal infection is a new area for research.

These developments in the field mean that earlier detection of fungal infection and antifungal resistance is becoming more feasible and newer antifungal agents are broadening treatment options.
September 28, 2019

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| 09:00 - 11:00 | S9-1 | Advances in “ART” (Antibacterial Resistance Testing)  
Robin Patel  
Mayo Clinic, USA |
|        | S9-2 | Detection methods for mcr and carbapenemase genes  
Hui Wang  
Peking University People’s Hospital, PR China |
|        | S9-3 | Syndromic approach for infectious agents detection  
Heungsup Sung  
Asan Medical Center, Korea |
|        | S9-4 | NGS based diagnosis of infectious diseases  
Dongeun Yong  
Yonsei University College of Medicine, Korea |
Microbial diagnostics are foundational in the practice of medicine. Outside of making specific diagnoses, they inform selection of correct antimicrobial therapy. In some situations, knowledge of the organism causing infection is sufficient to inform the choice of antimicrobial therapy. As a result of acquired resistance however, many microorganisms - particularly bacteria - no longer have predictable susceptibility to modern therapeutics. For this reason, beyond identification of pathogens causing infection, it is increasingly important to provide antimicrobial susceptibility. And, these results must be delivered and acted upon as quickly as possible. This permits treatment of patients with active agents, avoiding empirical approaches, which lead to both under- and over-treatment; the latter may select for further resistance, in addition to being associated with toxicity, microbiome disturbances, and, at times, unnecessary cost. Accordingly, assessing antibacterial resistance (and susceptibility) using rapid methods, and rapidly communicating those results - such that they are appropriately acted on - has become increasingly important in modern medicine.

While technology advances have the prospect to provide faster (and sometimes better) results, improvements don’t always come at reduced cost, and, as alluded to above, practical aspects of implementation must be considered, especially how results should be delivered such that they are appropriately and expeditiously responded to. For example, our group has shown that rapid blood culture identification of pathogens and assessment of their susceptibility has the most significant impact on patient outcomes when paired with real-time clinical decision-making support. Specifically, we executed a prospective, randomized, controlled, three-arm trial that appraised clinical and economic outcomes associated with the BioFire® FilmArray® Blood Culture Identification (BCID) Panel—a diagnostic that identifies multiple bacteria, fungi, and common antimicrobial-resistance genes (mecA, vanA/B, blaKPC) in about an hour following organism growth in blood culture bottles. (Other blood culture bottle tests with a more extensive array of analytes are now available, and will be discussed.) Our trial compared standard-of-care testing and reporting with two strategies to guide healthcare providers’ responses to the rapid results - electronic comments with treatment guidance alone or with active antimicrobial stewardship team oversight. Overall, microbial identification was faster in the BCID groups compared with the control group. Although groups did not differ in length of stay, hospitalization costs, mortality, adverse drug events, or Clostridoides difficile infection rates, there was less broad-spectrum antibiotic use, more narrow-spectrum antibiotic use, less treatment of contaminants, and faster antibiotic escalation, in the BCID arms compared with the control group. Notably however, faster antibiotic de-escalation occurred only in the group assigned to BCID plus stewardship.

The Accelerate PhenoTest™ BC Kit, performed on the Accelerate Pheno™ System, performs rapid bacterial identification in about 1.5 hours, followed by phenotypic susceptibility testing within approximately 7 hours directly from positive blood cultures. This system uses fluorescence in situ hybridization for bacterial identification and time-lapse microscopy for phenotypic susceptibility determination. Our experience with this system, alongside an assessment of other systems under development, will be presented.

Beyond applications of nucleic acid amplification resistance gene detection and rapid phenotypic susceptibility testing, the use of genome sequencing to predict antibiotic susceptibility and resistance is an emerging area. Our experience in this regard will be presented.
Multidrug resistance in gram-negative bacteria is one of the most critical public health threats, notably with the description of carbapenemase-producing Enterobacteriaceae. In recent years, significant increases in the prevalence of CRE have been reported in the world. Colistin has become the last resort for carbapenemase-producing Enterobacteriaceae. However, plasmid-mediated colistin resistance gene, mcr-1, has been identified with accelerating incidence in Enterobacteriaceae, isolated from environment, human and animals. The co-existence of mcr and carbapenemase genes has already been detected in clinical settings and resulted in few therapeutic options. There is thus an urgent need to improve the detection of carbapenemase and mcr for infection control and antibiotic stewardship initiatives. Currently, the main methods used to detect carbapenemase and mcr can be classified under phenotypic and genotypic methods. Phenotypic assays performed in clinical practice includes: (i) assays based on growth in the presence of carbapenems or dipicolinic acid, such as modified Hodge test, modified carbapenem inactivation method (mCIM), EDTA mCIM for carbapenemase, and Colistin-MAC for mcr; (ii) detection based on the product of hydrolysis that is catalyzed by carbapenemase, e.g. Carba NP and matrix-assisted laser desorption–ionization time of flight mass spectrometry (MALDI-TOF MS); and (iii) lateral flow immunoassays. Furthermore, the nucleic acid-based approaches, including conventional PCR, real time PCR, microarray, and whole-genome sequencing were also used for carbapenemase and mcr detection.
S9-3. Syndromic approach for infectious agents detection

Heungsup Sung
Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea

New molecular technologies continue to evolve and improve, cutting the time it takes to diagnose infectious disease. Such rapid results enable better individualized patient management. Molecular diagnostic testing has continuously moved toward a more broad syndromic screening and "sample-in, result-out" format. Yet challenges remain in regulatory barriers and successful clinical practice integrations. I would like to describe several emerging technologies, including multiplex syndromic molecular tests, molecular point-of-care (POC) tests, and other emerging tools, and discuss challenges in integrating these tests into clinical practice. Current diagnostic microbiology is increasingly adopting molecular techniques as front line tests for a variety of samples. This trend holds true for detection of respiratory pathogens, enteric pathogens, and central nervous system (CNS) infectious pathogens where nucleic acid amplification tests (NAAT) are well established as the new gold standard. Since the same clinical symptoms can be the result of different infectious agents in these infections, rapid syndromic NAAT are required. New highly multiplexed cartridge type molecular diagnostics can detect the majority of viral and bacterial pathogens that cause respiratory, gastrointestinal, or CNS infections within 20 minutes to 2 hours. In addition, these systems can detect several antimicrobial resistance genes.

As more new innovative technologies are introduced, significant challenges will be faced in interpreting the data. There is sometimes uncertainty of clinical significance when we using the multiplex syndromic tests. NAAT cannot distinguish commensal or colonizing pathogens and true pathogens. They also cannot distinguish viable and non-viable organisms although the disappearance of pathogen nucleic acids suggest the eradication. Therefore, laboratories will require strategies to assist clinicians in the interpretation of the results produced by multiplex NAAT or molecular POC.
S9-4. NGS based diagnosis of infectious diseases

Dongeun Yong
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Infection is one of the major cause of mortality in patients. Appropriate diagnosis is crucial for the management of infectious disease. In addition to conventional methods, including stain, culture, and immunological methods, currently genomic methods increase the spectrum of diagnosis. Rapidly declining costs for nucleotide sequencing and improvement in the technology will result in greater utilization of whole genome sequencing for infection diagnosis. Bacterial identification and antimicrobial susceptibility testing might be supported with rapidly improved NGS system. Surveillance, virulence determination, and microbiome analysis are also promising tasks to which NGS can contribute.

Through the import of these NGS technologies, genomics and whole genome sequencing of microorganisms have been in the scope of the clinical microbiology laboratories. A couple of factors should be considered before the set-up the NGS technologies in the laboratory, such as case, in-house vs. outsourcing, sequencing capacity, adaptability, and data quality, etc. The application of WGS in clinical microbiology would be pathogen identification (1) and detection (2), strain typing (3), resistance detection (4), virulence profiling (5), and metagenomics (6), etc.

The limitation of NGS should be recognized. The results are dependent on the quality of sequencing and assembly. And they are affected by the quality of the reference genome, also. The remarkable requirement in time for interpretation is a huddle in a clinical environment. In clinical microbiology laboratories, solid process for data validation, quality control and standardization will be essential. The guideline to determine the similarity between two isolates also is required to infer the transmission.
September 28, 2019

11:10 ~ 11:50 Plenary Lecture 3

P3-1 Prosthetic Joint Infection
Robin Patel
Mayo Clinic, USA
Rising numbers of prosthetic joint infections are being encountered in clinical practice due to the growing numbers of joint replacement surgeries being performed. As with other implant-associated infections, prosthetic joint infections are biofilm-associated. Some cases may be challenging to diagnose; misdiagnosis can result in mistreatment which may have adverse outcomes on the patient and the healthcare industry. In this presentation, Dr. Patel will review the pathogenesis, microbiology, diagnosis and management of prosthetic joint infection. She will focus on approaches to the diagnosis of prosthetic joint infection pre-operatively and, if not established before surgery, intra-operatively. She will cover novel approaches to prosthetic joint infection diagnosis, including biomarkers, as well as improved culture techniques, such as tissue cultures in blood culture bottles and methods directed at sampling biofilms on implant surfaces. In addition, she will overview her recent experience with and review the literature on molecular diagnostics for prosthetic joint infection, including 16S ribosomal RNA gene polymerase chain reaction/sequencing, panel nucleic acid amplification tests targeting specific microorganisms, and massive parallel sequencing.
September 28, 2019

11:50 ~ 12:30  Plenary Lecture 4

P4-1  High priority research areas for infectious diseases and AMR
Dennis Dixon
National Institutes of Health, USA
P4-1. High priority research areas for infectious diseases and AMR

Dennis M. Dixon
U.S. National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), USA

The U.S. NIH is the leading public funder of biomedical research worldwide. NIAID is the lead Institute of the 27 Institutes and Centers at NIH focused on infectious and immunologic diseases. Setting priorities is especially challenging when having to balance established and daunting diseases in addition to adjusting quickly to newly emerging infectious diseases. The process is based on public health needs and done in consultation with community and discipline-specific experts. Several obvious diseases of global significance rise to the top for attention. These include HIV, TB, malaria, and emerging infectious diseases and general issues such as antimicrobial resistance. Antimicrobial resistance in particular has resulted in significant scientific and political actions in the United States and globally. National and international communication, cooperation and collaboration are critical for combating antibiotic-resistant bacteria in these never-ending interactions between humans and microbes. NIH-supported AMR research activities will be summarized and placed into overall context. Future actions to be considered will be suggested.
September 28, 2019

15:10 ~ 15:50 Plenary Lecture 5

P5-1 Novel Agents for Emerging Multidrug-Resistant Gram-Negative Organisms
Po-Ren Hsueh
National Taiwan University Hospital, Taipei, Chinese Taipei
A gradual rise in drug-resistant trends among Gram-negative organisms, especially carbapenem-resistant (CR) Enterobacteriaceae (CRE), CR-Pseudomonas aeruginosa, and extensively-drug-resistant (XDR) Acinetobacter baumannii, poses an enormous threat to healthcare systems worldwide. In the last decade, many pharmaceutical companies have devoted enormous resources to the development of new potent antibiotics against XDR Gram-negative pathogens, particularly CRE. Some of these novel antibiotics against CRE strains are β-lactam/β-lactamase-inhibitor combination agents, while others belong to the non-β-lactam class. Most of these antibiotics display good in vitro activity against the producers of Ambler class A, C, and D β-lactamase, although avibactam and vaborbactam are not active in vitro against metallo-β-lactamase (MβL) enzymes. Nevertheless, in vitro efficacy against the producers of some or all class B enzymes (New Delhi MβL, Verona integron-encoded MβL, etc) has been shown with cefepime-zidebactam, aztreonam-avibactam, VNRX-5133, cefiderocol, plazomicin, and eravacycline. As of February 2019, drugs approved for treatment of some CRE-related infections by the US Food and Drug Administration included ceftazidime-avibactam, meropenem-vaborbactam, plazomicin, and eravacycline. Although active against extended-spectrum and AmpC β-lactamase-producing Enterobacteriaceae, delafloxacin does not show in vitro activity against CRE. Murepavadin is shown to be specifically active against CR- and colistin-resistant P. aeruginosa strains. Despite successful development of novel antibiotics, strict implementation of an antibiotic stewardship policy in combination with the use of well-established phenotypic tests and novel multiplex PCR methods for detection of the most commonly encountered β-lactamases/carbapenemases in hospitals is important for prescribing effective antibiotics against CRE and decreasing the resistance burden due to CRE. (Drugs 2019;79:705-714)
September 28, 2019

16:00 ~ 17:30 Symposium 10 Challenging cases (interactive session)

S10-1 Blood culture negative endocarditis and chronic arthritis
Didier Raoult
IHU Mediterranee Infection, France

S10-2 Chronic Fever in Diabetic Patient
Visanu Thamlikitkul
Siriraj Hospital, Thailand

S10-3 Infections in the immunocompromised host: challenging cases
Dong-Gun Lee
The Catholic University of Korea, Korea
September 28, 2019

16:00 ~ 17:30 Symposium 11 Strategies for diagnosing and treating Clostridium difficile infection

**S11-1** Changes in epidemiology and disease burden of *C. difficile* infection in Asia
Thomas Riley
*Murdoch University / Edith Cowan University, Australia*

**S11-2** Diagnostic Algorithms for *C. difficile* Infection
Karen Carroll
*Johns Hopkins University School of Medicine, USA*

**S11-3** New therapeutic options for *C. difficile* infection
Hyunjoo Pai
*Hanyang University Hospital, Korea*
**S11-1. Changes in epidemiology and disease burden of Clostridium difficile infection in Asia**

Thomas V Riley  
*School of Veterinary & Life Sciences, Murdoch University; School of Medical & Health Sciences, Edith Cowan University; Department of Microbiology, PathWest Laboratory Medicine, Perth, Western Australia*

*Clostridium difficile* is the most common cause of healthcare-related infection in the western world. Its highly resistant spores allow it to persist in healthcare facilities, causing diarrhoea primarily in patients who have recently been treated with antimicrobials. *C. difficile* infection (CDI) is also increasingly recognised in the community. CDI has been studied in detail in North America and Europe, where large outbreaks have occurred since the early 2000s, and Australia which has mainly been free of such outbreaks. However, the epidemiology of CDI in much of Asia is largely unknown due to a lack of local awareness and testing. Indeed, little is known about the strains of *C. difficile* circulating in this region of the World. In a recent survey of CDI performed in 13 countries in the Asia-Pacific region, the most common *C. difficile* strains isolated were ribotype (RT) 017 (16.7%) followed by RTs 014/020 (11.1%), 018 (9.9%), 002 (9.2%), 012 (4.8%) and 369 (4.1%), with wide variation between countries. Binary toxin-positive strains of *C. difficile* were detected rarely. Overall disease severity appeared milder, and mortality and recurrence were lower than in North America and Europe. Our laboratory has studied CDI and *C. difficile* carriage extensively in South-East Asia in Indonesia, Malaysia and Thailand. The most common strains isolated were non-toxigenic strains belonging to RTs not previously described, and there was great diversity. *C. difficile* RT 017 was again often found. There are at least five different clades of *C. difficile* circulating around the World. It is likely that the predominant molecular types of *C. difficile* found in Asia differ from other regions of the World. The diversity of RTs found suggests that Asia has its own clade of *C. difficile*, most likely clade 4. Clade 4 gained its pathogenicity locus quite late in evolutionary history, about 500 years ago, and RTs such as 017 only acquired a *tcdB* gene. It is possible that non-toxigenic strains are currently fulfilling a protective role in Asia, and the interplay of this feature and much antimicrobial misuse in the region is of great interest. Some Asian strains like RT 017 have travelled to other parts of the World where they have caused major outbreaks. This movement likely coincides with population movements, either human or animal. Very limited studies of production animals in Asia suggest two patterns of colonisation/disease, one where animals are colonised with strains of *C. difficile* similar to those found in animals in North America and Europe, and one where animals are colonised by local strains. Continued education about, and surveillance of, CDI in Asia are required to monitor the burden of disease and prevent the emergence of virulent antimicrobial-resistant strains. As with all *C. difficile* disease, a ”One Health” approach may be required to deal with this problem in Asia.
Abstracts of the ICIC & ISAAR 2019 / Infection & Chemotherapy 2019 Sep;51 (Suppl 1):S1-S70

**S11-2. Diagnostic Algorithms for *C. difficile* Infection**

Karen C Carroll  
*Professor of Pathology, Division of Medical Microbiology, Johns Hopkins University School of Medicine, USA*

*Clostridioides (Clostridium) difficile*, a toxigenic, spore-forming, gram-positive anaerobe, continues to cause significant colitis, especially among the elderly and other vulnerable populations. There has been a steady global increase in *C. difficile* disease along with significant increases in morbidity and mortality caused by the appearance of more virulent strains. Such strains include ribotype 027/NAP1/BI and newer variants that have mutations in the regulatory genes that control toxin expression concomitant with antimicrobial resistance. The diagnosis of *C. difficile* disease is controversial. It should begin with clinical suspicion in patients with risk factors and true diarrhea, followed by confirmation using a sensitive test. There are two main categories of tests available for detection of *C. difficile* infection—those that detect the organism (toxigenic culture and glutamate dehydrogenase) and those that detect toxin A and/or toxin B (cell culture cytotoxicity assay and enzyme immunoassays). Professional societies have published recommendations on diagnosis and treatment. A two-step approach that begins with screening for glutamate dehydrogenase (GDH) followed by a toxin test and/or molecular assay is the recommended approach in Europe. In the USA, toxin enzyme immunoassays are felt by some to be more likely predictors of true disease, although others still believe they are too insensitive to be used as standalone tests. Approximately 50% of the laboratories use a nucleic acid test that detects either the toxin A or toxin B genes, or both. To date, there are more than twelve FDA-approved assays available for the diagnosis of *C. difficile* encompassing a broad range of molecular platforms and methodologies. Some laboratories use a molecular test in a 3-step algorithm to adjudicate GDH positive, toxin negative samples to compensate for the poor analytical sensitivity of available toxin assays. For those laboratories that have chosen a molecular test as a single approach, steps should be taken to improve specificity by rejecting formed stools and eliminating test of cure and repeat testing of negative tests within seven days. Some laboratories are using laboratory information systems to improve best practices. Novel toxin tests for *C. difficile* disease, based upon single molecule array technologies that claim to be “ultrasensitive” are available or on the horizon. These assays have the ability to quantify toxin levels. More studies that are clinical are needed to determine the optimum toxin cut-off values for clinical care. This presentation will briefly review the history of antibiotic associated diarrhea and *C. difficile*. Current algorithms and problems with *C. difficile* testing will reviewed. Literature supporting the use of certain algorithms along with a discussion of the IDSA/SHEA guidelines will be incorporated into the presentation. Strategies to improve the predictive value of molecular assays will be addressed. Finally, a brief summary of novel platforms for toxin testing and how they are being used to understand disease will be included.
S11-3. New therapeutic options for *Clostridioides difficile* infection

Hyunjoo Pai
*Hanyang University Hospital, Korea*

*Clostridioides difficile* infection (CDI) is one of the most common hospital infections. During the past decade its incidence has increased markedly worldwide. Age over 65 years, use of antibiotics and prior hospital exposure are some of recognized risk factors for CDI. Current therapies are mainly directed at addressing primary CDIs with the use of antibiotics such as vancomycin, as well as treating recurrent disease with vancomycin or fidaxomicin. In repeatedly recurrent disease, additional current approaches use antibiotic tapers and fecal microbiota transplants (FMTs). Because of heavy burden of CDI in recent hospitals, newer therapies are being developed to reduce initial infection such as probiotics and vaccines. New treatments include narrow spectrum antibiotics, immunotherapies, and microbial replacement therapies. However, even with successful treatment, 20% of patients experience recurrent disease with an increased risk to recur following each recurrence, which implicates the importance of restoring the colonization resistance against *C. difficile*.

For the prevention of CDI, toxin vaccines and oral vaccine are in clinical trial (ACAM-CDIFF formalin inactivated toxin A &B vaccine discontinued phase III clinical trial). Oral β-lactamase which protects gut flora by inactivating the β-lactam antibiotics secreted into intestine from systemic administration and oral lactoferrin as growth modulator are in phase II clinical trial, and several probiotics mainly consisting of *Lactobacillus* and *Bifidobacterium* species are also in the process of clinical trials. New antibiotics against *C. difficile* which are minimally absorbed and reach high luminal concentrations with high activity against *C. difficile* without broad activity against other native bacteria are promising for the therapy of CDI: cadazolid, CRS3123, LFF571, MCB3681, nitazoxanide, ramoplanin, ridinilazole, surotomycin, and tigecycline. As for the medication to reduce the recurrence, systemic administration of monoclonal antibody against toxins showed a success in reducing the recurrence, and polyclonal antibodies are in development. Restoration of colonization is important for reducing the CDI recurrence, and can be achieved by supplementing the microbiota with bacterial replacement therapies (SER-109, CBM588, MET-2, RBX2600, and CP101). Non-toxigenic *C. difficile* (VP20261) to compete with toxigenic *C. difficile* is in clinical trial with a success.
September 28, 2019

16:00 ~ 17:30 Symposium 12 Current issues on HIV infection

S12-1 Curing HIV
Davey Smith
University of California San Diego, USA

S12-2 Mental health in people living with HIV (PLHIV): Risk factors, screening and interventions
Beena Rajasuriar
University of Malaya, Malaysia

S12-3 Pharmacologic Preventive Interventions: U=U, PrEP & STI
Bum Sik Chin
National Medical Center, Korea
S12-1. Curing HIV

Davey Smith

*University of California San Diego, USA*

This talk will review the latest effort to cure HIV, including broadly neutralization antibodies, genetic modifications with CRISPR and Zinc Fingers, and stem cell transplants. The study will also discuss results from a new peri-mortem cohort of people who participate in HIV research at the end of their life. These altruistic volunteers provide blood and other specimens in the months before they die and their whole bodies for rapid autopsy when they die. Such studies help identify HIV reservoirs throughout the body, which will be needed for cure studies that aim to eradicate all HIV reservoirs in tissues.
S12-2. Mental health in people living with HIV (PLHIV): Risk factors, screening and interventions

Reena Rajasuriar

*University of Malaya, Malaysia*
The current combination of widespread treatment and prevention against HIV, if effectively implemented, could theoretically end the HIV epidemic in the high income counties. Dr. Fauci laid out the national plan to end the epidemic in Unites States at CROI 2019, with a focus on increasing treatment and prevention in highly concentrated target populations. The four components of the plan are to 1) focus initially on high incidence geographic areas; 2) emphasize early diagnosis, immediate treatment, and engagement in care, with a plan to increase viral suppression from 60% to 90% nationally; 3) expand uptake of PrEP to at least 50% of those who need it; and 4) respond rapidly to emerging clusters of infection. While other measures matter, pharmacologic prevention is focusing on Treatment as prevention (TasP) as population scale, what is undetectable equals untransmittable (U=U) as individual scale, and PrEP. In addition, incidence of sexually transmitted disease (STD) besides HIV is rapidly increasing recently, and it is time to think of the pharmacologic prevention for STIs.

U=U was first mentioned by Swiss investigators in 2008 as the statement that persons on ART with suppressed viral load and without STIs were unable to transmit HIV to their partners, based on seeing no cases of documented transmission in this situation. While an UNAIDS Chief Scientific Officer noted about U=U at IAS 2008, Mexico that “we have to be very careful about what we are saying and to whom it applies, because it can have unintended, negative consequences,” data from HPTN 052, PARTNERS -1 and -2, and the Opposites Attract studies now provide compelling evidence that transmission does not occur when a person is fully virally suppressed on ART. U=U is not just viral phenomenon. U=U campaign has transformed social, sexual, and reproductive lives of people living with HIV/AIDS. It also dismantle stigma and people get tested and remain on treatment, leading to a strong public health argument for the necessity of access to care.

While U=U is clear, verification of viral suppression may matter. In one study, 47% of MSM who reported an undetectable viral load had some virus detected on dried blood spots and the role of PrEP is still also clear. While new diagnoses in MSM in Australia, England, and the United States recently declined substantially, increased testing and treatment as well as PrEP coincided with these declines in new diagnoses. Therefore, combination prevention strategy including PrEP may be needed for the substantial declines in incidence across populations. Various PrEP agents are under investigation. TAF/FTC was noninferior to TDF/FTC in preventing HIV infection among men who have sex with men and transgender women with better bone and renal safety outcomes. Rapidly dissolving inserts are being developed for on-demand topical PrEP. They are user-friendly and have a favorable safety profile with low systemic drug exposure.

Global epidemic of STIs among MSM is accompanying remarkable progress in HIV epidemic. While PrEP did not cause the STI epidemics among MSM, it has the potential to make the epidemic worse. Best practice clinical interventions should be widely implemented to increase STI testing including extragenital areas for gonorrhea and chlamydial infection. While we need to re-invigorate the efforts to promote condom use in all populations including MSM against STI epidemics, we need scientific innovation such as doxycycline STI pre- and post-exposure prophylaxis, rapid point of care tests for STI, and effective STI vaccines.