ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

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Speakers:
1 Kate Templeton, Edinburgh, United Kingdom
2 Jacob Moran-Gilad, Beer Sheva, Israel
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References

[Optional: Topic or topics]

1.1. David S, Afshar B, Mentasti M, Ginevra C, Podglajen I, Harris SR, Chalker VJ, Jarraud S, Harrison TG, Parkhill J. Seeding and establishment of Legionella pneumophila in hospitals; implications for genomic investigations of nosocomial Legionnaires' disease. Clin Infect Dis. 2017 Feb 17. doi: 10.1093/cid/cix153

Background: Legionnaires' disease is an important cause of hospital-acquired pneumonia and is caused by infection with the bacterium Legionella. Because current typing methods often fail to resolve the infection source in possible nosocomial cases, we aimed to determine whether whole-genome sequencing (WGS) could be used to support or refute suspected links between cases and hospitals. We focused on cases involving a major nosocomial-associated strain, L. pneumophila sequence type (ST) 1. Methods: WGS data from 229 L. pneumophila ST1 isolates were analyzed, including 99 isolates from the water systems of 17 hospitals and 42 clinical isolates from patients with confirmed or suspected hospital-acquired infections, as well as isolates obtained from or associated with community-acquired sources of Legionnaires' disease. Results: Phylogenetic analysis demonstrated that all hospitals from which multiple isolates were obtained have been colonized by 1 or more distinct ST1 populations. However, deep sampling of 1 hospital also revealed the existence of substantial diversity and ward-specific microevolution within the population. Across all hospitals, suspected links with cases were supported with WGS, although the degree of support was dependent on the depth of environmental sampling and available contextual information. Finally, phylogeographic analysis revealed that hospitals have been seeded with L. pneumophila via both local and international spread of ST1. Conclusions: WGS can be used to support or refute suspected links between hospitals and Legionnaires' disease cases. However, deep hospital sampling is frequently required due to the potential coexistence of multiple populations, existence of substantial diversity, and similarity of hospital isolates to local populations.

1.2 de Oliveira WK, Carmo EH, Henriques CM, Coelho G, Vazquez E, Cortez-Escalante J, Molina J, Aldighieri S, Espinal MA, Dye C. Zika Virus Infection and Associated Neurologic Disorders in Brazil. N Engl J Med. 2017 Apr 20;376(16):1591-1593. doi: 10.1056/NEJMc1608612. Epub 2017 Mar 29.

No abstract available

1.3 Dela Cruz FN Jr, Li L, Delwart E, Pesavento PA. A novel pulmonary polyomavirus in alpacas (Vicugna pacos). Vet Microbiol. 2017 Mar;201:49-55. doi: 10.1016/j.vetmic.2017.01.005. Epub 2017 Jan 6.

Viral metagenomic analysis detected a novel polyomavirus in a 6-month old female alpaca (Vicugna pacos) euthanized after a diagnosis of disseminated lymphosarcoma. The viral genome was fully sequenced, found to be similar to other polyomaviruses in gene architecture and provisionally named Alpaca polyomavirus or AlPyV. Viral nucleic acid was detected by PCR in venous blood, spleen, thymus, and lung. AlPyV phylogenetically clustered in the "Wuki" group of PyVs, which includes WU and KI polyomaviruses, commonly found in human respiratory samples. In an ISH analysis of 17 alpaca necropsies, 7 had detectable virus within the lung. In animals without pneumonia, probe hybridization was restricted to the nuclei of scattered individual bronchiolar epithelial cells. Three of the ISH positive alpacas had interstitial pneumonia of unknown origin, and in these animals there was viral nucleic acid detected in bronchiolar epithelium, type II pneumocytes, and alveolar macrophages. The pattern of AlPyV distribution is consistent with a persistent respiratory virus that has a possible role in respiratory disease.

1.4 Delacroix R, Morel SN, Hervé L, Bordy T, Dinten JM, Drancourt M, Allier C. Cerebrospinal fluid lens-free microscopy: a new tool for the laboratory diagnosis of meningitis. Sci Rep. 2017 Jan 3;7:39893. doi: 10.1038/srep39893.

Cerebrospinal fluid cytology is performed by operator-dependant light microscopy as part of the routine laboratory work-flow diagnosis of meningitis. We evaluated operator-independent lens-free microscopy numeration of erythrocytes and leukocytes for the cytological diagnosis of meningitis. In a first step, prospective optical microscopy counts of leukocytes done by five different operators yielded an overall 16.7% misclassification of 72 cerebrospinal fluid specimens in meningitis/non-meningitis categories using a 10 leukocyte/µL cut-off. In a second step, the lens-free microscopy algorithm adapted for counting cerebrospinal fluid cells and discriminating leukocytes from erythrocytes was modified step-by-step in the prospective analysis of 215 cerebrospinal fluid specimens. The definite algorithm yielded a 100% sensitivity and a 86% specificity compared to confirmed diagnostics. In a third step, a blind lens-free microscopic analysis of 116 cerebrospinal fluid specimens, including six cases of microbiology-confirmed infectious meningitis, yielded a 100% sensitivity and a 79% specificity. Adapted lens-free microscopy is thus emerging as an operator-independent technique for the rapid numeration of leukocytes and erythrocytes in cerebrospinal fluid. In particular, this technique is well suited to the rapid diagnosis of meningitis at point-of-care laboratories.

1.5 Doting M, Weel J, Niesters H, Riezebos-Brilman A, Brandenburg A. The added value of hepatitis E diagnostics in determining causes of hepatitis in routine diagnostic settings in the Netherlands. Clin Microbiol Infect. 2017 Mar 7. pii: S1198-743X(17)30123-4. doi: 10.1016/j.cmi.2017.02.026. [Epub ahead of print]

OBJECTIVES: Hepatitis E virus (HEV) genotype 3 is endemic in Europe and an underdiagnosed and emerging (public) health issue. In recent years commercial enzyme immunoassays (EIAs) that detect antibodies to HEV more adequately, became available. We investigated the added value of this HEV serology in the diagnostic work flow to detect viral causes of recent hepatitis.

METHODS: During a two year period (May 2013 - May 2015), HEV serology was added to the hepatitis work flow, consisting of serological detection of hepatitis A-B-C virus (HAV, HBV, HCV), Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV). Samples positive for HEV IgM were also analysed using PCR to detect HEV RNA. If positive, HEV sequencing was performed for genotyping purposes. RESULTS: In 235 out of 2521 patients (9.3%), a viral cause for hepatitis was found. Recent HAV, HBV, HCV, EBV or CMV infections were serologically diagnosed in three, 34, 10, 69 and 42 patients respectively. Seventy-eight patients (3.1%) had a recent HEV infection. In 49 of them, sufficient HEV RNA was present for genotyping. All patients were infected with HEV genotype 3. CONCLUSIONS: In our region, a HEV infection is the most frequently diagnosed viral cause for a recent hepatitis. These results indicate that, in a country where HEV is endemic, serological HEV diagnostics should be added to the standard work-up for viral hepatitis.

1.6 Dyrdak R, Grabbe M, Hammas B, Ekwall J, Hansson KE, Luthander J, Naucler P, Reinius H, Rotzén-Östlund M, Albert J. Outbreak of enterovirus D68 of the new B3 lineage in Stockholm, Sweden, August to September 2016. Euro Surveill. 2016 Nov 17;21(46). pii: 30403. doi: 10.2807/1560-7917.ES.2016.21.46.30403.

We report an enterovirus D68 (EV-D68) outbreak in Stockholm Sweden in 2016. Between 22 August and 25 September EV-D68 was detected in 74/495 respiratory samples analysed at the Karolinska University Hospital. During the peak week, 30/91 (33%) samples were EV-D68 positive. Viral protein (VP)P4/VP2 sequencing revealed that cases were caused by B3 lineage strains. Forty-four (59%) EV-D68-positive patients were children aged ≤ 5 years. Ten patients had severe respiratory or neurological symptoms and one died.

1.7 Feigelman R, Kahlert CR, Baty F, Rassouli F, Kleiner RL, Kohler P, Brutsche MH, von Mering C. Sputum DNA sequencing in cystic fibrosis: non-invasive access to the lung microbiome and to pathogen details. Microbiome. 2017 Feb 10;5(1):20. doi: 10.1186/s40168-017-0234-1.

BACKGROUND: Cystic fibrosis (CF) is a life-threatening genetic disorder, characterized by chronic microbial lung infections due to abnormally viscous mucus secretions within airways. The clinical management of CF typically involves regular respiratory-tract cultures in order to identify pathogens and to guide treatment. However, culture-based methods can miss atypical or slow-growing microbes. Furthermore, the isolated microbes are often not classified at the strain level due to limited taxonomic resolution. RESULTS: Here, we show that untargeted metagenomic sequencing of sputum DNA can provide valuable information beyond the possibilities of culture-based diagnosis. We sequenced the sputum of six CF patients and eleven control samples (including healthy subjects and chronic obstructive pulmonary disease patients) without prior depletion of human DNA or cell size selection, thus obtaining the most unbiased and comprehensive characterization of CF respiratory tract microbes to date. We present detailed descriptions of the CF and healthy lung microbiome, reconstruct near complete pathogen genomes, and confirm that the CF lungs consistently exhibit reduced microbial diversity. Crucially, the obtained genomic sequences enabled a detailed identification of the exact pathogen strain types, when analyzed in conjunction with existing multi-locus sequence typing databases. We also detected putative pathogenicity islands and indicators of antibiotic resistance, in good agreement with independent clinical tests. CONCLUSIONS: Unbiased sputum metagenomics provides an in-depth profile of the lung pathogen microbiome, which is complementary to and more detailed than standard culture-based reporting. Furthermore, functional and taxonomic features of the dominant pathogens, including antibiotics resistances, can be deduced-supporting accurate and non-invasive clinical diagnosis.

1.8 Freidl GS, Sonder GJ, Bovée LP, Friesema IH, van Rijckevorsel GG, Ruijs WL, van Schie F, Siedenburg EC, Yang JY, Vennema H. Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017. Euro Surveill. 2017 Feb 23;22(8). pii: 30468. doi: 10.2807/1560-7917.ES.2017.22.8.30468.

Between July 2016 and February 2017, 48 male cases of hepatitis A were notified in the Netherlands. Of these, 17 identified as men who have sex with men (MSM). Ten of the 13 cases for whom sequencing information was available, were infected with a strain linked with the EuroPride that took place in Amsterdam in 2016. This strain is identical to a strain that has been causing a large outbreak among MSM in Taiwan.

1.9 Gong YN, Yang SL, Shih SR, Huang YC, Chang PY, Huang CG, Kao KC, Hu HC, Liu YC, Tsao KC. Molecular evolution and the global reemergence of enterovirus D68 by genome-wide analysis. Medicine (Baltimore). 2016 Aug;95(31):e4416. doi: 10.1097/MD.0000000000004416.

Human enterovirus D68 (EV-D68) was first reported in the United States in 1962; thereafter, a few cases were reported from 1970 to 2005, but 2 outbreaks occurred in the Philippines (2008) and the United States (2014). However, little is known regarding the molecular evolution of this globally reemerging virus due to a lack of whole-genome sequences and analyses. Here, all publically available sequences including 147 full and 1248 partial genomes from GenBank were collected and compared at the clade and subclade level; 11 whole genomes isolated in Taiwan (TW) in 2014 were also added to the database. Phylogenetic trees were constructed to identify a new subclade, B3, and represent clade circulations among strains. Nucleotide sequence identities of the VP1 gene were 94% to 95% based on a comparison of subclade B3 to B1 and B2 and 87% to 91% when comparing A, C, and D. The patterns of clade circulation need to be clarified to improve global monitoring of EV-D68, even though this virus showed lower diversity among clades compared with the common enterovirus EV-71. Notably, severe cases isolated from Taiwan and China in 2014 were found in subclade B3. One severe case from Taiwan occurred in a female patient with underlying angioimmunoblastic T-cell lymphoma, from whom a bronchoalveolar lavage specimen was obtained. Although host factors play a key role in disease severity, we cannot exclude the possibility that EV-D68 may trigger clinical symptoms or death. To further investigate the genetic diversity of EV-D68, we reported 34 amino acid (aa) polymorphisms identified by comparing subclade B3 to B1 and B2. Clade D strains had a 1-aa deletion and a 2-aa insertion in the VP1 gene, and 1 of our TW/2014 strains had a shorter deletion in the 5' untranslated region than a previously reported deletion. In summary, a new subclade, genetic indels, and polymorphisms in global strains were discovered elucidating evolutionary and epidemiological trends of EV-D68, and 11 genomes were added to the database. Virus variants may contribute to disease severity and clinical manifestations, and further studies are needed to investigate the associations between genetic diversity and clinical outcomes.

1.10 Hixon AM, Yu G, Leser JS, Yagi S, Clarke P, Chiu CY, Tyler KL. A mouse model of paralytic myelitis caused by enterovirus D68. PLoS Pathog. 2017 Feb 23;13(2):e1006199. doi: 10.1371/journal.ppat.1006199. eCollection 2017.

In 2014, the United States experienced an epidemic of acute flaccid myelitis (AFM) cases in children coincident with a nationwide outbreak of enterovirus D68 (EV-D68) respiratory disease. Up to half of the 2014 AFM patients had EV-D68 RNA detected by RT-PCR in their respiratory secretions, although EV-D68 was only detected in cerebrospinal fluid (CSF) from one 2014 AFM patient. Given previously described molecular and epidemiologic associations between EV-D68 and AFM, we sought to develop an animal model by screening seven EV-D68 strains for the ability to induce neurological disease in neonatal mice. We found that four EV-D68 strains from the 2014 outbreak (out of five tested) produced a paralytic disease in mice resembling human AFM. The remaining 2014 strain, as well as 1962 prototype EV-D68 strains Fermon and Rhyne, did not produce, or rarely produced, paralysis in mice. In-depth examination of the paralysis caused by a representative 2014 strain, MO/14-18947, revealed infectious virus, virion particles, and viral genome in the spinal cords of paralyzed mice. Paralysis was elicited in mice following intramuscular, intracerebral, intraperitoneal, and intranasal infection, in descending frequency, and was associated with infection and loss of motor neurons in the anterior horns of spinal cord segments corresponding to paralyzed limbs. Virus isolated from spinal cords of infected mice transmitted disease when injected into naïve mice, fulfilling Koch's postulates in this model. Finally, we found that EV-D68 immune sera, but not normal mouse sera, protected mice from development of paralysis and death when administered prior to viral challenge. These studies establish an experimental model to study EV-D68-induced myelitis and to better understand disease pathogenesis and develop potential therapies.

1.11 Kato K, Nagao M, Miyamoto K, Oka K, Takahashi M, Yamamoto M, Matsumura Y, Kaido T, Uemoto S, Ichiyama S. Longitudinal Analysis of the Intestinal Microbiota in Liver Transplantation.Transplant Direct. 2017 Mar 10;3(4):e144. doi: 10.1097/TXD.0000000000000661. eCollection 2017.

BACKGROUND: Increasing evidence suggests that the intestinal microbiota plays an important role in liver diseases. However, the dynamics of the intestinal microbiota during liver transplantation (LT) and its potential role in clinical course remain unknown. METHODS: We prospectively analyzed the intestinal microbiota of 38 patients who underwent LT in Kyoto University Hospital. We characterized the microbial compositions of fecal specimens from LT patients using a metagenomics approach by an Illumina MiSeq platform. We analyzed the diversity of microbiota sequentially from pretransplantation until 2 months after LT and also compared the microbiota during an episode of acute cellular rejection (ACR) and bloodstream infections (BSI) to the microbial composition of time-matched fecal specimens obtained from patients who did not experience ACR or BSI, respectively. RESULTS: Three hundred twenty fecal specimens were analyzed. Dynamic changes were observed in the microbial composition of LT recipients during the perioperative period. Over the course of LT, the mean diversity index decreased during the first 3 weeks after LT and gradually increased during our observation period. The loss of intestinal microbiota diversity was associated with high Child-Pugh scores, high model for end-stage liver disease scores, ACR, and BSI. At the family level, Bacteroides, Enterobacteriaceae, Streptococcaceae, and Bifidobacteriaceae were increased whereas Enterococcaceae, Lactobacillaceae, Clostridiaceae, Ruminococcaceae, and Peptostreptococcaceae were decreased in ACR patients. CONCLUSIONS: The microbiota of LT patients was associated with the severity of liver diseases and the presence of ACR and BSI. These results lay the groundwork for more comprehensive investigations of microbiota characteristics to identify diagnostic markers for transplant health and to guide intervention strategies to improve transplant outcomes.

1.12 Leruez-Ville M, Magny JF, Couderc S, Pichon C, Parodi M, Bussières L, Guilleminot T, Ghout I, Ville Y. Risks factors for congenital CMV infection following primary and non-primary maternal infection: a prospective neonatal screening study using PCR in saliva. Clin Infect Dis. 2017 Apr 17. doi: 10.1093/cid/cix337. [Epub ahead of print]

Background: The design of diagnostic and preventive strategies have been prevented by gaps in knowledge of the epidemiology of congenital CMV (cCMV) with the type of maternal infection as well as the lack of large-scale neonatal screening tools. Methods: 11,715 consecutive newborns were screened for cCMV by PCR in saliva. Prevalence, type of maternal infection, socio-demographic, obstetrical and serological data were analyzed. Results: Positive predictive value of CMV PCR in saliva was 59%, false positive results were associated with lower viral loads ($p<0.001$). Maternal seroprevalence was 61%, birth prevalence was 0.37%, resulting from primary and non-primary infections in 52% and 47.7% of cases respectively. The risk to deliver an infected baby after primary infection was increased in younger (OD=7.9), parous (OD=4.1) women born in high resources countries (OD=5.2) and from higher income groups ($p=0.019$). The only 2 risk factors to deliver an infected baby after non-primary infection were to be young (OD=4.6) and unemployed (OD=5.8). The risk to deliver an infected baby was 4-fold higher in women seronegative before their pregnancy ($p=0.021$). Conclusions: A positive CMV PCR in newborns' saliva should always be confirmed in a repeat-sample. Socio-demographic characteristics of women giving birth to an infected baby after primary and non-primary infection are different. Seronegative, parous women represent the highest risk population for cCMV in countries with low to intermediate seroprevalence. Urgent action is needed to stop the cCMV' epidemic, particularly in this population easily identifiable by maternal serology and amenable to prevention messages.

1.13 Loubet P, Lenzi N, Valette M, Foulongne V, Krivine A, Houhou N, Lagathu G, Rogez S, Alain S, Duval X, Galtier F, Postil D, Tattevin P, Vanhems P, Carrat F, Lina B, Launay O; FLUVAC Study Group. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. Clin Microbiol Infect. 2017 Apr;23(4):253-259. doi: 10.1016/j.cmi.2016.11.014. Epub 2016 Nov 27.

OBJECTIVES: The aim of this study was to analyse characteristics and outcome of respiratory syncytial virus (RSV) infection in adults hospitalized with influenza-like illness (ILI). METHODS: Patients hospitalized with ILI were included in this prospective, multicentre study carried out in six French hospitals during three consecutive influenza seasons (2012-2015). RSV and other respiratory viruses were detected by multiplex PCR in nasopharyngeal swabs. Risk factors for RSV infection were identified by backward stepwise logistic regression analysis. RESULTS: A total of 1452 patients hospitalized with ILI were included, of whom 59% (861/1452) were >65 years and 83% (1211/1452) had underlying chronic illnesses. RSV was detected in 4% (59/1452), and influenza virus in 39% (566/1452). Risk factors for RSV infection were cancer (adjusted OR 2.1, 95% CI 1.1-4.1, p 0.04), and immunosuppressive treatment (adjusted OR 2.0, 95% CI 1.1-3.8, p 0.03). Patients with RSV had a median length of stay of 9 days (6-25), and 57% of them (30/53) had complications, including pneumonia (23/53, 44%) and respiratory failure (15/53, 28%). Fifteen per cent (8/53) were admitted to an intensive care unit, and the in-hospital mortality rate was 8% (4/53). Pneumonia was more likely to occur in patients with RSV than in patients with RSV-negative ILI (44% (23/53) versus 26% (362/1393), p 0.006) or with influenza virus infection (44% versus 28% (157/560), p 0.02). CONCLUSION: RSV is an infrequent cause of ILI during periods of influenza virus circulation but can cause severe complications in hospitalized adults. Risk factors for RSV detection in adults hospitalized with ILI include cancer and immunosuppressive treatment. Specific immunization and antiviral therapy might benefit patients at risk.

1.14 McMurray CL, Hardy KJ, Calus ST, Loman NJ, Hawkey PM. Staphylococcal species heterogeneity in the nasal microbiome following antibiotic prophylaxis revealed by tuf gene deep sequencing. Microbiome. 2016 Dec 2;4(1):63.

BACKGROUND: Staphylococci are a major constituent of the nasal microbiome and a frequent cause of hospital-acquired infection. Antibiotic surgical prophylaxis is administered prior to surgery to reduce a patient's risk of postoperative infection. The impact of surgical prophylaxis on the nasal staphylococcal microbiome is largely unknown. Here, we report the species present in the nasal staphylococcal microbiome and the impact of surgical prophylaxis revealed by a novel culture independent technique. Daily nasal samples from 18 hospitalised patients, six of whom received no antibiotics and 12 of whom received antibiotic surgical prophylaxis (flucloxacillin and gentamicin or teicoplanin +/- gentamicin), were analysed by tuf gene fragment amplicon sequencing. RESULTS: On admission to hospital, the species diversity of the nasal staphylococcal microbiome varied from patient to patient ranging from 4 to 10 species. Administration of surgical prophylaxis did not substantially alter the diversity of the staphylococcal species present in the nose; however, surgical prophylaxis did impact on the relative abundance of the staphylococcal species present. The dominant staphylococcal species present in all patients on admission was Staphylococcus epidermidis, and antibiotic administration resulted in an increase in species relative abundance. Following surgical prophylaxis, a reduction in the abundance of Staphylococcus aureus was observed in carriers, but not a complete eradication. CONCLUSIONS: Utilising the tuf gene fragment has enabled a detailed study of the staphylococcal microbiome in the nose and highlights that although there is no change in the heterogeneity of species present, there are changes in abundance. The sensitivity of the methodology has revealed that the abundance of S. aureus is reduced to a low level by surgical prophylaxis and therefore reduces the potential risk of infection following surgery but also highlights that S. aureus does persist.

1.15 Moritz ED, Winton CS, Tonnetti L, Townsend RL, Berardi VP, Hewins ME, Weeks KE, Dodd RY, Stramer SL. Screening for Babesia microti in the U.S. Blood Supply. N Engl J Med. 2016 Dec 8;375(23):2236-2245.

Background Babesia microti, a tickborne intraerythrocytic parasite that can be transmitted by means of blood transfusion, is responsible for the majority of cases of transfusion-transmitted babesiosis in the United States. However, no licensed test exists for screening for B. microti in donated blood. We assessed data from a large-scale, investigational product-release screening and donor follow-up program. Methods From June 2012 through September 2014, we performed arrayed fluorescence immunoassays (AFIAs) for B. microti antibodies and real-time polymerase-chain-reaction (PCR) assays for B. microti DNA on blood-donation samples obtained in Connecticut, Massachusetts, Minnesota, and Wisconsin. We determined parasite loads with the use of quantitative PCR testing and assessed infectivity by means of the inoculation of hamsters and the subsequent examination for parasitemia. Donors with test-reactive samples were followed. Using data on cases of transfusion-transmitted babesiosis, we compared the proportions of screened versus unscreened donations that were infectious. Results Of 89,153 blood-donation samples tested, 335 (0.38%) were confirmed to be positive, of which 67 (20%) were PCR-positive; 9 samples were antibody-negative (i.e., 1 antibody-negative sample per 9906 screened samples), representing 13% of all PCR-positive samples. PCR-positive samples were identified all through the year; antibody-negative infections occurred from June through September. Approximately one third of the red-cell samples from PCR-positive or high-titer AFIA-positive donations infected hamsters. Follow-up showed DNA clearance in 86% of the donors but antibody seroreversion in 8% after 1 year. In Connecticut and Massachusetts, no reported cases of transfusion-transmitted babesiosis were associated with screened donations (i.e., 0 cases per 75,331 screened donations), as compared with 14 cases per 253,031 unscreened donations (i.e., 1 case per 18,074 unscreened donations) (odds ratio, 8.6; 95% confidence interval, 0.51 to 144; P=0.05). Overall, 29 cases of transfusion-transmitted babesiosis were linked to blood from infected donors, including blood obtained from 10 donors whose samples tested positive on the PCR assay 2 to 7 months after the implicated donation. Conclusions Blood-donation screening for antibodies to and DNA from B. microti was associated with a decrease in the risk of transfusion-transmitted babesiosis. (Funded by the American Red Cross and Imugen; ClinicalTrials.gov number, NCT01528449 .).

1.16 Papp JR, Abrams AJ, Nash E, Katz AR, Kirkcaldy RD, O'Connor NP, O'Brien PS, Harauchi DH, Maningas EV, Soge OO, Kersh EN, Komeya A, Tomas JE, Wasserman GM, Kunimoto GY, Trees DL, Whelen AC. Azithromycin Resistance and Decreased Ceftriaxone Susceptibility in Neisseria gonorrhoeae, Hawaii, USA. Emerg Infect Dis. 2017 May;23(5):830-832. doi: 10.3201/eid2305.170088.

During 2016, eight Neisseria gonorrhoeae isolates from 7 patients in Hawaii were resistant to azithromycin; 5 had decreased in vitro susceptibility to ceftriaxone. Genomic analysis demonstrated a distinct phylogenetic clade when compared with local contemporary strains. Continued evolution and widespread transmission of these strains might challenge the effectiveness of current therapeutic options.

1.17 Salzberg SL, Breitwieser FP, Kumar A, Hao H, Burger P, Rodriguez FJ, Lim M, Quiñones-Hinojosa A, Gallia GL, Tornheim JA, Melia MT, Sears CL, Pardo CA. Next-generation sequencing in neuropathologic diagnosis of infections of the nervous system. Neurol Neuroimmunol Neuroinflamm. 2016 Jun 13;3(4):e251. doi: 10.1212/NXI.0000000000000251. eCollection 2016.

OBJECTIVE: To determine the feasibility of next-generation sequencing (NGS) microbiome approaches in the diagnosis of infectious disorders in brain or spinal cord biopsies in patients with suspected CNS infections. METHODS: In a prospective pilot study, we applied NGS in combination with a new computational analysis pipeline to detect the presence of pathogenic microbes in brain or spinal cord biopsies from 10 patients with neurologic problems indicating possible infection but for whom conventional clinical and microbiology studies yielded negative or inconclusive results. RESULTS: Direct DNA and RNA sequencing of brain tissue biopsies generated 8.3 million to 29.1

million sequence reads per sample, which successfully identified with high confidence the infectious agent in 3 patients for whom validation techniques confirmed the pathogens identified by NGS. Although NGS was unable to identify with precision infectious agents in the remaining cases, it contributed to the understanding of neuropathologic processes in 5 others, demonstrating the power of large-scale unbiased sequencing as a novel diagnostic tool. Clinical outcomes were consistent with the findings yielded by NGS on the presence or absence of an infectious pathogenic process in 8 of 10 cases, and were noncontributory in the remaining 2. CONCLUSIONS: NGS-guided metagenomic studies of brain, spinal cord, or meningeal biopsies offer the possibility for dramatic improvements in our ability to detect (or rule out) a wide range of CNS pathogens, with potential benefits in speed, sensitivity, and cost. NGS-based microbiome approaches present a major new opportunity to investigate the potential role of infectious pathogens in the pathogenesis of neuroinflammatory disorders.

1.18 Schiemann M, Puchhammer-Stöckl E, Eskandary F, Kohlbeck P, Rasoul-Rockenschaub S, Heilos A, Kozakowski N, Görzer I, Kikić Ž, Herkner H, Böhmig GA, Bond G. Torque Teno Virus Load-Inverse Association With Antibody-Mediated Rejection After Kidney Transplantation. Transplantation. 2017 Feb;101(2):360-367. doi: 10.1097/TP.0000000000001455.

BACKGROUND: Antibody-mediated rejection (AMR) represents one of the cardinal causes of late allograft loss after kidney transplantation, and there is great need for noninvasive tools improving early diagnosis of this rejection type. One promising strategy might be the quantification of peripheral blood DNA levels of the highly prevalent and apathogenic Torque Teno virus (TTV), which might mirror the overall level of immunosuppression and thus help determine the risk of alloimmune response. METHODS: To assess the association between TTV load in the peripheral blood and AMR, 715 kidney transplant recipients (median, 6.3 years posttransplantation) were subjected to a systematical cross-sectional AMR screening and, in parallel, TTV quantification. RESULTS: Eighty-six of these recipients had donor-specific antibodies and underwent protocol biopsy, AMR-positive patients (n = 46) showed only 25% of the TTV levels measured in patients without AMR (P = 0.003). In a generalized linear model, higher TTV levels were associated with a decreased risk for AMR after adjustment for potential confounders (risk ratio 0.94 per TTV log level; 95% confidence interval 0.90-0.99; P = 0.02). CONCLUSIONS: Future studies will have to clarify whether longitudinal assessment of TTV load might predict AMR risk and help guide the type and intensity of immunosuppression to prevent antibody-mediated graft injury.

1.19 Sheppard AE, Stoesser N, Wilson DJ, Sebra R, Kasarskis A, Anson LW, Giess A, Pankhurst LJ, Vaughan A, Grim CJ, Cox HL, Yeh AJ; Modernising Medical Microbiology (MMM) Informatics Group, Sifri CD, Walker AS, Peto TE, Crook DW, Mathers AJ. Nested Russian Doll-Like Genetic Mobility Drives Rapid Dissemination of the Carbapenem Resistance Gene blaKPC. Antimicrob Agents Chemother. 2016 May 23;60(6):3767-78. doi: 10.1128/AAC.00464-16. Print 2016 Jun.

The recent widespread emergence of carbapenem resistance in Enterobacteriaceae is a major public health concern, as carbapenems are a therapy of last resort against this family of common bacterial pathogens. Resistance genes can mobilize via various mechanisms, including conjugation and transposition; however, the importance of this mobility in short-term evolution, such as within nosocomial outbreaks, is unknown. Using a combination of short- and long-read whole-genome sequencing of 281 blaKPC-positive Enterobacteriaceae isolates from a single hospital over 5 years, we demonstrate rapid dissemination of this carbapenem resistance gene to multiple species, strains, and plasmids. Mobility of blaKPC occurs at multiple nested genetic levels, with transmission of blaKPC strains between individuals, frequent transfer of blaKPC plasmids between strains/species, and frequent transposition of blaKPC transposon Tn4401 between plasmids. We also identify a common insertion site for Tn4401 within various Tn2-like elements, suggesting that homologous recombination between Tn2-like elements has enhanced the spread of Tn4401 between different plasmid vectors. Furthermore, while short-read sequencing has known limitations for plasmid assembly, various studies have attempted to overcome this by the use of reference-

based methods. We also demonstrate that, as a consequence of the genetic mobility observed in this study, plasmid structures can be extremely dynamic, and therefore these reference-based methods, as well as traditional partial typing methods, can produce very misleading conclusions. Overall, our findings demonstrate that nonclonal resistance gene dissemination can be extremely rapid, presenting significant challenges for public health surveillance and achieving effective control of antibiotic resistance.

1.20 Wind CM, de Vries E, Schim van der Loeff MF, van Rooijen MS, van Dam AP, Demczuk WH, Martin I, de Vries HJ. Decreased azithromycin susceptibility of Neisseria gonorrhoeae isolates in patients recently treated with azithromycin. Clin Infect Dis. 2017 Mar 24. doi: 10.1093/clinid/cix249. [Epub ahead of print]

Background: Increasing azithromycin usage and resistance in Neisseria gonorrhoeae threatens current dual treatment. Because antimicrobial exposure influences resistance, we analysed the association between azithromycin exposure and decreased susceptibility of N. gonorrhoeae. Methods: We included N. gonorrhoeae isolates of patients visiting the Amsterdam STI Clinic between 1999 and 2013 (t0), with another visit in the previous 60 days (t-1). Exposure was defined as the prescription of azithromycin at t-1. We included one isolate per patient. Using multivariable linear regression we assessed the association between exposure and azithromycin minimum inhibitory concentration (MIC). Whole genome sequencing (WGS) was performed to produce a phylogeny, identify multilocus sequence types (MLST), multiantigen sequence types (NG-MAST), and molecular markers of azithromycin resistance. Results: We included 323 isolates: 212 were unexposed to azithromycin, 14 were exposed ≤30 days, and 97 were exposed between 31-60 days before isolation. Mean azithromycin MIC was 0.28 mg/L (range: <0.016-24 mg/L). Linear regression adjusted for age, ethnicity, infection site, and calendar year showed a significant association between azithromycin exposure ≤30 days and MIC (β: 1.00, 95%-CI: 0.44-1.56, p=0.002). WGS was performed on 31 isolates: 14 unexposed, 14 exposed to azithromycin ≤30 days before isolation, and three t-1 isolates. Exposure to azithromycin was significantly associated with A39T or G45D mtrR mutations (p=0.046), but not with MLST or NG-MAST molecular types. Conclusions: The results suggest that frequent azithromycin use in populations at high risk of contracting N. gonorrhoeae induces an increase in MIC, and may result in resistance.

1.21 Zhao G, Wu G, Lim ES, Droit L, Krishnamurthy S, Barouch DH, Virgin HW, Wang D. VirusSeeker, a computational pipeline for virus discovery and virome composition analysis. Virology. 2017 Mar;503:21-30. doi: 10.1016/j.virol.2017.01.005. Epub 2017 Jan 18.

The advent of Next Generation Sequencing (NGS) has vastly increased our ability to discover novel viruses and to systematically define the spectrum of viruses present in a given specimen. Such studies have led to the discovery of novel viral pathogens as well as broader associations of the virome with diverse diseases including inflammatory bowel disease, severe acute malnutrition and HIV/AIDS. Critical to the success of these efforts are robust bioinformatic pipelines for rapid classification of microbial sequences. Existing computational tools are typically focused on either eukaryotic virus discovery or virome composition analysis but not both. Here we present VirusSeeker, a BLAST-based NGS data analysis pipeline designed for both purposes. VirusSeeker has been successfully applied in several previously published virome studies. Here we demonstrate the functionality of VirusSeeker in both novel virus discovery and virome composition analysis.

2.1 Ellington MJ, Ekelund O, Aarestrup FM, Canton R, Doumith M, Giske C, Grundman H, Hasman H, Holden MT, Hopkins KL, Iredell J, Kahlmeter G, Köser CU, MacGowan A, Mevius D, Mulvey M, Naas T, Peto T, Rolain JM, Samuelsen Ø, Woodford N. The role of whole genome sequencing in antimicrobial susceptibility testing of bacteria: report from the EUCAST Subcommittee. Clin Microbiol Infect. 2017 Jan;23(1):2-22. doi: 10.1016/j.cmi.2016.11.012. Epub 2016 Nov 23.

Whole genome sequencing (WGS) offers the potential to predict antimicrobial susceptibility from a single assay. The European Committee on Antimicrobial Susceptibility Testing established a subcommittee to review the current development status of WGS for bacterial antimicrobial susceptibility testing (AST). The published evidence for using WGS as a tool to infer antimicrobial susceptibility accurately is currently either poor or non-existent and the evidence / knowledge base requires significant expansion. The primary comparators for assessing genotypic-phenotypic concordance from WGS data should be changed to epidemiological cut-off values in order to improve differentiation of wild-type from non-wild-type isolates (harbouring an acquired resistance). Clinical breakpoints should be a secondary comparator. This assessment will reveal whether genetic predictions could also be used to guide clinical decision making. Internationally agreed principles and quality control (QC) metrics will facilitate early harmonization of analytical approaches and interpretive criteria for WGS-based predictive AST. Only data sets that pass agreed QC metrics should be used in AST predictions. Minimum performance standards should exist and comparative accuracies across different WGS laboratories and processes should be measured. To facilitate comparisons, a single public database of all known resistance loci should be established, regularly updated and strictly curated using minimum standards for the inclusion of resistance loci. For most bacterial species the major limitations to widespread adoption for WGS-based AST in clinical laboratories remain the current high-cost and limited speed of inferring antimicrobial susceptibility from WGS data as well as the dependency on previous culture because analysis directly on specimens remains challenging. For most bacterial species there is currently insufficient evidence to support the use of WGS-inferred AST to guide clinical decision making. WGS-AST should be a funding priority if it is to become a rival to phenotypic AST. This report will be updated as the available evidence increases.

2.2 Ribeiro-Gonçalves B, Francisco AP, Vaz C, Ramirez M, Carriço JA. PHYLOViZ Online: web-based tool for visualization, phylogenetic inference, analysis and sharing of minimum spanning trees. Nucleic Acids Res. 2016 Jul 8;44(W1):W246-51. doi: 10.1093/nar/gkw359. Epub 2016 Apr 29.

High-throughput sequencing methods generated allele and single nucleotide polymorphism information for thousands of bacterial strains that are publicly available in online repositories and created the possibility of generating similar information for hundreds to thousands of strains more in a single study. Minimum spanning tree analysis of allelic data offers a scalable and reproducible methodological alternative to traditional phylogenetic inference approaches, useful in epidemiological investigations and population studies of bacterial pathogens. PHYLOViZ Online was developed to allow users to do these analyses without software installation and to enable easy accessing and sharing of data and analyses results from any Internet enabled computer. PHYLOViZ Online also offers a RESTful API for programmatic access to data and algorithms, allowing it to be seamlessly integrated into any third party web service or software. PHYLOViZ Online is freely available at https://online.phyloviz.net.

2.3 Harrison EM, Ludden C, Brodrick HJ, Blane B, Brennan G, Morris D, Coll F, Reuter S, Brown NM, Holmes MA, O'Connell B, Parkhill J, Török ME, Cormican M, Peacock SJ. Transmission of methicillin-resistant Staphylococcus aureus in long-term care facilities and their related healthcare networks. Genome Med. 2016 Oct 3;8(1):102.

BACKGROUND: Long-term care facilities (LTCF) are potential reservoirs for methicillin-resistant Staphylococcus aureus (MRSA), control of which may reduce MRSA transmission and infection elsewhere in the healthcare system. Whole-genome sequencing (WGS) has been used successfully to understand MRSA epidemiology and transmission in hospitals and has the potential to identify transmission between these and LTCF. METHODS: Two prospective observational studies of MRSA carriage were conducted in LTCF in England and Ireland. MRSA isolates were whole-genome sequenced and analyzed using established methods. Genomic data were available for MRSA isolated in the local healthcare systems (isolates submitted by hospitals and general practitioners). RESULTS: We sequenced a total of 181 MRSA isolates from the two study sites. The majority of MRSA were multilocus sequence type (ST)22. WGS identified one likely transmission event between residents in the English LTCF and three putative transmission events in the Irish LTCF. WGS also identified closely related isolates present in colonized Irish residents and their immediate environment. Based on phylogenetic reconstruction, closely related MRSA clades were identified between the LTCF and their healthcare referral network, together with putative MRSA acquisition by LTCF residents during hospital admission.

CONCLUSIONS: These data confirm that MRSA is transmitted between residents of LTCF and is both acquired and transmitted to others in referral hospitals and beyond. Our data present compelling evidence for the importance of environmental contamination in MRSA transmission, reinforcing the importance of environmental cleaning. The use of WGS in this study highlights the need to consider infection control in hospitals and community healthcare facilities as a continuum

2.4 Lees JA, Kremer PH, Manso AS, Croucher NJ, Ferwerda B, Serón MV, Oggioni MR, Parkhill J, Brouwer MC, van der Ende A, van de Beek D, Bentley SD. Large scale genomic analysis shows no evidence for pathogen adaptation between the blood and cerebrospinal fluid niches during bacterial meningitis. Microb Genom. 2017 Jan 31;3(1):e000103. doi: 10.1099/mgen.0.000103. eCollection 2017.

Recent studies have provided evidence for rapid pathogen genome diversification, some of which could potentially affect the course of disease. We have previously described such variation seen between isolates infecting the blood and cerebrospinal fluid (CSF) of a single patient during a case of bacterial meningitis. Here, we performed whole-genome sequencing of paired isolates from the blood and CSF of 869 meningitis patients to determine whether such variation frequently occurs between these two niches in cases of bacterial meningitis. Using a combination of reference-free variant calling approaches, we show that no genetic adaptation occurs in either invaded niche during bacterial meningitis for two major pathogen species, Streptococcus pneumoniae and Neisseria meningitidis. This study therefore shows that the bacteria capable of causing meningitis are already able to do this upon entering the blood, and no further sequence change is necessary to cross the blood-brain barrier. Our findings place the focus back on bacterial evolution between nasopharyngeal carriage and invasion, or diversity of the host, as likely mechanisms for determining invasiveness.

2.5 Lesho E, Clifford R, Onmus-Leone F, Appalla L, Snesrud E, Kwak Y, Ong A, Maybank R, Waterman P, Rohrbeck P, Julius M, Roth A, Martinez J, Nielsen L, Steele E[4], McGann P, Hinkle M. The Challenges of Implementing Next Generation Sequencing Across a Large Healthcare System, and the Molecular Epidemiology and Antibiotic Susceptibilities of Carbapenemase-Producing Bacteria in the Healthcare System of the U.S. Department of Defense. PLoS One. 2016 May 19;11(5):e0155770. doi: 10.1371/journal.pone.0155770. eCollection 2016.

OBJECTIVE: We sought to: 1) provide an overview of the genomic epidemiology of an extensive collection of carbapenemase-producing bacteria (CPB) collected in the U.S. Department of Defense health system; 2) increase awareness of the public availability of the sequences, isolates, and customized antimicrobial resistance database of that system; and 3) illustrate challenges and offer mitigations for implementing next generation sequencing (NGS) across large health systems. DESIGN: Prospective surveillance and system-wide implementation of NGS. SETTING: 288-hospital healthcare network. METHODS: All phenotypically carbapenem resistant bacteria underwent CarbaNP® testing and PCR, followed by NGS. Commercial (Newbler and Geneious), on-line (ResFinder), and open-source software (Btrim, FLASh, Bowtie2, an Samtools) were used for assembly, SNP detection and clustering. Laboratory capacity, throughput, and response time were assessed. RESULTS: From 2009 through 2015, 27,000 multidrug-resistant Gram-negative isolates were submitted. 225 contained carbapenemase-encoding genes (most commonly blaKPC, blaNDM, and blaOXA23). These were found in 15 species from 146 inpatients in 19 facilities. Genetically related CPB were found in more than one hospital. Other clusters or outbreaks were not clonal and involved genetically related plasmids, while some involved several unrelated plasmids. Relatedness depended on the clustering algorithm used. Transmission patterns of plasmids and other mobile genetic elements could not be determined without ultra-long read, single-molecule real-time sequencing. 80% of carbapenem-resistant phenotypes retained susceptibility to aminoglycosides, and 70% retained susceptibility to fluoroquinolones. However, among the CPB-confirmed genotypes, fewer than 25% retained susceptibility to aminoglycosides or fluoroquinolones. CONCLUSION: Although NGS is increasingly acclaimed to revolutionize clinical practice, resource-constrained environments, large or geographically dispersed healthcare networks, and military or government-funded public health laboratories are likely to encounter constraints and challenges as they implement NGS across their health systems. These include lack of standardized definitions and quality control metrics, limitations of short-read sequencing, insufficient bandwidth, and the current limited availability of very expensive and scarcely available sequencing platforms. Possible solutions and mitigations are also proposed

2.6 Meinel DM, Kuehl R, Zbinden R, Boskova V, Garzoni C, Fadini D, Dolina M, Blümel B, Weibel T, Tschudin-Sutter S, Widmer AF, Bielicki JA, Dierig A, Heininger U, Konrad R, Berger A, Hinic V, Goldenberger D, Blaich A, Stadler T, Battegay M, Sing A, Egli A Outbreak investigation for toxigenic Corynebacterium diphtheriae wound infections in refugees from Northeast Africa and Syria in Switzerland and Germany by whole genome sequencing. Clin Microbiol Infect. 2016 Dec;22(12):1003.e1-1003.e8. doi: 10.1016/j.cmi.2016.08.010. Epub 2016 Aug 30.

Toxigenic Corynebacterium diphtheriae is an important and potentially fatal threat to patients and public health. During the current dramatic influx of refugees into Europe, our objective was to use whole genome sequencing for the characterization of a suspected outbreak of C. diphtheriae wound infections among refugees. After conventional culture, we identified C. diphtheriae using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) and investigated toxigenicity by PCR. Whole genome sequencing was performed on a MiSeq Illumina with >70×coverage, 2×250 bp read length, and mapping against a reference genome. Twenty cases of cutaneous C. diphtheriae in refugees from East African countries and Syria identified between April and August 2015 were included. Patients presented with

wound infections shortly after arrival in Switzerland and Germany. Toxin production was detected in 9/20 (45%) isolates. Whole genome sequencing-based typing revealed relatedness between isolates using neighbour-joining algorithms. We detected three separate clusters among epidemiologically related refugees. Although the isolates within a cluster showed strong relatedness, isolates differed by >50 nucleotide polymorphisms. Toxigenic C. diphtheriae associated wound infections are currently observed more frequently in Europe, due to refugees travelling under poor hygienic conditions. Close genetic relatedness of C. diphtheriae isolates from 20 refugees with wound infections indicates likely transmission between patients. However, the diversity within each cluster and phylogenetic time-tree analysis suggest that transmissions happened several months ago, most likely outside Europe. Whole genome sequencing offers the potential to describe outbreaks at very high resolution and is a helpful tool in infection tracking and identification of transmission routes.

2.7 Mellmann A, Bletz S, Böking T, Kipp F, Becker K, Schultes A, Prior K, Harmsen D. Real-Time Genome Sequencing of Resistant Bacteria Provides Precision Infection Control in an Institutional Setting. J Clin Microbiol. 2016 Dec;54(12):2874-2881. Epub 2016 Aug 24.

The increasing prevalence of multidrug-resistant (MDR) bacteria is a serious global challenge. Here, we studied prospectively whether bacterial whole-genome sequencing (WGS) for real-time MDR surveillance is technical feasible, returns actionable results, and is cost-beneficial. WGS was applied to all MDR isolates of four species (methicillin-resistant Staphylococcus aureus [MRSA], vancomycin-resistant Enterococcus faecium, MDR Escherichia coli, and MDR Pseudomonas aeruginosa) at the University Hospital Muenster, Muenster, Germany, a tertiary care hospital with 1,450 beds, during two 6-month intervals. Turnaround times (TAT) were measured, and total costs for sequencing per isolate were calculated. After cancelling prior policies of preemptive isolation of patients harboring certain Gram-negative MDR bacteria in risk areas, the second interval was conducted. During interval I, 645 bacterial isolates were sequenced. From culture, TATs ranged from 4.4 to 5.3 days, and costs were €202.49 per isolate. During interval II, 550 bacterial isolates were sequenced. Hospital-wide transmission rates of the two most common species (MRSA and MDR E. coli) were low during interval I (5.8% and 2.3%, respectively) and interval II (4.3% and 5.0%, respectively). Cancellation of isolation of patients infected with non-pan-resistant MDR E. coli in risk wards did not increase transmission. Comparing sequencing costs with avoided costs mostly due to fewer blocked beds during interval II, we saved in excess of €200,000. Real-time microbial WGS in our institution was feasible, produced precise actionable results, helped us to monitor transmission rates that remained low following a modification in isolation procedures, and ultimately saved costs

2.8 Mellmann A, Andersen PS, Bletz S, Friedrich AW, Kohl TA, Lilje B, Niemann S, Prior K, Rossen JW, Harmsen D. High Interlaboratory Reproducibility and Accuracy of Next-Generation-Sequencing-Based Bacterial Genotyping in a Ring Trial. J Clin Microbiol. 2017 Mar;55(3):908-913. doi: 10.1128/JCM.02242-16. Epub 2017 Jan 4.

Today, next-generation whole-genome sequencing (WGS) is increasingly used to determine the genetic relationships of bacteria on a nearly whole-genome level for infection control purposes and molecular surveillance. Here, we conducted a multicenter ring trial comprising five laboratories to determine the reproducibility and accuracy of WGS-based typing. The participating laboratories sequenced 20 blind-coded Staphylococcus aureus DNA samples using 250-bp paired-end chemistry for library preparation in a single sequencing run on an Illumina MiSeq sequencer. The run acceptance criteria were sequencing outputs >5.6 Gb and Q30 read quality scores of >75%. Subsequently, spa typing, multilocus sequence typing (MLST), ribosomal MLST, and core genome MLST (cgMLST) were performed by the participants. Moreover, discrepancies in cgMLST target sequences in comparisons with the included and also published sequence of the quality control strain ATCC 25923 were resolved using Sanger sequencing. All

five laboratories fulfilled the run acceptance criteria in a single sequencing run without any repetition. Of the 400 total possible typing results, 394 of the reported spa types, sequence types (STs), ribosomal STs (rSTs), and cgMLST cluster types were correct and identical among all laboratories; only six typing results were missing. An analysis of cgMLST allelic profiles corroborated this high reproducibility; only 3 of 183,927 (0.0016%) cgMLST allele calls were wrong. Sanger sequencing confirmed all 12 discrepancies of the ring trial results in comparison with the published sequence of ATCC 25923. In summary, this ring trial demonstrated the high reproducibility and accuracy of current next-generation sequencing-based bacterial typing for molecular surveillance when done with nearly completely locked-down methods.

2.9 Runcharoen C, Moradigaravand D, Blane B, Paksanont S, Thammachote J, Anun S, Parkhill J, Chantratita N, Peacock SJ. Whole genome sequencing reveals high-resolution epidemiological links between clinical and environmental Klebsiella pneumoniae. Genome Med. 2017 Jan 24;9(1):6. doi: 10.1186/s13073-017-0397-1.

BACKGROUND: Klebsiella pneumoniae is a gram-negative bacterial species capable of occupying a broad range of environmental and clinical habitats. Known as an opportunistic pathogen, it has recently become a major causative agent of clinical infections worldwide. Despite growing knowledge about the highly diverse population of K. pneumoniae, the evolution and clinical significance of environmental K. pneumoniae, as well as the relationship between clinical and environmental K. pneumoniae, are poorly defined. METHODS: We isolated and sequenced K. pneumoniae from in-patients in a single hospital in Thailand, as well as hospital sewage, and surrounding canals and farms within a 20-km radius. RESULTS: Phylogenetic analysis of 77 K. pneumoniae (48 clinical and 29 non-clinical isolates) demonstrated that the two groups were intermixed throughout the tree and in some cases resided in the same clade, suggesting recent divergence from a common ancestor. Phylogenetic comparison of the 77 Thai genomes with 286 K. pneumoniae from a global collection showed that Thai isolates were closely related to the clinical sub-population of the global collection, indicating that Thai clinical isolates belonged to globally circulating lineages. Dating of four Thai K. pneumoniae clades indicated that they emerged between 50 and 150 years ago. Despite their phylogenetic relatedness, virulence factors and β-lactamase resistance genes were more numerous in clinical than in environmental isolates. Our results indicate that clinical and environmental K. pneumoniae are closely related, but that hospitals may select for isolates with a more resistant and virulent genotype. CONCLUSIONS: These findings highlight the clinical relevance of environmental K. pneumoniae isolates.

2.10 Thomsen MC, Ahrenfeldt J, Cisneros JL, Jurtz V, Larsen MV, Hasman H, Aarestrup FM, Lund O. A Bacterial Analysis Platform: An Integrated System for Analysing Bacterial Whole Genome Sequencing Data for Clinical Diagnostics and Surveillance. PLoS One. 2016 Jun 21;11(6):e0157718. doi: 10.1371/journal.pone.0157718. eCollection 2016.

Recent advances in whole genome sequencing have made the technology available for routine use in microbiological laboratories. However, a major obstacle for using this technology is the availability of simple and automatic bioinformatics tools. Based on previously published and already available web-based tools we developed a single pipeline for batch uploading of whole genome sequencing data from multiple bacterial isolates. The pipeline will automatically identify the bacterial species and, if applicable, assemble the genome, identify the multilocus sequence type, plasmids, virulence genes and antimicrobial resistance genes. A short printable report for each sample will be provided and an Excel spreadsheet containing all the metadata and a summary of the results for all submitted samples can be downloaded. The pipeline was benchmarked using datasets previously used to test the individual services. The reported results enable a rapid overview of the major results, and comparing that to the previously found results showed that the platform is reliable and able to correctly predict the species and find most of the

expected genes automatically. In conclusion, a combined bioinformatics platform was developed and made publicly available, providing easy-to-use automated analysis of bacterial whole genome sequencing data. The platform may be of immediate relevance as a guide for investigators using whole genome sequencing for clinical diagnostics and surveillance. The platform is freely available at: https://cge.cbs.dtu.dk/services/CGEpipeline-1.1 and it is the intention that it will continue to be expanded with new features as these become available.

2.11 Eyre DW, De Silva D, Cole K, Peters J, Cole MJ, Grad YH, Demczuk W, Martin I, Mulvey MR, Crook DW, Walker AS, Peto TE, Paul J. WGS to predict antibiotic MICs for Neisseria gonorrhoeae. J Antimicrob Chemother. 2017 Mar 10. doi: 10.1093/jac/dkx067. [Epub ahead of print]

Background: Tracking the spread of antimicrobial-resistant Neisseria gonorrhoeae is a major priority for national surveillance programmes. Objectives: We investigate whether WGS and simultaneous analysis of multiple resistance determinants can be used to predict antimicrobial susceptibilities to the level of MICs in N. gonorrhoeae. Methods: WGS was used to identify previously reported potential resistance determinants in 681 N. gonorrhoeae isolates, from England, the USA and Canada, with phenotypes for cefixime, penicillin, azithromycin, ciprofloxacin and tetracycline determined as part of national surveillance programmes. Multivariate linear regression models were used to identify genetic predictors of MIC. Model performance was assessed using leave-one-out cross-validation. Results: Overall 1785/3380 (53%) MIC values were predicted to the nearest doubling dilution and 3147 (93%) within ±1 doubling dilution and 3314 (98%) within ±2 doubling dilutions. MIC prediction performance was similar across the five antimicrobials tested. Prediction models included the majority of previously reported resistance determinants. Applying EUCAST breakpoints to MIC predictions, the overall very major error (VME; phenotypically resistant, WGS-prediction susceptible) rate was 21/1577 (1.3%, 95% CI 0.8%-2.0%) and the major error (ME; phenotypically susceptible, WGS-prediction resistant) rate was 20/1186 (1.7%, 1.0%-2.6%). VME rates met regulatory thresholds for all antimicrobials except cefixime and ME rates for all antimicrobials except tetracycline. Country of testing was a strongly significant predictor of MIC for all five antimicrobials. Conclusions: We demonstrate a WGS-based MIC prediction approach that allows reliable MIC prediction for five gonorrhoea antimicrobials. Our approach should allow reasonably precise prediction of MICs for a range of bacterial species.

2.12 Fiebig L, Kohl TA, Popovici O, Mühlenfeld M, Indra A, Homorodean D, Chiotan D, Richter E, Rüsch-Gerdes S, Schmidgruber B, Beckert P, Hauer B, Niemann S, Allerberger F, Haas W. A joint cross-border investigation of a cluster of multidrug-resistant tuberculosis in Austria, Romania and Germany in 2014 using classic, genotyping and whole genome sequencing methods: lessons learnt. Euro Surveill. 2017 Jan 12;22(2). pii: 30439. doi: 10.2807/1560-7917.ES.2017.22.2.30439.

Molecular surveillance of multidrug-resistant tuberculosis (MDR-TB) using 24-loci MIRU-VNTR in the European Union suggests the occurrence of international transmission. In early 2014, Austria detected a molecular MDR-TB cluster of five isolates. Links to Romania and Germany prompted the three countries to investigate possible cross-border MDR-TB transmission jointly. We searched genotyping databases, genotyped additional isolates from Romania, used whole genome sequencing (WGS) to infer putative transmission links, and investigated pairwise epidemiological links and patient mobility. Ten isolates from 10 patients shared the same 24-loci MIRU-VNTR pattern. Within this cluster, WGS defined two subgroups of four patients each. The first comprised an MDR-TB patient from Romania who had sought medical care in Austria and two patients from Austria. The second comprised patients, two of them epidemiologically linked, who lived in three different countries but had the same city of provenance in Romania. Our findings strongly suggested that the two cases in Austrian citizens resulted from a newly introduced MDR-TB strain, followed by domestic transmission. For the other cases, transmission probably occurred in the same city of provenance. To prevent further MDR-TB transmission, we need to ensure universal access to early and adequate therapy and collaborate closely in tuberculosis care beyond administrative borders.

2.13 Votintseva AA, Bradley P, Pankhurst L, Del Ojo Elias C, Loose M, Nilgiriwala K, Chatterjee A, Smith EG, Sanderson N, Walker TM, Morgan MR, Wyllie DH, Walker AS, Peto TE, Crook DW, Iqbal Z. Same-day diagnostic and surveillance data for tuberculosis via whole genome sequencing of direct respiratory samples. J Clin Microbiol. 2017 Mar 8. pii: JCM.02483-16. doi: 10.1128/JCM.02483-16. [Epub ahead of print]

Routine full characterization of Mycobacterium tuberculosis (TB) is culture-based, taking many weeks. Whole-genome sequencing (WGS) can generate antibiotic susceptibility profiles to inform treatment, augmented with strain information for global surveillance; such data could be transformative if provided at or near point of care.We demonstrate a low-cost DNA extraction method for TB WGS direct from patient samples. We initially evaluated the method using the Illumina MiSeq sequencer (40 smear-positive respiratory samples, obtained after routine clinical testing, and 27 matched liquid cultures). M. tuberculosis was identified in all 39 samples from which DNA was successfully extracted. Sufficient data for antibiotic susceptibility prediction was obtained from 24 (62%) samples; all results were concordant with reference laboratory phenotypes. Phylogenetic placement was concordant between direct and cultured samples. Using an Illumina MiSeq/MiniSeq the workflow from patient sample to results can be completed in 44/16 hours at a reagent cost of £96/£198 per sample.We then employed a non-specific PCR-based library preparation method for sequencing on an Oxford Nanopore Technologies MinION sequencer. We applied this to cultured Mycobacterium bovis BCG strain (BCG), and to combined culture-negative sputum DNA and BCG DNA. For flowcell version R9.4, the estimated turnaround time from patient to identification of BCG, detection of pyrazinamide resistance, and phylogenetic placement was 7.5 hours, with full susceptibility results 5 hours later. Antibiotic susceptibility predictions were fully concordant. A critical advantage of the MinION is the ability to continue sequencing until sufficient coverage is obtained, providing a potential solution to the problem of variable amounts of M. tuberculosis in direct samples.

2.14 Doan T, Wilson MR, Crawford ED, Chow ED, Khan LM, Knopp KA, O'Donovan BD, Xia D, Hacker JK, Stewart JM, Gonzales JA, Acharya NR, DeRisi JL. Illuminating uveitis: metagenomic deep sequencing identifies common and rare pathogens. Genome Med. 2016 Aug 25;8(1):90. doi: 10.1186/s13073-016-0344-6.

Erratum to: Illuminating uveitis: metagenomic deep sequencing identifies common and rare pathogens. Genome Med. 2016 Nov 22;8(1):123.

BACKGROUND: Ocular infections remain a major cause of blindness and morbidity worldwide. While prognosis is dependent on the timing and accuracy of diagnosis, the etiology remains elusive in ~50 % of presumed infectious uveitis cases. The objective of this study is to determine if unbiased metagenomic deep sequencing (MDS) can accurately detect pathogens in intraocular fluid samples of patients with uveitis. METHODS: This is a proof-of-concept study, in which intraocular fluid samples were obtained from five subjects with known diagnoses, and one subject with bilateral chronic uveitis without a known etiology. Samples were subjected to MDS, and results were compared with those from conventional diagnostic tests. Pathogens were identified using a rapid computational pipeline to analyze the non-host sequences obtained from MDS. RESULTS: Unbiased MDS of intraocular fluid produced results concordant with known diagnoses in subjects with (n = 4) and without (n = 1) uveitis. Samples positive for Cryptococcus neoformans, Toxoplasma gondii, and herpes simplex virus 1 as tested by a Clinical Laboratory Improvement Amendments-certified laboratory were correctly identified with MDS. Rubella virus was identified in one case of chronic bilateral idiopathic uveitis. The subject's strain was most closely related to a German rubella virus strain isolated in 1992, one year before he developed a fever and rash while living in Germany. The pattern and the number of viral identified mutations present in the

patient's strain were consistent with long-term viral replication in the eye. CONCLUSIONS: MDS can identify fungi, parasites, and DNA and RNA viruses in minute volumes of intraocular fluid samples. The identification of chronic intraocular rubella virus infection highlights the eye's role as a long-term pathogen reservoir, which has implications for virus eradication and emerging global epidemics.

2.15 Feigelman R, Kahlert CR, Baty F, Rassouli F, Kleiner RL, Kohler P, Brutsche MH, von Mering C. Sputum DNA sequencing in cystic fibrosis: non-invasive access to the lung microbiome and to pathogen details. Microbiome. 2017 Feb 10;5(1):20. doi: 10.1186/s40168-017-0234-1.

BACKGROUND: Cystic fibrosis (CF) is a life-threatening genetic disorder, characterized by chronic microbial lung infections due to abnormally viscous mucus secretions within airways. The clinical management of CF typically involves regular respiratory-tract cultures in order to identify pathogens and to guide treatment. However, culture-based methods can miss atypical or slow-growing microbes. Furthermore, the isolated microbes are often not classified at the strain level due to limited taxonomic resolution. RESULTS: Here, we show that untargeted metagenomic sequencing of sputum DNA can provide valuable information beyond the possibilities of culture-based diagnosis. We sequenced the sputum of six CF patients and eleven control samples (including healthy subjects and chronic obstructive pulmonary disease patients) without prior depletion of human DNA or cell size selection, thus obtaining the most unbiased and comprehensive characterization of CF respiratory tract microbes to date. We present detailed descriptions of the CF and healthy lung microbiome, reconstruct near complete pathogen genomes, and confirm that the CF lungs consistently exhibit reduced microbial diversity. Crucially, the obtained genomic sequences enabled a detailed identification of the exact pathogen strain types, when analyzed in conjunction with existing multi-locus sequence typing databases. We also detected putative pathogenicity islands and indicators of antibiotic resistance, in good agreement with independent clinical tests. CONCLUSIONS: Unbiased sputum metagenomics provides an in-depth profile of the lung pathogen microbiome, which is complementary to and more detailed than standard culture-based reporting. Furthermore, functional and taxonomic features of the dominant pathogens, including antibiotics resistances, can be deduced-supporting accurate and non-invasive clinical diagnosis.

2.16 Flygare S, Simmon K, Miller C, Qiao Y, Kennedy B, Di Sera T, Graf EH, Tardif KD, Kapusta A, Rynearson S, Stockmann C, Queen K, Tong S, Voelkerding KV, Blaschke A, Byington CL, Jain S, Pavia A, Ampofo K, Eilbeck K, Marth G, Yandell M, Schlaberg R. Taxonomer: an interactive metagenomics analysis portal for universal pathogen detection and host mRNA expression profiling. Genome Biol. 2016 May 26;17(1):111. doi: 10.1186/s13059-016-0969-1.

BACKGROUND: High-throughput sequencing enables unbiased profiling of microbial communities, universal pathogen detection, and host response to infectious diseases. However, computation times and algorithmic inaccuracies have hindered adoption. RESULTS: We present Taxonomer, an ultrafast, web-tool for comprehensive metagenomics data analysis and interactive results visualization. Taxonomer is unique in providing integrated nucleotide and protein-based classification and simultaneous host messenger RNA (mRNA) transcript profiling. Using real-world case-studies, we show that Taxonomer detects previously unrecognized infections and reveals antiviral host mRNA expression profiles. To facilitate data-sharing across geographic distances in outbreak settings, Taxonomer is publicly available through a web-based user interface. CONCLUSIONS: Taxonomer enables rapid, accurate, and interactive analyses of metagenomics data on personal computers and mobile devices.

2.17 Gyarmati P, Kjellander C, Aust C, Song Y, Öhrmalm L, Giske CG. Metagenomic analysis of bloodstream infections in patients with acute leukemia and therapy-induced neutropenia. Sci Rep. 2016 Mar 21;6:23532. doi: 10.1038/srep23532.

Leukemic patients are often immunocompromised due to underlying conditions, comorbidities and the effects of chemotherapy, and thus at risk for developing systemic infections. Bloodstream infection (BSI) is a severe complication in neutropenic patients, and is associated with increased mortality. BSI is routinely diagnosed with blood culture, which only detects culturable pathogens. We analyzed 27 blood samples from 9 patients with acute leukemia and suspected BSI at different time points of their antimicrobial treatment using shotgun metagenomics sequencing in order to detect unculturable and non-bacterial pathogens. Our findings confirm the presence of bacterial, fungal and viral pathogens alongside antimicrobial resistance genes. Decreased white blood cell (WBC) counts were associated with the presence of microbial DNA, and was inversely proportional to the number of sequencing reads. This study could indicate the use of high-throughput sequencing for personalized antimicrobial treatments in BSIs.

2.18 Joensen KG, Engsbro AL, Lukjancenko O, Kaas RS, Lund O, Westh H, Aarestrup FM. Evaluating next-generation sequencing for direct clinical diagnostics in diarrhoeal disease. Eur J Clin Microbiol Infect Dis. 2017 Mar 11. doi: 10.1007/s10096-017-2947-2. [Epub ahead of print]

The accurate microbiological diagnosis of diarrhoea involves numerous laboratory tests and, often, the pathogen is not identified in time to guide clinical management. With next-generation sequencing (NGS) becoming cheaper, it has huge potential in routine diagnostics. The aim of this study was to evaluate the potential of NGS-based diagnostics through direct sequencing of faecal samples. Fifty-eight clinical faecal samples were obtained from patients with diarrhoea as part of the routine diagnostics at Hvidovre University Hospital, Denmark. Ten samples from healthy individuals were also included. DNA was extracted from faecal samples and sequenced on the Illumina MiSeq system. Species distribution was determined with MGmapper and NGS-based diagnostic prediction was performed based on the relative abundance of pathogenic bacteria and Giardia and detection of pathogen-specific virulence genes. NGS-based diagnostic results were compared to conventional findings for 55 of the diarrhoeal samples; 38 conventionally positive for bacterial pathogens, two positive for Giardia, four positive for virus and 11 conventionally negative. The NGS-based approach enabled detection of the same bacterial pathogens as the classical approach in 34 of the 38 conventionally positive bacterial samples and predicted the responsible pathogens in five of the 11 conventionally negative samples. Overall, the NGS-based approach enabled pathogen detection comparable to conventional diagnostics and the approach has potential to be extended for the detection of all pathogens. At present, however, this approach is too expensive and time-consuming for routine diagnostics.

2.19 Parize P, Muth E, Richaud C, Gratigny M, Pilmis B, Lamamy A, Mainardi JL, Cheval J, de Visser L, Jagorel F, Ben Yahia L, Bamba G, Dubois M, Join-Lambert O, Leruez-Ville M, Nassif X, Lefort A, Lanternier F, Suarez F, Lortholary O, Lecuit M, Eloit M. Untargeted next-generation sequencing-based first-line diagnosis of infection in immunocompromised adults: a multicentre, blinded, prospective study. Clin Microbiol Infect. 2017 Feb 10. pii: S1198-743X(17)30094-0. doi: 10.1016/j.cmi.2017.02.006. [Epub ahead of print]

OBJECTIVE: Infections are the major cause of morbidity and mortality in immunocompromised patients. Improving microbiological diagnosis in these patients is of paramount clinical importance. METHODS: We performed this multicentre, blinded, prospective, proof-of-concept study, to compare untargeted next-

generation sequencing with conventional microbiological methods for first-line diagnosis of infection in 101 immunocompromised adults. Patients were followed for 30 days and their blood samples, and in some cases nasopharyngeal swabs and/or biological fluids, were analysed. At the end of the study, expert clinicians evaluated the results of both methods. The primary outcome measure was the detection rate of clinically relevant viruses and bacteria at inclusion. RESULTS: Clinically relevant viruses and bacteria identified by untargeted next-generation sequencing and conventional methods were concordant for 72 of 101 patients in samples taken at inclusion (κ test=0.2, 95% CI 0.03-0.48). However, clinically relevant viruses and bacteria were detected in a significantly higher proportion of patients with untargeted next-generation sequencing than conventional methods at inclusion (36/101 (36%) vs. 11/101 (11%), respectively, p <0.001), and even when the latter were continued over 30 days (19/101 (19%), p 0.003). Untargeted next-generation sequencing had a high negative predictive value compared with conventional methods (64/65, 95% CI 0.95-1). CONCLUSIONS: Untargeted next-generation sequencing has a high negative predictive value and detects more clinically relevant viruses and bacteria than conventional microbiological methods. Untargeted next-generation sequencing is therefore a promising method for microbiological diagnosis in immunocompromised adults.

2.20 Schlaberg R, Chiu CY, Miller S, Procop GW, Weinstock G; Professional Practice Committee and Committee on Laboratory Practices of the American Society for Microbiology; Microbiology Resource Committee of the College of American Pathologists Validation of Metagenomic Next-Generation Sequencing Tests for Universal Pathogen Detection. Arch Pathol Lab Med. 2017 Feb 7. doi: 10.5858/arpa.2016-0539-RA. [Epub ahead of print]

CONTEXT: Metagenomic sequencing can be used for detection of any pathogens using unbiased, shotgun next-generation sequencing (NGS), without the need for sequence-specific amplification. Proof-of-concept has been demonstrated in infectious disease outbreaks of unknown causes and in patients with suspected infections but negative results for conventional tests. Metagenomic NGS tests hold great promise to improve infectious disease diagnostics, especially in immunocompromised and critically ill patients. OBJECTIVE: To discuss challenges and provide example solutions for validating metagenomic pathogen detection tests in clinical laboratories. A summary of current regulatory requirements, largely based on prior guidance for NGS testing in constitutional genetics and oncology, is provided. DATA SOURCES: -Examples from 2 separate validation studies are provided for steps from assay design, and validation of wet bench and bioinformatics protocols, to quality control and assurance. CONCLUSIONS: Although laboratory and data analysis workflows are still complex, metagenomic NGS tests for infectious diseases are increasingly being validated in clinical laboratories. Many parallels exist to NGS tests in other fields. Nevertheless, specimen preparation, rapidly evolving data analysis algorithms, and incomplete reference sequence databases are idiosyncratic to the field of microbiology and often overlooked.

In our region, a HEV infection is the most frequently diagnosed viral cause for a recent hepatitis. These results indicate that, in a country where HEV is endemic, serological HEV diagnostics should be added to the standard work-up for viral hepatitis.

3.1 Bongianni, M., et al. (2017). "Diagnosis of Human Prion Disease Using Real-Time Quaking-Induced Conversion Testing of Olfactory Mucosa and Cerebrospinal Fluid Samples." JAMA Neurol 74(2): 155-162.

Importance: Early and accurate in vivo diagnosis of Creutzfeldt-Jakob disease (CJD) is necessary for quickly distinguishing treatable from untreatable rapidly progressive dementias and for future therapeutic trials. This early diagnosis is becoming possible using the real-time quaking-induced conversion (RT-QuIC) seeding assay, which detects minute amounts of the disease-specific pathologic prion protein in cerebrospinal fluid (CSF) or olfactory mucosa (OM) samples. Objective: To develop an algorithm for accurate and early diagnosis of CJD by using the RT-QuIC assay on CSF samples, OM samples, or both. Design, Setting, and Participants: In this case-control study, samples of CSF and OM were collected from 86 patients with a clinical diagnosis of probable (n = 51), possible (n = 24), or suspected (n = 11) CJD and 104 negative control samples (54 CSF and 50 OM). The CSF and OM samples were analyzed using conventional RT-QuIC. The CSF samples underwent further testing using improved RT-QuIC conditions. In addition, the diagnostic performance of a novel, easy-to-use, gentle flocked swab for sampling of OM was evaluated. Data were collected from January 1 to June 30, 2015. Main Outcome and Measures: Correlations between RT-QuIC results and the final diagnosis of recruited patients. Results: Among the 86 patients (37 men [43%] and 49 women [57%]; mean [SD] age, 65.7 [11.5] years) included for analysis, all 61 patients with sporadic CJD had positive RT-QuIC findings using OM or CSF samples or both for an overall RT-QuIC diagnostic sensitivity of 100% (95% CI, 93%-100%). All patients with a final diagnosis of non-prion disease (71 CSF and 67 OM samples) had negative RT-QuIC findings for 100% specificity (95% CI, 94%-100%). Of 8 symptomatic patients with various mutations causing CJD or Gerstmann-Straussler-Scheinker syndrome, 6 had positive and 2 had negative RT-QuIC findings for a sensitivity of 75% (95% CI, 36%-96%). Conclusions and Relevance: A proposed diagnostic algorithm for sporadic CJD combines CSF and OM RT-QuIC testing to provide virtually 100% diagnostic sensitivity and specificity in the clinical phase of the disease.

3.2 Foutz, A., et al. (2017). "Diagnostic and prognostic value of human prion detection in cerebrospinal fluid." Ann Neurol 81(1): 79-92.

OBJECTIVE: Several prion amplification systems have been proposed for detection of prions in cerebrospinal fluid (CSF), most recently, the measurements of prion seeding activity with second-generation real-time quaking-induced conversion (RT-QuIC). The objective of this study was to investigate the diagnostic performance of the RT-QuIC prion test in the broad phenotypic spectrum of prion diseases. METHODS: We performed CSF RT-QuIC testing in 2,141 patients who had rapidly progressive neurological disorders, determined diagnostic sensitivity and specificity in 272 cases that were autopsied, and evaluated the impact of mutations and polymorphisms in the PRNP gene, and type 1 or type 2 human prions on diagnostic performance. RESULTS: The 98.5% diagnostic specificity and 92% sensitivity of CSF RT-QuIC in a blinded retrospective analysis matched the 100% specificity and 95% sensitivity of a blind prospective study. The CSF RT-QuIC differentiated 94% of cases of sporadic Creutzfeldt-Jakob disease (sCJD) MM1 from the sCJD MM2 phenotype, and 80% of sCJD VV2 from sCJD VV1. The mixed prion type 1-2 and cases heterozygous for codon 129 generated intermediate CSF RT-QuIC patterns, whereas genetic prion diseases revealed distinct profiles for each PRNP gene mutation. INTERPRETATION: The diagnostic performance of the improved CSF RT-QuIC is superior to surrogate marker tests for prion diseases such as 14-3-3 and tau proteins, and together with PRNP gene sequencing the test allows the major prion subtypes to be differentiated in vivo. This differentiation facilitates prediction of the clinicopathological phenotype and duration of the disease-two important considerations for envisioned therapeutic interventions. ANN NEUROL 2017;81:79-92.

3.3 Yoon, J., et al. (2017). "The use of saliva specimens for detection of influenza A and B viruses by rapid influenza diagnostic tests." J Virol Methods 243: 15-19.

BACKGROUND AND OBJECTIVES: Diagnostic tests for influenza infection commonly use nasopharyngeal swabs (NPS) even though these are invasive to obtain. As an alternative specimen, we evaluated the diagnostic usefulness of saliva samples with rapid influenza diagnostic tests (RIDTs). STUDY DESIGN: Both NPS and saliva samples were collected from 385 influenza suspected patients and analyzed using Sofia Influenza A+B Fluorescence Immunoassay (Quidel Corporation, San Diego, CA, USA), ichroma TRIAS Influenza A+B (Boditech, Chuncheon, Korea), SD Bioline Influenza Ag (Standard Diagnostic, Yonggin, Korea), BinaxNOW Influenza A/B antigen kit (Alere Inc., Waltham, MA, USA), and real-time reverse transcriptase PCR (RT-PCR). RESULTS: Of the 385 patients, 31.2% (120/385) were positive for influenza A, and 7.5% (29/385) were positive for influenza B virus with saliva or NPS by RT-PCR. The diagnostic sensitivity was slightly higher in NPS than in saliva samples for both influenza A and B by all of the four RIDTs. The diagnostic sensitivities of Sofia and ichroma TRIAS were significantly superior to those of the other conventional influenza RIDTs with both types of sample. The sensitivities of Sofia and ichroma TRIAS with saliva specimens were comparable to the sensitivities of the other two conventional RIDTs with NPS specimens. The simultaneous use of saliva and NPS samples exhibited improved sensitivity from 10.0% to 13.3% for influenza A and from 10.3% to 17.2% for influenza B compared to using NPS alone. CONCLUSIONS: This study demonstrates that saliva is a useful specimen for influenza detection, and that the combination of saliva and NPS could improve the sensitivities of influenza RIDTs.

3.4 Wahrenbrock, M. G., et al. (2016). "Comparison of Cepheid Xpert Flu/RSV XC and BioFire FilmArray for Detection of Influenza A, Influenza B, and Respiratory Syncytial Virus." J Clin Microbiol 54(7): 1902-1903.

The Xpert Flu/RSV XC was compared to the FilmArray respiratory panel for detection of influenza (Flu) A, Flu B, and respiratory syncytial virus (RSV), using 128 nasopharyngeal swabs. Positive agreements were 100% for Flu A and RSV and 92.3% for Flu B. The Xpert may be useful in clinical situations when extensive testing is not required and may serve an important role in laboratories already performing broader respiratory panel testing.

3.5 Subramony, A., et al. (2016). "Impact of Multiplex Polymerase Chain Reaction Testing for Respiratory Pathogens on Healthcare Resource Utilization for Pediatric Inpatients." J Pediatr 173: 196-201.e192.

OBJECTIVE: To assess whether multiplex polymerase chain reaction (mPCR) vs non-mPCR testing impacts the use of antibiotics, chest radiographs, and isolation precautions. STUDY DESIGN: We retrospectively compared use of antibiotics, chest radiographs, and isolation precautions for patients <18 years old (excluding neonates) hospitalized at a tertiary referral center tested for respiratory pathogens in the emergency department or during the first 2 hospital days, during 2 periods: June 2010-June 2012 (non-mPCR group) vs October 2012-May 2014 (mPCR group). RESULTS: Subjects (n = 2430) in the mPCR group were older, had more complex chronic conditions, and were admitted to the pediatric intensive care unit more often compared with the non-mPCR (n = 2349) group. Subjects in the mPCR group had more positive tests (42.4% vs 14.4%, P < .01), received fewer days of antibiotics (4 vs 5 median antibiotic days, P < .01), fewer chest radiographs performed, (59% vs 78%, P < .01), and were placed in isolation longer (20 vs 0 median isolation-hours, P < .01) compared with the non-mPCR group. In multivariable regression, patients tested with mPCR were less likely to receive antibiotics for >/=2 days (OR 0.5, 95% CI 0.5-0.6), chest radiographs at admission (OR 0.4, 95% CI 0.3-0.4), and more likely to be in isolation for >/=2 days (OR 2.4, 95% CI 2.1-2.8) compared with the non-mPCR group. CONCLUSIONS: Use of mPCR testing for respiratory viruses among hospitalized patients was significantly associated with decreased healthcare resource utilization, including decreased use of antibiotics and chest radiographs, and increased use of isolation precautions.

3.6 Jefferies, S., et al. (2016). "Randomized controlled trial of the effect of regular paracetamol on influenza infection." Respirology 21(2): 370-377.

BACKGROUND AND OBJECTIVE: Anti-pyretic treatment is recommended in the management of influenza infection. In animal models anti-pyretic treatment increases mortality from influenza. We investigated the effects of paracetamol on viral and clinical outcomes in adults with influenza infection. METHODS: This is a randomized, double-blind, placebo-controlled trial of adults aged 18-65 years with influenza-like illness and positive influenza rapid antigen test. Treatments were 1 g paracetamol four times a day, or matching placebo, for 5 days. Pernasal swabs were taken for influenza quantitative RT-PCR at Baseline and Days 1, 2 and 5. Temperature and symptom scores were recorded for 5-14 days or time of resolution respectively. The primary outcome variable was area under the curve (AUC) for quantitative PCR log10 viral load from Baseline to Day 5. RESULTS: A total of 80 participants were randomized: no one was lost to follow up, and one withdrew after 4 days. There were 22 and 24 participants who were influenza PCR-positive in placebo and in paracetamol groups respectively. Mean (SD) AUC PCR log10 viral load was 4.40 (0.91) in placebo and 4.64 (0.88) in paracetamol; difference was -0.24, 95% CI: -0.78 to 0.29, P = 0.36. In all participants there were no differences in symptom scores, temperature, time to resolution of illness and health status, with no interaction between randomized treatment and whether influenza was detected by PCR. CONCLUSION: Regular paracetamol had no effect on viral shedding, temperature or clinical symptoms in patients with PCR-confirmed influenza. There remains an insufficient evidence base for paracetamol use in influenza infection. CLINICAL TRIAL REGISTRATION: ACTRN12611000497909 at the Australian New Zealand Clinical Trials Registry.

3.7 Black, S., et al. (2016). "Influence of Statins on Influenza Vaccine Response in Elderly Individuals." J Infect Dis 213(8): 1224-1228.

Influenza vaccination strategies have targeted elderly individuals because they are at high risk of disease complications and mortality. Statins are a class of drugs used to treat hypercholesterolemia and are frequently used in the elderly population to reduce the risk of cardiovascular disease. However, statins are also known to have immunomodulatory effects that could impact influenza vaccine response. In a post hoc analysis, we performed a cross-sectional observational study nested within a comparative immunogenicity clinical trial of adjuvanted versus unadjuvanted influenza vaccine in elderly persons to evaluate the influence of statin therapy on the immune response to vaccination. Overall, data on >5000 trial participants were available for analysis. Comparison of hemagglutination-inhibiting geometric mean titers to influenza A(H1N1), A(H3N2), and B strains revealed that titers were 38% (95% confidence interval [CI], 27%-50%), 67% (95% CI, 54%-80%), and 38% (95% CI, 28%-29%) lower, respectively, in subjects receiving chronic statin therapy, compared with those not receiving chronic statin therapy. This apparent immunosuppressive effect of statins on the vaccine immune response was most dramatic in individuals receiving synthetic statins. These effects were seen in both the adjuvanted and unadjuvanted vaccine groups in the clinical trial. These results, if confirmed, could have implications both for future clinical trials design, as well as for vaccine use recommendations for elderly individuals.

3.8 Loubet, P., et al. (2017). "Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France." Clin Microbiol Infect 23(4): 253-259.

OBJECTIVES: The aim of this study was to analyse characteristics and outcome of respiratory syncytial virus (RSV) infection in adults hospitalized with influenza-like illness (ILI). METHODS: Patients hospitalized with ILI were included in this prospective, multicentre study carried out in six French hospitals during three consecutive influenza seasons (2012-2015). RSV and other respiratory viruses were detected by multiplex PCR in nasopharyngeal swabs. Risk factors for RSV infection were identified by backward stepwise logistic regression analysis. RESULTS: A total of 1452 patients hospitalized with ILI were included, of whom 59% (861/1452) were >65 years and 83% (1211/1452) had underlying chronic illnesses. RSV was detected in 4% (59/1452), and influenza virus in 39% (566/1452). Risk factors for RSV infection were cancer (adjusted OR 2.1, 95% CI 1.1-4.1, p 0.04), and immunosuppressive treatment (adjusted OR 2.0, 95% CI 1.1-3.8, p 0.03). Patients with RSV had a median length of stay of 9 days (6-25), and 57% of them (30/53) had complications, including pneumonia (23/53, 44%) and respiratory

failure (15/53, 28%). Fifteen per cent (8/53) were admitted to an intensive care unit, and the in-hospital mortality rate was 8% (4/53). Pneumonia was more likely to occur in patients with RSV than in patients with RSV-negative ILI (44% (23/53) versus 26% (362/1393), p 0.006) or with influenza virus infection (44% versus 28% (157/560), p 0.02). CONCLUSION: RSV is an infrequent cause of ILI during periods of influenza virus circulation but can cause severe complications in hospitalized adults. Risk factors for RSV detection in adults hospitalized with ILI include cancer and immunosuppressive treatment. Specific immunization and antiviral therapy might benefit patients at risk.

3.9 Hauser, R. G., et al. (2017). "Cost-Effectiveness Study of Criteria to Screen Herpes Simplex PCR Tests from Cerebrospinal Fluid." J Clin Microbiol.

Background: The absence of markers of inflammation in the cerebrospinal fluid (CSF) commonly predict the absence of herpes simplex virus (HSV) central nervous system (CNS) infection. Consequently, multiple authors have proposed and validated criteria to defer HSV PCR tests from CSF in immune competent hosts with normal CSF white cells and protein (</=5 cells/mm3, </=50 mg/dL, respectively). Immune competence equates to age >/=2 years without HIV or transplant. Adoption of the criteria may erroneously exclude HSV infected persons from a necessary diagnostic test, or alternatively, reduce the costs associated with HSV tests with minimal to no effect on patient care. Little is known about the cost-effectiveness of this approach. Methods: A decision analysis model was developed to evaluate the adoption of criteria to screen HSV tests in CSF. Estimates of input parameter values combined available literature with a multiyear, multisite review at two of the largest healthcare systems in the United States. Results: Adoption of criteria to screen HSV tests proved cost-effective when less than 1 in 200 patients deferred from testing truly had an HSV CNS infection. Similar to prior studies, none of the deferred cases had HSV encephalitis (n=3120). Adoption of the criteria in the United States would save an estimated $127 million ($95 million to $158 million, +/-25%) annually. The model calculations remained robust to variation in test cost, prevalence of HSV infection, and random variation to study assumptions. Conclusion: The adoption of criteria to screen HSV PCR tests in CSF represents a cost-effective approach.

3.10 Cunningham, A. L., et al. (2016). "Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older." N Engl J Med 375(11): 1019-1032.

BACKGROUND: A trial involving adults 50 years of age or older (ZOE-50) showed that the herpes zoster subunit vaccine (HZ/su) containing recombinant varicella-zoster virus glycoprotein E and the AS01B adjuvant system was associated with a risk of herpes zoster that was 97.2% lower than that associated with placebo. A second trial was performed concurrently at the same sites and examined the safety and efficacy of HZ/su in adults 70 years of age or older (ZOE-70). METHODS: This randomized, placebo-controlled, phase 3 trial was conducted in 18 countries and involved adults 70 years of age or older. Participants received two doses of HZ/su or placebo (assigned in a 1:1 ratio) administered intramuscularly 2 months apart. Vaccine efficacy against herpes zoster and postherpetic neuralgia was assessed in participants from ZOE-70 and in participants pooled from ZOE-70 and ZOE-50. RESULTS: In ZOE-70, 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%). In pooled analyses of data from participants 70 years of age or older in ZOE-50 and ZOE-70 (16,596 participants), vaccine efficacy against herpes zoster was 91.3% (95% CI, 86.8 to 94.5; P<0.001), and vaccine efficacy against postherpetic neuralgia was 88.8% (95% CI, 68.7 to 97.1; P<0.001). Solicited reports of injection-site and systemic reactions within 7 days after injection were more frequent among HZ/su recipients than among placebo recipients (79.0% vs. 29.5%). Serious adverse events, potential immune-mediated diseases, and deaths occurred with similar frequencies in the two study groups. CONCLUSIONS: In our trial, HZ/su was found to reduce the risks of herpes zoster and postherpetic neuralgia among adults 70 years of age or older. (Funded by GlaxoSmithKline Biologicals; ZOE-50 and ZOE-70 ClinicalTrials.gov numbers, NCT01165177 and NCT01165229 .).

3.11 Agnandji, S. T., et al. (2016). "Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe." N Engl J Med 374(17): 1647-1660.

BACKGROUND: The replication-competent recombinant vesicular stomatitis virus (rVSV)-based vaccine expressing a Zaire ebolavirus (ZEBOV) glycoprotein was selected for rapid safety and immunogenicity testing before its use in West Africa. METHODS: We performed three open-label, dose-escalation phase 1 trials and one randomized, double-blind, controlled phase 1 trial to assess the safety, side-effect profile, and immunogenicity of rVSV-ZEBOV at various doses in 158 healthy adults in Europe and Africa. All participants were injected with doses of vaccine ranging from 300,000 to 50 million plaque-forming units (PFU) or placebo. RESULTS: No serious vaccine-related adverse events were reported. Mild-to-moderate early-onset reactogenicity was frequent but transient (median, 1 day). Fever was observed in up to 30% of vaccinees. Vaccine viremia was detected within 3 days in 123 of the 130 participants (95%) receiving 3 million PFU or more; rVSV was not detected in saliva or urine. In the second week after injection, arthritis affecting one to four joints developed in 11 of 51 participants (22%) in Geneva, with pain lasting a median of 8 days (interquartile range, 4 to 87); 2 self-limited cases occurred in 60 participants (3%) in Hamburg, Germany, and Kilifi, Kenya. The virus was identified in one synovial-fluid aspirate and in skin vesicles of 2 other vaccinees, showing peripheral viral replication in the second week after immunization. ZEBOV-glycoprotein-specific antibody responses were detected in all the participants, with similar glycoprotein-binding antibody titers but significantly higher neutralizing antibody titers at higher doses. Glycoprotein-binding antibody titers were sustained through 180 days in all participants. CONCLUSIONS: In these studies, rVSV-ZEBOV was reactogenic but immunogenic after a single dose and warrants further evaluation for safety and efficacy. (Funded by the Wellcome Trust and others; ClinicalTrials.gov numbers, NCT02283099, NCT02287480, and NCT02296983; Pan African Clinical Trials Registry number, PACTR201411000919191.).

3.12 Ewer, K., et al. (2016). "A Monovalent Chimpanzee Adenovirus Ebola Vaccine Boosted with MVA." N Engl J Med 374(17): 1635-1646.

BACKGROUND: The West African outbreak of Ebola virus disease that peaked in 2014 has caused more than 11,000 deaths. The development of an effective Ebola vaccine is a priority for control of a future outbreak. METHODS: In this phase 1 study, we administered a single dose of the chimpanzee adenovirus 3 (ChAd3) vaccine encoding the surface glycoprotein of Zaire ebolavirus (ZEBOV) to 60 healthy adult volunteers in Oxford, United Kingdom. The vaccine was administered in three dose levels--1x10(10) viral particles, 2.5x10(10) viral particles, and 5x10(10) viral particles--with 20 participants in each group. We then assessed the effect of adding a booster dose of a modified vaccinia Ankara (MVA) strain, encoding the same Ebola virus glycoprotein, in 30 of the 60 participants and evaluated a reduced prime-boost interval in another 16 participants. We also compared antibody responses to inactivated whole Ebola virus virions and neutralizing antibody activity with those observed in phase 1 studies of a recombinant vesicular stomatitis virus-based vaccine expressing a ZEBOV glycoprotein (rVSV-ZEBOV) to determine relative potency and assess durability. RESULTS: No safety concerns were identified at any of the dose levels studied. Four weeks after immunization with the ChAd3 vaccine, ZEBOV-specific antibody responses were similar to those induced by rVSV-ZEBOV vaccination, with a geometric mean titer of 752 and 921, respectively. ZEBOV neutralization activity was also similar with the two vaccines (geometric mean titer, 14.9 and 22.2, respectively). Boosting with the MVA vector increased virus-specific antibodies by a factor of 12 (geometric mean titer, 9007) and increased glycoprotein-specific CD8+ T cells by a factor of 5. Significant increases in neutralizing antibodies were seen after boosting in all 30 participants (geometric mean titer, 139; P<0.001). Virus-specific antibody responses in participants primed with ChAd3 remained positive 6 months after vaccination (geometric mean titer, 758) but were significantly higher in those who had received the MVA booster (geometric mean titer, 1750; P<0.001). CONCLUSIONS: The ChAd3 vaccine boosted with MVA elicited B-cell and T-cell immune responses to ZEBOV that were superior to those induced by the ChAd3 vaccine alone. (Funded by the Wellcome Trust and others; ClinicalTrials.gov number, NCT02240875.).

3.13 Regules, J. A., et al. (2017). "A Recombinant Vesicular Stomatitis Virus Ebola Vaccine." N Engl J Med 376(4): 330-341.

Background The worst Ebola virus disease (EVD) outbreak in history has resulted in more than 28,000 cases and 11,000 deaths. We present the final results of two phase 1 trials of an attenuated, replication-competent, recombinant vesicular stomatitis virus (rVSV)-based vaccine candidate designed to prevent EVD. Methods We conducted two phase 1, placebo-controlled, double-blind, dose-escalation trials of an rVSV-based vaccine candidate expressing the glycoprotein of a Zaire strain of Ebola virus (ZEBOV). A total of 39 adults at each site (78 participants in all) were consecutively enrolled into groups of 13. At each site, volunteers received one of three doses of the rVSV-ZEBOV vaccine (3 million plaque-forming units [PFU], 20 million PFU, or 100 million PFU) or placebo. Volunteers at one of the sites received a second dose at day 28. Safety and immunogenicity were assessed. Results The most common adverse events were injection-site pain, fatigue, myalgia, and headache. Transient rVSV viremia was noted in all the vaccine recipients after dose 1. The rates of adverse events and viremia were lower after the second dose than after the first dose. By day 28, all the vaccine recipients had seroconversion as assessed by an enzyme-linked immunosorbent assay (ELISA) against the glycoprotein of the ZEBOV-Kikwit strain. At day 28, geometric mean titers of antibodies against ZEBOV glycoprotein were higher in the groups that received 20 million PFU or 100 million PFU than in the group that received 3 million PFU, as assessed by ELISA and by pseudovirion neutralization assay. A second dose at 28 days after dose 1 significantly increased antibody titers at day 56, but the effect was diminished at 6 months. Conclusions This Ebola vaccine candidate elicited anti-Ebola antibody responses. After vaccination, rVSV viremia occurred frequently but was transient. These results support further evaluation of the vaccine dose of 20 million PFU for preexposure prophylaxis and suggest that a second dose may boost antibody responses. (Funded by the National Institutes of Health and others; rVSVG-ZEBOV-GP ClinicalTrials.gov numbers, NCT02269423 and NCT02280408 .).

3.14 Emonet, S., et al. (2016). "Rapid molecular determination of methicillin resistance in staphylococcal bacteraemia improves early targeted antibiotic prescribing: a randomized clinical trial." Clin Microbiol Infect 22(11): 946.e949-946.e915.

Empiric therapy of methicillin-susceptible Staphylococcus aureus (MSSA) infections with vancomycin is associated with poorer outcome than targeted therapy with beta-lactams. Our objective was to evaluate whether rapid determination of methicillin resistance shortens the time from Gram stain to targeted antimicrobial therapy in staphylococcal bacteraemia, thereby reducing vancomycin overuse. This was a single-centre open parallel RCT. Gram-positive cocci in clusters in positive blood culture underwent real-time PCR for rapid species and methicillin resistance determination parallel to conventional microbiology. Patients were randomized 1:1 so that clinicians would be informed of PCR results (intervention group) or not (control group). Eighty-nine patients (intervention 48, control 41) were analysed. MRSA was identified in seven patients, MSSA in 46, and CoNS in 36. PCR results were highly concordant (87/89) with standard microbiology. Median time (hours) from Gram stain to transmission of methicillin-susceptibility was 3.9 (2.8-4.3) vs. 25.4 (24.4-26-7) in intervention vs. control groups (p <0.001). Median time (hours) from Gram stain to targeted treatment was similar for 'all staphylococci' [6 (3.8-10) vs. 8 (1-36) p 0.13] but shorter in the intervention group when considering S. aureus only [5 (3-7) vs. 25.5 (3.8-54) p <0.001]. When standard susceptibility testing was complete, 41/48 (85.4%) patients in the intervention group were already receiving targeted therapy compared with 23/41 (56.1%) in the control group (p 0.004). There was no significant effect on clinical outcomes. Rapid determination of methicillin resistance in staphylococcal bacteraemia is accurate and reduces significantly the time to targeted antibiotic therapy in the subgroup of S. aureus, thereby avoiding unnecessary exposure to vancomycin.

3.15 Dunne, M. W., et al. (2016). "A Randomized Clinical Trial of Single-Dose Versus Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection." Clin Infect Dis 62(5): 545-551.

BACKGROUND: Acute bacterial skin and skin structure infections (ABSSSIs) are a cause of significant morbidity and therapy can be a burden to the healthcare system. New antibiotics that simplify treatment and avoid hospitalization are needed. This study compared the safety and efficacy of a single intravenous

infusion of 1500 mg of dalbavancin to the 2-dose regimen. METHODS: This study was a randomized, double-blind trial in patients aged >18 years with ABSSSIs. Patients were randomized to dalbavancin 1500 mg either as a single intravenous (IV) infusion or 1000 mg IV on day 1 followed 1 week later by 500 mg IV. The primary endpoint was a >/=20% reduction in the area of erythema at 48-72 hours in the intent-to-treat population. Noninferiority was to be declared if the lower limit of the 95% confidence interval (CI) on the difference in the outcomes was greater than -10%. Clinical outcome was also assessed at days 14 and 28. RESULTS: Six hundred ninety-eight patients were randomized. Demographic characteristics were similar on each regimen, although there were more patients with methicillin-resistant Staphylococcus aureus (MRSA) at baseline on the 2-dose regimen (36/210 [17.1%] vs 61/220 [27.7%]). Dalbavancin delivered as a single dose was noninferior to a 2-dose regimen (81.4% vs 84.2%; difference, -2.9% [95% CI, -8.5% to 2.8%]). Clinical outcomes were also similar at day 14 (84.0% vs 84.8%), day 28 (84.5% vs 85.1%), and day 14 in clinically evaluable patients with MRSA in a baseline culture (92.9% vs 95.3%) in the single- and 2-dose regimens, respectively. Treatment-emergent adverse events occurred in 20.1% of the single-dose patients and 19.9% on the 2-dose regimen. CONCLUSIONS: A single 1500-mg infusion of dalbavancin is noninferior to a 2-dose regimen, has a similar safety profile, and removes logistical constraints related to delivery of the second dose. CLINICAL TRIALS REGISTRATION: NCT02127970.

3.16 Davis, J. S., et al. (2016). "Combination of Vancomycin and beta-Lactam Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: A Pilot Multicenter Randomized Controlled Trial." Clin Infect Dis 62(2): 173-180.

BACKGROUND: In vitro laboratory and animal studies demonstrate a synergistic role for the combination of vancomycin and antistaphylococcal beta-lactams for methicillin-resistant Staphylococcus aureus (MRSA) bacteremia. Prospective clinical data are lacking. METHODS: In this open-label, multicenter, clinical trial, adults with MRSA bacteremia received vancomycin 1.5 g intravenously twice daily and were randomly assigned (1:1) to receive intravenous flucloxacillin 2 g every 6 hours for 7 days (combination group) or no additional therapy (standard therapy group). Participants were stratified by hospital and randomized in permuted blocks of variable size. Randomization codes were kept in sealed, sequentially numbered, opaque envelopes. The primary outcome was the duration of MRSA bacteremia in days. RESULTS: We randomly assigned 60 patients to receive vancomycin (n = 29), or vancomycin plus flucloxacillin (n = 31). The mean duration of bacteremia was 3.00 days in the standard therapy group and 1.94 days in the combination group. According to a negative binomial model, the mean time to resolution of bacteremia in the combination group was 65% (95% confidence interval, 41%-102%; P = .06) that in the standard therapy group. There was no difference in the secondary end points of 28- and 90-day mortality, metastatic infection, nephrotoxicity, or hepatotoxicity. CONCLUSIONS: Combining an antistaphylococcal beta-lactam with vancomycin may shorten the duration of MRSA bacteremia. Further trials with a larger sample size and objective clinically relevant end points are warranted. Australian New Zealand Clinical Trials Registry: ACTRN12610000940077 (www.anzctr.org.au).

3.17 Butin, M., et al. (2017). "Worldwide Endemicity of a Multidrug-Resistant Staphylococcus capitis Clone Involved in Neonatal Sepsis." Emerg Infect Dis 23(3): 538-539.

A multidrug-resistant Staphylococcus capitis clone, NRCS-A, has been isolated from neonatal intensive care units in 17 countries throughout the world. S. capitis NRCS-A prevalence is high in some neonatal intensive care units in France. These data highlight the worldwide endemicity and epidemiologic relevance of this multidrug-resistant, coagulase-negative staphylococci clone.

3.18 Ben Said, M., et al. (2016). "Late-onset sepsis due to Staphylococcus capitis 'neonatalis' in low-birthweight infants: a new entity?" J Hosp Infect 94(1): 95-98.

During hospitalization, sepsis occurs in one of every five very-low-birthweight infants. The emergence of Staphylococcus capitis (SC)-related sepsis in preterm infants was observed recently. This study aimed to evaluate the clinical severity of SC-related sepsis in preterm infants. Of the 105 infants who presented

with sepsis related to coagulase-negative staphylococci, 74 were SC. Severe morbidity was more common in the SC group (55.4%) than in the non-SC coagulase-negative staphylococci group (32.0%) (P=0.03). Multi-variate analysis identified SC-related sepsis as an independent risk factor for severe morbidity.

3.19 Lee, C. H., et al. (2016). "Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial." Jama 315(2): 142-149.

IMPORTANCE: Clostridium difficile infection (CDI) is a major burden in health care and community settings. CDI recurrence is of particular concern because of limited treatment options and associated clinical and infection control issues. Fecal microbiota transplantation (FMT) is a promising, but not readily available, intervention. OBJECTIVE: To determine whether frozen-and-thawed (frozen, experimental) FMT is noninferior to fresh (standard) FMT in terms of clinical efficacy among patients with recurrent or refractory CDI and to assess the safety of both types of FMT. DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, noninferiority trial enrolling 232 adults with recurrent or refractory CDI, conducted between July 2012 and September 2014 at 6 academic medical centers in Canada. INTERVENTIONS: Patients were randomly allocated to receive frozen (n = 114) or fresh (n = 118) FMT via enema. MAIN OUTCOMES AND MEASURES: The primary outcome measures were clinical resolution of diarrhea without relapse at 13 weeks and adverse events. Noninferiority margin was set at 15%. RESULTS: A total of 219 patients (n = 108 in the frozen FMT group and n = 111 in the fresh FMT group) were included in the modified intention-to-treat (mITT) population and 178 (frozen FMT: n = 91, fresh FMT: n = 87) in the per-protocol population. In the per-protocol population, the proportion of patients with clinical resolution was 83.5% for the frozen FMT group and 85.1% for the fresh FMT group (difference, -1.6% [95% CI, -10.5% to infinity]; P = .01 for noninferiority). In the mITT population the clinical resolution was 75.0% for the frozen FMT group and 70.3% for the fresh FMT group (difference, 4.7% [95% CI, -5.2% to infinity]; P < .001 for noninferiority). There were no differences in the proportion of adverse or serious adverse events between the treatment groups. CONCLUSIONS AND RELEVANCE: Among adults with recurrent or refractory CDI, the use of frozen compared with fresh FMT did not result in worse proportion of clinical resolution of diarrhea. Given the potential advantages of providing frozen FMT, its use is a reasonable option in this setting. TRIAL REGISTRATION: clinicaltrials.gov Identifier:NCT01398969.

3.20 Wilcox, M. H., et al. (2017). "Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection." N Engl J Med 376(4): 305-317.

Background Clostridium difficile is the most common cause of infectious diarrhea in hospitalized patients. Recurrences are common after antibiotic therapy. Actoxumab and bezlotoxumab are human monoclonal antibodies against C. difficile toxins A and B, respectively. Methods We conducted two double-blind, randomized, placebo-controlled, phase 3 trials, MODIFY I and MODIFY II, involving 2655 adults receiving oral standard-of-care antibiotics for primary or recurrent C. difficile infection. Participants received an infusion of bezlotoxumab (10 mg per kilogram of body weight), actoxumab plus bezlotoxumab (10 mg per kilogram each), or placebo; actoxumab alone (10 mg per kilogram) was given in MODIFY I but discontinued after a planned interim analysis. The primary end point was recurrent infection (new episode after initial clinical cure) within 12 weeks after infusion in the modified intention-to-treat population. Results In both trials, the rate of recurrent C. difficile infection was significantly lower with bezlotoxumab alone than with placebo (MODIFY I: 17% [67 of 386] vs. 28% [109 of 395]; adjusted difference, -10.1 percentage points; 95% confidence interval [CI], -15.9 to -4.3; P<0.001; MODIFY II: 16% [62 of 395] vs. 26% [97 of 378]; adjusted difference, -9.9 percentage points; 95% CI, -15.5 to -4.3; P<0.001) and was significantly lower with actoxumab plus bezlotoxumab than with placebo (MODIFY I: 16% [61 of 383] vs. 28% [109 of 395]; adjusted difference, -11.6 percentage points; 95% CI, -17.4 to -5.9; P<0.001; MODIFY II: 15% [58 of 390] vs. 26% [97 of 378]; adjusted difference, -10.7 percentage points; 95% CI, -16.4 to -5.1; P<0.001). In prespecified subgroup analyses (combined data set), rates of recurrent infection were lower in both groups that received bezlotoxumab than in the placebo group in subpopulations at high risk for recurrent infection or for an adverse outcome. The rates of initial clinical cure were 80% with bezlotoxumab alone, 73% with actoxumab plus bezlotoxumab, and 80% with placebo; the rates of sustained cure (initial clinical cure without recurrent infection in 12 weeks) were 64%, 58%, and 54%, respectively. The rates of adverse events were similar among these groups; the most common events

were diarrhea and nausea. Conclusions Among participants receiving antibiotic treatment for primary or recurrent C. difficile infection, bezlotoxumab was associated with a substantially lower rate of recurrent infection than placebo and had a safety profile similar to that of placebo. The addition of actoxumab did not improve efficacy. (Funded by Merck; MODIFY I and MODIFY II ClinicalTrials.gov numbers, NCT01241552 and NCT01513239 .).

3.21 Timbrook, T. T., et al. (2017). "The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis." Clin Infect Dis 64(1): 15-23.

BACKGROUND: Previous reports on molecular rapid diagnostic testing (mRDT) do not consistently demonstrate improved clinical outcomes in bloodstream infections (BSIs). This meta-analysis seeks to evaluate the impact of mRDT in improving clinical outcomes in BSIs. METHODS: We searched PubMed, CINAHL, Web of Science, and EMBASE through May 2016 for BSI studies comparing clinical outcomes between mRDT and conventional microbiology methods. RESULTS: Thirty-one studies were included with 5920 patients. The mortality risk was significantly lower with mRDT than with conventional microbiology methods (odds ratio [OR], 0.66; 95% confidence interval [CI], .54-.80), yielding a number needed to treat of 20. The mortality risk was slightly lower with mRDT in studies with antimicrobial stewardship programs (ASPs) (OR, 0.64; 95% CI, .51-.79), and non-ASP studies failed to demonstrate a significant decrease in mortality risk (0.72; .46-1.12). Significant decreases in mortality risk were observed with both gram-positive (OR, 0.73; 95% CI, .55-.97) and gram-negative organisms (0.51; .33-.78) but not yeast (0.90; .49-1.67). Time to effective therapy decreased by a weighted mean difference of -5.03 hours (95% CI, -8.60 to -1.45 hours), and length of stay decreased by -2.48 days (-3.90 to -1.06 days). CONCLUSIONS: For BSIs, mRDT was associated with significant decreases in mortality risk in the presence of a ASP, but not in its absence. mRDT also decreased the time to effective therapy and the length of stay. mRDT should be considered as part of the standard of care in patients with BSIs.

3.22 Walker, T., et al. (2016). "Clinical Impact of Laboratory Implementation of Verigene BC-GN Microarray-Based Assay for Detection of Gram-Negative Bacteria in Positive Blood Cultures." J Clin Microbiol 54(7): 1789-1796.

Gram-negative bacteremia is highly fatal, and hospitalizations due to sepsis have been increasing worldwide. Molecular tests that supplement Gram stain results from positive blood cultures provide specific organism information to potentially guide therapy, but more clinical data on their real-world impact are still needed. We retrospectively reviewed cases of Gram-negative bacteremia in hospitalized patients over a 6-month period before (n = 98) and over a 6-month period after (n = 97) the implementation of a microarray-based early identification and resistance marker detection system (Verigene BC-GN; Nanosphere) while antimicrobial stewardship practices remained constant. Patient demographics, time to organism identification, time to effective antimicrobial therapy, and other key clinical parameters were compared. The two groups did not differ statistically with regard to comorbid conditions, sources of bacteremia, or numbers of intensive care unit (ICU) admissions, active use of immunosuppressive therapy, neutropenia, or bacteremia due to multidrug-resistant organisms. The BC-GN panel yielded an identification in 87% of Gram-negative cultures and was accurate in 95/97 (98%) of the cases compared to results using conventional culture. Organism identifications were achieved more quickly post-microarray implementation (mean, 10.9 h versus 37.9 h; $P < 0.001$). Length of ICU stay, 30-day mortality, and mortality associated with multidrug-resistant organisms were significantly lower in the postintervention group ($P < 0.05$). More rapid implementation of effective therapy was statistically significant for postintervention cases of extended-spectrum beta-lactamase-producing organisms ($P = 0.049$) but not overall ($P = 0.12$). The Verigene BC-GN assay is a valuable addition for the early identification of Gram-negative organisms that cause bloodstream infections and can significantly impact patient care, particularly when resistance markers are detected.

3.23 Sommerstein, R., et al. (2016). "Transmission of Mycobacterium chimaera from Heater-Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System." Emerg Infect Dis 22(6): 1008-1013.

Heater-cooler units (HCUs) were recently identified as a source of Mycobacterium chimaera causing

surgical site infections. We investigated transmission of this bacterium from HCUs to the surgical field by using a thermic anemometer and particle counter, videotape of an operating room equipped with an ultraclean laminar airflow ventilation system, and bacterial culture sedimentation plates in a nonventilated room. Smoke from the HCU reached the surgical field in 23 s by merging with ultraclean air. The HCU produced on average 5.2, 139, and 14.8 particles/min in the surgical field at positions Off, On/oriented toward, and On/oriented away, respectively. Culture plates were positive for M. chimaera <5 m from the HCU in the test room. These experiments confirm airborne transmission of M. chimaera aerosols from a contaminated HCU to an open surgical field despite ultraclean air ventilation. Efforts to mitigate infectious risks during surgery should consider contamination from water sources and airflow-generating devices.

3.24 Haller, S., et al. (2016). "Contamination during production of heater-cooler units by Mycobacterium chimaera potential cause for invasive cardiovascular infections: results of an outbreak investigation in Germany, April 2015 to February 2016." Euro Surveill 21(17).

Invasive infections with Mycobacterium chimaera were reported in patients with previous open chest surgery and exposure to contaminated heater-cooler units (HCUs). We present results of the surveillance of clinical cases and of contaminated HCUs as well as environmental investigations in Germany up until February 2016. Clinical infections occurred in five male German cases over 50 years of age (range 53-80). Cases had been exposed to HCUs from one single manufacturer during open chest surgery up to five years prior to onset of symptoms. During environmental investigations, M. chimaera was detected in samples from used HCUs from three different countries and samples from new HCUs as well as in the environment at the manufacturing site of one manufacturer in Germany. Our investigation suggests that at least some of the M. chimaera infections may have been caused by contamination of HCUs at manufacturing site. We recommend that until sustainable measures for safe use of HCUs in operation theatres are implemented, users continue to adhere to instructions for use of HCUs and Field Safety Notices issued by the manufacturer, implement local monitoring for bacterial contamination and continuously check the websites of national and European authorities for current recommendations for the safe operation of HCUs.

3.25 Perkins, K. M., et al. (2016). "Notes from the Field: Mycobacterium chimaera Contamination of Heater-Cooler Devices Used in Cardiac Surgery - United States." MMWR Morb Mortal Wkly Rep 65(40): 1117-1118.

In the spring of 2015, investigators in Switzerland reported a cluster of six patients with invasive infection with Mycobacterium chimaera, a species of nontuberculous mycobacterium ubiquitous in soil and water. The infected patients had undergone open-heart surgery that used contaminated heater-cooler devices during extracorporeal circulation (1). In July 2015, a Pennsylvania hospital also identified a cluster of invasive nontuberculous mycobacterial infections among open-heart surgery patients. Similar to the Swiss report, a field investigation by the Pennsylvania Department of Health, with assistance from CDC, used both epidemiologic and laboratory evidence to identify an association between invasive Mycobacterium avium complex, including M. chimaera, infections and exposure to contaminated Stockert 3T heater-cooler devices, all manufactured by LivaNova PLC (formerly Sorin Group Deutschland GmbH) (2). M. chimaera was described as a distinct species of M. avium complex in 2004 (3). The results of the field investigation prompted notification of approximately 1,300 potentially exposed patients.* Although heater-cooler devices are used to regulate patients' blood temperature during cardiopulmonary bypass through water circuits that are closed, these reports suggest that aerosolized M. chimaera from the devices resulted in the invasive infections (1,2). The Food and Drug Administration (FDA) and CDC have issued alerts regarding the need to follow updated manufacturer's instructions for use of the devices, evaluate the devices for contamination, remain vigilant for new infections, and continue to monitor reports from the United States and overseas (2).

3.26 Calvo, B., et al. (2016). "First report of Candida auris in America: Clinical and microbiological aspects of 18 episodes of candidemia." J Infect 73(4): 369-374.

OBJECTIVES: Characterization of a hospital outbreak of Candida auris candidemia that involved 18 critically ill patients in Venezuela. METHOD: Bloodstream isolates of C. auris obtained from 18 patients

admitted at a medical center in Maracaibo, between March, 2012 and July, 2013 were included. Species identification was confirmed by ITS rDNA sequencing. Isolates were subsequently typed by amplified fragment length polymorphism fingerprinting (AFLP). Susceptibility testing was performed according to CLSI. Clinical data were collected from all cases by using a standard clinical form. RESULTS: A total of 13 critically ill pediatric and 5 adult patients, with a median age of 26 days, were included. All were previously exposed to antibiotics and multiple invasive medical procedures. Clinical management included prompt catheter removal and antifungal therapy. Thirteen patients (72%) survived up to 30 days after onset of candidemia. AFLP fingerprinting of all C. auris isolates suggested a clonal outbreak. The isolates were considered resistant to azoles, but susceptible to anidulafungin and 50% of isolates exhibited amphotericin B MIC values of >1 mug/ml. CONCLUSIONS: The study demonstrated that C. auris is a multiresistant yeast pathogen that can be a source of health-care associated infections in tertiary care hospitals with a high potential for nosocomial horizontal transmission.

3.27 Lockhart, S. R., et al. (2017). "Simultaneous Emergence of Multidrug-Resistant Candida auris on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses." Clin Infect Dis 64(2): 134-140.

BACKGROUND: Candida auris, a multidrug-resistant yeast that causes invasive infections, was first described in 2009 in Japan and has since been reported from several countries. METHODS: To understand the global emergence and epidemiology of C. auris, we obtained isolates from 54 patients with C. auris infection from Pakistan, India, South Africa, and Venezuela during 2012-2015 and the type specimen from Japan. Patient information was available for 41 of the isolates. We conducted antifungal susceptibility testing and whole-genome sequencing (WGS). RESULTS: Available clinical information revealed that 41% of patients had diabetes mellitus, 51% had undergone recent surgery, 73% had a central venous catheter, and 41% were receiving systemic antifungal therapy when C. auris was isolated. The median time from admission to infection was 19 days (interquartile range, 9-36 days), 61% of patients had bloodstream infection, and 59% died. Using stringent break points, 93% of isolates were resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins; 41% were resistant to 2 antifungal classes and 4% were resistant to 3 classes. WGS demonstrated that isolates were grouped into unique clades by geographic region. Clades were separated by thousands of single-nucleotide polymorphisms, but within each clade isolates were clonal. Different mutations in ERG11 were associated with azole resistance in each geographic clade. CONCLUSIONS: C. auris is an emerging healthcare-associated pathogen associated with high mortality. Treatment options are limited, due to antifungal resistance. WGS analysis suggests nearly simultaneous, and recent, independent emergence of different clonal populations on 3 continents. Risk factors and transmission mechanisms need to be elucidated to guide control measures.

3.28 Ruiz Gaitan, A. C., et al. (2017). "Nosocomial fungemia by Candida auris: First four reported cases in continental Europe." Rev Iberoam Micol 34(1): 23-27.

BACKGROUND: Candida auris is an emerging multidrug-resistant yeast that can cause invasive infections and is associated with high mortality. It is typically resistant to fluconazole and voriconazole and, some cases, also to echinocandins and amphotericin B. This species, phylogenetically related to Candida haemulonii, is frequently misidentified by commercial identification techniques in clinical laboratories; therefore, the real prevalence of C. auris infections may be underestimated. AIMS: To describe the clinical and microbiological features of the first four cases of C. auris fungemia episodes observed in the European continent. METHODS: The four patients were hospitalized in the adult surgical intensive care unit. A total of 8 isolates (two per patient) from blood and catheter tip were analyzed. RESULTS: All isolates were misidentified as Saccharomyces cerevisiae by AuxaColor 2, and as Candida sake by API ID20C. VITEK MS technology misidentified one isolate as Candida lusitaniae, another as C. haemulonii and could not identify the other six. C. auris identification was confirmed by ITS rDNA sequencing. All isolates were fluconazole (MIC >256mg/l) and voriconazole (MIC 2mg/l) resistant and susceptible to posaconazole, itraconazole, echinocandins and amphotericin B. CONCLUSIONS: C. auris should be regarded as an emerging pathogen, which requires molecular methods for definitive identification. Our isolates were highly resistant to fluconazole and resistant to voriconazole, but susceptible to the other antifungals tested, which emphasizes the importance of accurately identifying this species to avoid therapeutic failures.

3.29 Borman, A. M., et al. (2016). "Comparative Pathogenicity of United Kingdom Isolates of the Emerging Pathogen Candida auris and Other Key Pathogenic Candida Species." mSphere 1(4).

Candida auris, first described in 2009, has since emerged as an important, multidrug-resistant, nosocomial agent of candidemia, with large outbreaks reported worldwide and high mortality rates associated with therapeutic failure. The current study employed C. auris isolates from a variety of centers in the United Kingdom to evaluate the pathogenicity of this emerging pathogen compared to that of other common pathogenic yeast species in the invertebrate Galleria mellonella infection model. We showed that C. auris isolates differ in their growth characteristics in vitro, with a proportion of isolates failing to release daughter cells after budding, resulting in the formation of large aggregates of cells that cannot be physically disrupted. Our results also demonstrate strain-specific differences in the behavior of C. auris in G. mellonella, with the aggregate-forming isolates exhibiting significantly less pathogenicity than their nonaggregating counterparts. Importantly, the nonaggregating isolates exhibited pathogenicity comparable to that of C. albicans, which is currently accepted as the most pathogenic member of the genus, despite the fact that C. auris isolates do not produce hyphae and produce only rudimentary pseudohyphae either in vitro or in G. mellonella. IMPORTANCE The incidence of invasive candidiasis, which includes candidemia and deep tissue infections, continues to rise and is associated with considerable mortality rates. Candida albicans remains the most common cause of invasive candidiasis, although the prevalence of non-albicans species has increased over recent years. Since its first description in 2009, Candida auris has emerged as a serious nosocomial health risk, with widespread outbreaks in numerous hospitals worldwide. However, despite receiving considerable attention, little is known concerning the pathogenicity of this emerging fungal pathogen. Here, using the Galleria mellonella insect systemic infection model, we show strain-specific differences in the virulence of C. auris, with the most virulent isolates exhibiting pathogenicity comparable to that of C. albicans, which is currently accepted as the most pathogenic member of the genus.

3.30 Schelenz, S., et al. (2016). "First hospital outbreak of the globally emerging Candida auris in a European hospital." Antimicrob Resist Infect Control 5: 35.

BACKGROUND: Candida auris is a globally emerging multidrug resistant fungal pathogen causing nosocomial transmission. We report an ongoing outbreak of C. auris in a London cardio-thoracic center between April 2015 and July 2016. This is the first report of C. auris in Europe and the largest outbreak so far. We describe the identification, investigation and implementation of control measures. METHODS: Data on C. auris case demographics, environmental screening, implementation of infection prevention/control measures, and antifungal susceptibility of patient isolates were prospectively recorded then analysed retrospectively. Speciation of C. auris was performed by MALDI-TOF and typing of outbreak isolates performed by amplified fragment length polymorphism (AFLP). RESULTS: This report describes an ongoing outbreak of 50 C. auris cases over the first 16 month (April 2015 to July 2016) within a single Hospital Trust in London. A total of 44 % (n = 22/50) patients developed possible or proven C. auris infection with a candidaemia rate of 18 % (n = 9/50). Environmental sampling showed persistent presence of the yeast around bed space areas. Implementation of strict infection and prevention control measures included: isolation of cases and their contacts, wearing of personal protective clothing by health care workers, screening of patients on affected wards, skin decontamination with chlorhexidine, environmental cleaning with chorine based reagents and hydrogen peroxide vapour. Genotyping with AFLP demonstrated that C. auris isolates from the same geographic region clustered. CONCLUSION: This ongoing outbreak with genotypically closely related C. auris highlights the importance of appropriate species identification and rapid detection of cases in order to contain hospital acquired transmission.

3.31 Vallabhaneni, S., et al. (2016). "Investigation of the First Seven Reported Cases of Candida auris, a Globally Emerging Invasive, Multidrug-Resistant Fungus - United States, May 2013-August 2016." MMWR Morb Mortal Wkly Rep 65(44): 1234-1237.

Candida auris, an emerging fungus that can cause invasive infections, is associated with high mortality and is often resistant to multiple antifungal drugs. C. auris was first described in 2009 after being isolated from external ear canal discharge of a patient in Japan (1). Since then, reports of C. auris infections, including bloodstream infections, have been published from several countries, including Colombia, India, Israel, Kenya, Kuwait, Pakistan, South Africa, South Korea, Venezuela, and the United Kingdom (2-7). To

determine whether C. auris is present in the United States and to prepare for the possibility of transmission, CDC issued a clinical alert in June 2016 informing clinicians, laboratorians, infection control practitioners, and public health authorities about C. auris and requesting that C. auris cases be reported to state and local health departments and CDC (8). This report describes the first seven U.S. cases of C. auris infection reported to CDC as of August 31, 2016. Data from these cases suggest that transmission of C. auris might have occurred in U.S. health care facilities and demonstrate the need for attention to infection control measures to control the spread of this pathogen.

3.32 Garcia, H. H., et al. (2016). "Elimination of Taenia solium Transmission in Northern Peru." N Engl J Med 374(24): 2335-2344.

BACKGROUND: Taeniasis and cysticercosis are major causes of seizures and epilepsy. Infection by the causative parasite Taenia solium requires transmission between humans and pigs. The disease is considered to be eradicable, but data on attempts at regional elimination are lacking. We conducted a three-phase control program in Tumbes, Peru, to determine whether regional elimination would be feasible. METHODS: We systematically tested and compared elimination strategies to show the feasibility of interrupting the transmission of T. solium infection in a region of highly endemic disease in Peru. In phase 1, we assessed the effectiveness and feasibility of six intervention strategies that involved screening of humans and pigs, antiparasitic treatment, prevention education, and pig replacement in 42 villages. In phase 2, we compared mass treatment with mass screening (each either with or without vaccination of pigs) in 17 villages. In phase 3, we implemented the final strategy of mass treatment of humans along with the mass treatment and vaccination of pigs in the entire rural region of Tumbes (107 villages comprising 81,170 people and 55,638 pigs). The effect of the intervention was measured after phases 2 and 3 with the use of detailed necropsy to detect pigs with live, nondegenerated cysts capable of causing new infection. The necropsy sampling was weighted in that we preferentially included more samples from seropositive pigs than from seronegative pigs. RESULTS: Only two of the strategies implemented in phase 1 resulted in limited control over the transmission of T. solium infection, which highlighted the need to intensify the subsequent strategies. After the strategies in phase 2 were implemented, no cyst that was capable of further transmission of T. solium infection was found among 658 sampled pigs. One year later, without further intervention, 7 of 310 sampled pigs had live, nondegenerated cysts, but no infected pig was found in 11 of 17 villages, including all the villages in which mass antiparasitic treatment plus vaccination was implemented. After the final strategy was implemented in phase 3, a total of 3 of 342 pigs had live, nondegenerated cysts, but no infected pig was found in 105 of 107 villages. CONCLUSIONS: We showed that the transmission of T. solium infection was interrupted on a regional scale in a highly endemic region in Peru. (Funded by the Bill and Melinda Gates Foundation and others.).

3.33 Smith, M. N., et al. (2017). "Clinical utility of methicillin-resistant Staphylococcus aureus nasal polymerase chain reaction assay in critically ill patients with nosocomial pneumonia." J Crit Care 38: 168-171.

PURPOSE: This study investigated the diagnostic performance characteristics of a methicillin-resistant Staphylococcus aureus (MRSA) nasal polymerase chain reaction (PCR) assay in critically ill patients with nosocomial pneumonia. MATERIALS AND METHODS: This retrospective, single-center study included adult patients admitted to an intensive care unit with suspected nosocomial pneumonia. Patients must have received an MRSA nasal PCR assay and respiratory culture within predetermined time intervals. The primary outcome included the diagnostic performance characteristics of the assay. Secondary outcomes included the change in negative predictive value (NPV) over time, rate of acute kidney injury, and cost avoidance associated with vancomycin and monitoring. RESULTS: In 400 patients meeting inclusion criteria, the prevalence of culture confirmed MRSA pneumonia was 9.3%. When compared to initial cultures, the PCR assay demonstrated 91.89% sensitivity and 84.3% specificity with a positive predictive value and NPV of 37.36% and 99.03%. The NPV decreased to 87.5% at 21.9 days. No difference was found in rates of acute kidney injury. A cost avoidance of $108 per patient was estimated in patients de-escalated based on negative results. CONCLUSION: In critically ill patients, an MRSA nasal PCR assay has a high NPV for nosocomial pneumonia and can be used to guide vancomycin de-escalation.

3.34 Paling, F. P., et al. (2017). "Staphylococcus aureus colonization at ICU admission as a risk factor for developing S. aureus ICU pneumonia." Clin Microbiol Infect 23(1): 49.e49-49.e14.

OBJECTIVE: To quantify the incidence of intensive care unit (ICU)-acquired pneumonia caused by Staphylococcus aureus (S. aureus) and its association with S. aureus colonization at ICU admission. METHODS: This was a post-hoc analysis of two cohort studies in critically ill patients. The primary outcome was the incidence of microbiologically confirmed S. aureus ICU-acquired pneumonia. Incidences of S. aureus ICU pneumonia and associations with S. aureus colonization at ICU admission were determined using competing risks analyses. In all ICUs, patients were screened for respiratory tract S. aureus carriage on admission as part of infection control policies. Pooling of data was not deemed possible because of heterogeneity in baseline differences in patient population. RESULTS: The two cohort studies contained data of 9156 ICU patients. The average carriage rate of S. aureus among screened patients was 12.7%. In total, 1185 (12.9%) patients developed ICU pneumonia. Incidences of S. aureus ICU pneumonia were 1.33% and 1.08% in cohorts 1 and 2, respectively. After accounting for competing events, the adjusted subdistribution hazard ratio (SHR) of S. aureus colonization at admission for developing S. aureus ICU pneumonia was 9.55 (95% CI 5.31-17.18) in cohort 1 and 14.54 (95% CI 7.24-29.21) in cohort 2. CONCLUSION: The overall cumulative incidence of S. aureus ICU pneumonia in these ICUs was low. Patients colonized with S. aureus at ICU admission had an up to 15 times increased risk for developing this outcome compared with non-colonized patients.

3.35 Conway Morris, A., et al. (2016). "16S pan-bacterial PCR can accurately identify patients with ventilator-associated pneumonia." Thorax.

Ventilator-associated pneumonia (VAP) remains a challenge to intensive care units, with secure diagnosis relying on microbiological cultures that take up to 72 hours to provide a result. We sought to derive and validate a novel, real-time 16S rRNA gene PCR for rapid exclusion of VAP. Bronchoalveolar lavage (BAL) was obtained from two independent cohorts of patients with suspected VAP. Patients were recruited in a 2-centre derivation cohort and a 12-centre confirmation cohort. Confirmed VAP was defined as growth of >104 colony forming units/ml on semiquantitative culture and compared with a 16S PCR assay. Samples were tested from 67 patients in the derivation cohort, 10 (15%) of whom had confirmed VAP. Using cycles to cross threshold (Ct) values as the result of the 16S PCR test, the area under the receiver operating characteristic (ROC) curve (AUROC) was 0.94 (95% CI 0.86 to 1.0, p<0.0001). Samples from 92 patients were available from the confirmation cohort, 26 (28%) of whom had confirmed VAP. The AUROC for Ct in this cohort was 0.89 (95% CI 0.83 to 0.95, p<0.0001). This study has derived and assessed the diagnostic accuracy of a novel application for 16S PCR. This suggests that 16S PCR in BAL could be used as a rapid test in suspected VAP and may allow better stewardship of antibiotics. TRIAL REGISTRATION NUMBER: VAPRAPID trial ref NCT01972425.

3.36 Gadsby, N. J., et al. (2016). "Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia." Clin Infect Dis 62(7): 817-823.

BACKGROUND: The frequent lack of a microbiological diagnosis in community-acquired pneumonia (CAP) impairs pathogen-directed antimicrobial therapy. This study assessed the use of comprehensive multibacterial, multiviral molecular testing, including quantification, in adults hospitalized with CAP. METHODS: Clinical and laboratory data were collected for 323 adults with radiologically-confirmed CAP admitted to 2 UK tertiary care hospitals. Sputum (96%) or endotracheal aspirate (4%) specimens were cultured as per routine practice and also tested with fast multiplex real-time polymerase-chain reaction (PCR) assays for 26 respiratory bacteria and viruses. Bacterial loads were also calculated for 8 bacterial pathogens. Appropriate pathogen-directed therapy was retrospectively assessed using national guidelines adapted for local antimicrobial susceptibility patterns. RESULTS: Comprehensive molecular testing of single lower respiratory tract (LRT) specimens achieved pathogen detection in 87% of CAP patients compared with 39% with culture-based methods. Haemophilus influenzae and Streptococcus pneumoniae were the main agents detected, along with a wide variety of typical and atypical pathogens. Viruses were present in 30% of cases; 82% of these were codetections with bacteria. Most (85%) patients had received antimicrobials in the 72 hours before admission. Of these, 78% had a bacterial pathogen detected by PCR but only 32% were culture-positive (P < .0001). Molecular testing had the potential to enable de-escalation in number and/or spectrum of antimicrobials in 77% of patients.

CONCLUSIONS: Comprehensive molecular testing significantly improves pathogen detection in CAP, particularly in antimicrobial-exposed patients, and requires only a single LRT specimen. It also has the potential to enable early de-escalation from broad-spectrum empirical antimicrobials to pathogen-directed therapy.

3.37 Sanges, S., et al. (2017). "Diagnosis of primary antibody and complement deficiencies in young adults after a first invasive bacterial infection." Clin Microbiol Infect.

OBJECTIVES: Screening for primary immunodeficiencies (PIDs) in adults is recommended after two severe bacterial infections. We aimed to evaluate if screening should be performed after the first invasive infection in young adults. METHODS: Eligible patients were retrospectively identified using hospital discharge and bacteriology databases in three centres during a 3-year period. Eighteen to 40-year-old patients were included if they had experienced an invasive infection with encapsulated bacteria commonly encountered in PIDs (Streptococcus pneumoniae (SP), Neisseria meningitidis (NM), Neisseria gonorrhoeae (NG), Haemophilus influenzae (HI), or group A Streptococcus (GAS)). They were excluded in case of general or local predisposing factors. Immunological explorations and PIDs diagnoses were retrieved from medical records. Serum complement and IgG/A/M testings were systematically proposed at the time of study to patients with previously incomplete PID screening. RESULTS: The study population comprised 38 patients. Thirty-six had experienced a first invasive episode and a PID was diagnosed in seven (19%): two cases of common variable immunodeficiency revealed by SP bacteraemia, one case of idiopathic primary hypogammaglobulinaemia, and two cases of complement (C6 and C7) deficiency revealed by NM meningitis, one case of IgG2/IgG4 subclasses deficiency revealed by GAS bacteraemia, and one case of specific polysaccharide antibody deficiency revealed by HI meningitis. Two patients had previously experienced an invasive infection before the study period: in both cases, a complement deficiency was diagnosed after a second NM meningitis and a second NG bacteraemia, respectively. CONCLUSION: PID screening should be considered after a first unexplained invasive encapsulated-bacterial infection in young adults.

3.38 Talan, D. A., et al. (2016). "Trimethoprim-Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess." N Engl J Med 374(9): 823-832.

BACKGROUND: U.S. emergency department visits for cutaneous abscess have increased with the emergence of methicillin-resistant Staphylococcus aureus (MRSA). The role of antibiotics for patients with a drained abscess is unclear. METHODS: We conducted a randomized trial at five U.S. emergency departments to determine whether trimethoprim-sulfamethoxazole (at doses of 320 mg and 1600 mg, respectively, twice daily, for 7 days) would be superior to placebo in outpatients older than 12 years of age who had an uncomplicated abscess that was being treated with drainage. The primary outcome was clinical cure of the abscess, assessed 7 to 14 days after the end of the treatment period. RESULTS: The median age of the participants was 35 years (range, 14 to 73); 45.3% of the participants had wound cultures that were positive for MRSA. In the modified intention-to-treat population, clinical cure of the abscess occurred in 507 of 630 participants (80.5%) in the trimethoprim-sulfamethoxazole group versus 454 of 617 participants (73.6%) in the placebo group (difference, 6.9 percentage points; 95% confidence interval [CI], 2.1 to 11.7; P=0.005). In the per-protocol population, clinical cure occurred in 487 of 524 participants (92.9%) in the trimethoprim-sulfamethoxazole group versus 457 of 533 participants (85.7%) in the placebo group (difference, 7.2 percentage points; 95% CI, 3.2 to 11.2; P<0.001). Trimethoprim-sulfamethoxazole was superior to placebo with respect to most secondary outcomes in the per-protocol population, resulting in lower rates of subsequent surgical drainage procedures (3.4% vs. 8.6%; difference, -5.2 percentage points; 95% CI, -8.2 to -2.2), skin infections at new sites (3.1% vs. 10.3%; difference, -7.2 percentage points; 95% CI, -10.4 to -4.1), and infections in household members (1.7% vs. 4.1%; difference, -2.4 percentage points; 95% CI, -4.6 to -0.2) 7 to 14 days after the treatment period. Trimethoprim-sulfamethoxazole was associated with slightly more gastrointestinal side effects (mostly mild) than placebo. At 7 to 14 days after the treatment period, invasive infections had developed in 2 of 524 participants (0.4%) in the trimethoprim-sulfamethoxazole group and in 2 of 533 participants (0.4%) in the placebo group; at 42 to 56 days after the treatment period, an invasive infection had developed in 1 participant (0.2%) in the trimethoprim-sulfamethoxazole group. CONCLUSIONS: In settings in which MRSA was prevalent, trimethoprim-sulfamethoxazole treatment resulted in a higher cure rate among patients with a drained cutaneous abscess than placebo. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00729937.).

3.39 Lamb, M. J., et al. (2017). "Elimination of Screening Urine Cultures Prior to Elective Joint Arthroplasty." Clin Infect Dis 64(6): 806-809.

Discontinuing routine processing of screening urine cultures prior to elective joint arthroplasty resulted in substantial reduction in urine cultures ordered and antimicrobial prescriptions for asymptomatic bacteriuria, without any significant impact on incidence of prosthetic joint infection. This simple change would be scalable across institutions with potential for significant healthcare savings.

3.40 Juthani-Mehta, M., et al. (2016). "Effect of Cranberry Capsules on Bacteriuria Plus Pyuria Among Older Women in Nursing Homes: A Randomized Clinical Trial." Jama 316(18): 1879-1887.

Importance: Bacteriuria plus pyuria is highly prevalent among older women living in nursing homes. Cranberry capsules are an understudied, nonantimicrobial prevention strategy used in this population. Objective: To test the effect of 2 oral cranberry capsules once a day on presence of bacteriuria plus pyuria among women residing in nursing homes. Design, Setting, and Participants: Double-blind, randomized, placebo-controlled efficacy trial with stratification by nursing home and involving 185 English-speaking women aged 65 years or older, with or without bacteriuria plus pyuria at baseline, residing in 21 nursing homes located within 50 miles (80 km) of New Haven, Connecticut (August 24, 2012-October 26, 2015). Interventions: Two oral cranberry capsules, each capsule containing 36 mg of the active ingredient proanthocyanidin (ie, 72 mg total, equivalent to 20 ounces of cranberry juice) vs placebo administered once a day in 92 treatment and 93 control group participants. Main Outcomes and Measures: Presence of bacteriuria (ie, at least 105 colony-forming units [CFUs] per milliliter of 1 or 2 microorganisms in urine culture) plus pyuria (ie, any number of white blood cells on urinalysis) assessed every 2 months over the 1-year study surveillance; any positive finding was considered to meet the primary outcome. Secondary outcomes were symptomatic urinary tract infection (UTI), all-cause death, all-cause hospitalization, all multidrug antibiotic-resistant organisms, antibiotics administered for suspected UTI, and total antimicrobial administration. Results: Of the 185 randomized study participants (mean age, 86.4 years [SD, 8.2], 90.3% white, 31.4% with bacteriuria plus pyuria at baseline), 147 completed the study. Overall adherence was 80.1%. Unadjusted results showed the presence of bacteriuria plus pyuria in 25.5% (95% CI, 18.6%-33.9%) of the treatment group and in 29.5% (95% CI, 22.2%-37.9%) of the control group. The adjusted generalized estimating equations model that accounted for missing data and covariates showed no significant difference in the presence of bacteriuria plus pyuria between the treatment group vs the control group (29.1% vs 29.0%; OR, 1.01; 95% CI, 0.61-1.66; P = .98). There were no significant differences in number of symptomatic UTIs (10 episodes in the treatment group vs 12 in the control group), rates of death (17 vs 16 deaths; 20.4 vs 19.1 deaths/100 person-years; rate ratio [RR], 1.07; 95% CI, 0.54-2.12), hospitalization (33 vs 50 admissions; 39.7 vs 59.6 hospitalizations/100 person-years; RR, 0.67; 95% CI, 0.32-1.40), bacteriuria associated with multidrug-resistant gram-negative bacilli (9 vs 24 episodes; 10.8 vs 28.6 episodes/100 person-years; RR, 0.38; 95% CI, 0.10-1.46), antibiotics administered for suspected UTIs (692 vs 909 antibiotic days; 8.3 vs 10.8 antibiotic days/person-year; RR, 0.77; 95% CI, 0.44-1.33), or total antimicrobial utilization (1415 vs 1883 antimicrobial days; 17.0 vs 22.4 antimicrobial days/person-year; RR, 0.76; 95% CI, 0.46-1.25). Conclusions and Relevance: Among older women residing in nursing homes, administration of cranberry capsules vs placebo resulted in no significant difference in presence of bacteriuria plus pyuria over 1 year. Trial Registration: clinicaltrials.gov Identifier: NCT01691430.

3.41 Tita, A. T., et al. (2016). "Adjunctive Azithromycin Prophylaxis for Cesarean Delivery." N Engl J Med 375(13): 1231-1241.

Background The addition of azithromycin to standard regimens for antibiotic prophylaxis before cesarean delivery may further reduce the rate of postoperative infection. We evaluated the benefits and safety of azithromycin-based extended-spectrum prophylaxis in women undergoing nonelective cesarean section. Methods In this trial conducted at 14 centers in the United States, we studied 2013 women who had a singleton pregnancy with a gestation of 24 weeks or more and who were undergoing cesarean delivery during labor or after membrane rupture. We randomly assigned 1019 to receive 500 mg of intravenous azithromycin and 994 to receive placebo. All the women were also scheduled to receive standard antibiotic prophylaxis. The primary outcome was a composite of endometritis, wound infection, or other

infection occurring within 6 weeks. Results The primary outcome occurred in 62 women (6.1%) who received azithromycin and in 119 (12.0%) who received placebo (relative risk, 0.51; 95% confidence interval [CI], 0.38 to 0.68; P<0.001). There were significant differences between the azithromycin group and the placebo group in rates of endometritis (3.8% vs. 6.1%, P=0.02), wound infection (2.4% vs. 6.6%, P<0.001), and serious maternal adverse events (1.5% vs. 2.9%, P=0.03). There was no significant between-group difference in a secondary neonatal composite outcome that included neonatal death and serious neonatal complications (14.3% vs. 13.6%, P=0.63). Conclusions Among women undergoing nonelective cesarean delivery who were all receiving standard antibiotic prophylaxis, extended-spectrum prophylaxis with adjunctive azithromycin was more effective than placebo in reducing the risk of postoperative infection. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development; C/SOAP ClinicalTrials.gov number, NCT01235546 .).

3.42 Bibbins-Domingo, K., et al. (2016). "Serologic Screening for Genital Herpes Infection: US Preventive Services Task Force Recommendation Statement." Jama 316(23): 2525-2530.

Importance: Genital herpes is a prevalent sexually transmitted infection in the United States, occurring in almost 1 in 6 persons aged 14 to 49 years. Infection is caused by 2 subtypes of the herpes simplex virus (HSV), HSV-1 and HSV-2. Antiviral medications may provide symptomatic relief from outbreaks but do not cure HSV infection. Neonatal herpes infection, while uncommon, can result in substantial morbidity and mortality. Objective: To update the 2005 US Preventive Services Task Force (USPSTF) recommendation on screening for genital herpes. Evidence Review: The USPSTF reviewed the evidence on the accuracy, benefits, and harms of serologic screening for HSV-2 infection in asymptomatic persons, including those who are pregnant, as well as the effectiveness and harms of preventive medications and behavioral counseling interventions to reduce future symptomatic episodes and transmission to others. Findings: Based on the natural history of HSV infection, its epidemiology, and the available evidence on the accuracy of serologic screening tests, the USPSTF concluded that the harms outweigh the benefits of serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant. Conclusions and Recommendation: The USPSTF recommends against routine serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant. (D recommendation).

3.43 (2016). WHO Guidelines Approved by the Guidelines Review Committee. WHO Guidelines for the Treatment of Treponema pallidum (Syphilis). Geneva, World Health Organization.

Since the publication of the WHO Guidelines for the management of sexually transmitted infections in 2003, changes in the epidemiology of STIs and advancements in prevention, diagnosis and treatment necessitate changes in STI management. These guidelines provide updated treatment recommendations for treatment of Treponema pallidum (syphilis) based on the most recent evidence. They form one of several modules of guidelines for specific STIs. Other modules will focus on treatments for Chlamydia trachomatis (chlamydia), Neisseria gonorrhoeae (gonorrhoea) and genital herpes simplex virus (genital HSV). In addition, future work will provide guidance for syphilis screening and treatment of pregnant women, STI syndromic approach, clinical management, STI prevention, and treatments of other STIs. It is strongly recommended that countries take updated global guidance into account as they establish standardized national protocols and adapt it to the local epidemiological situation and antimicrobial susceptibility data. The objectives of these guidelines are: to provide evidence-based guidance on treatment of infection with Treponema pallidum; and to support countries to update their national guidelines for treatment of Treponema pallidum.

3.44 Wilson, A. P., et al. (2016). "Prevention and control of multi-drug-resistant Gram-negative bacteria: recommendations from a Joint Working Party." J Hosp Infect 92 Suppl 1: S1-44.

No abstract

3.45 Sokol, H., et al. (2016). "Faecal microbiota transplantation in recurrent Clostridium difficile infection: Recommendations from the French Group of Faecal microbiota Transplantation." Dig Liver Dis 48(3): 242-247.

Faecal microbiota transplantation is effective for treating recurrent forms of Clostridium difficile infection and its use in this indication is recommended in the most recent European and North American guidelines. In this context, faecal microbiota transplantation is beginning to be performed in France in clinical practice, while the rules governing this procedure have been defined in France only for clinical trials. To unify, secure, and evaluate practice in this field in France, the French Group of Faecal microbiota Transplantation (FGFT) was created in October 2014 with the support of the French National Society of Gastroenterology, the French Infectious Disease Society, and the National Academy of Pharmacy. We present here the deliberations of this group regarding the use of faecal microbiota transplantation for recurrent Clostridium difficile infection. The issues addressed are the indications, therapeutic sequence, delivery procedures, donor selection, methods and conditions of specimen preparation, and traceability.

3.46 Pappas, P. G., et al. (2016). "Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America." Clin Infect Dis 62(4): e1-50.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

3. 47 Tunkel, A. R., et al. (2017). "2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis." Clin Infect Dis.

No abstract

3.48 van de Beek, D., et al. (2016). "ESCMID guideline: diagnosis and treatment of acute bacterial meningitis." Clin Microbiol Infect 22 Suppl 3: S37-62.

No abstract

3.49 McGill, F., et al. (2016). "The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults." J Infect 72(4): 405-438.

Bacterial meningitis and meningococcal sepsis are rare conditions with high case fatality rates. Early recognition and prompt treatment saves lives. In 1999 the British Infection Society produced a consensus statement for the management of immunocompetent adults with meningitis and meningococcal sepsis. Since 1999 there have been many changes. We therefore set out to produce revised guidelines which provide a standardised evidence-based approach to the management of acute community acquired meningitis and meningococcal sepsis in adults. A working party consisting of infectious diseases physicians, neurologists, acute physicians, intensivists, microbiologists, public health experts and patient group representatives was formed. Key questions were identified and the literature reviewed. All recommendations were graded and agreed upon by the working party. The guidelines, which for the first time include viral meningitis, are written in accordance with the AGREE 2 tool and recommendations graded according to the GRADE system. Main changes from the original statement include the indications for pre-hospital antibiotics, timing of the lumbar puncture and the indications for neuroimaging. The list of investigations has been updated and more emphasis is placed on molecular diagnosis. Approaches to both antibiotic and steroid therapy have been revised. Several recommendations have

been given regarding the follow-up of patients.

3.50 Lipsky, B. A., et al. (2016). "IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes." Diabetes Metab Res Rev 32 Suppl 1: 45-74.

No abstract available

3.51 National Guideline, C. (2016). National Institute for Health and Care Excellence: Guidance. Sepsis: Recognition, Assessment and Early Management. London, National Institute for Health and Care Excellence (UK). Copyright (c) National Institute for Health and Care Excellence, 2016.

Sepsis is a clinical syndrome caused by the body's immune and coagulation systems being switched on by an infection. Sepsis with shock is a life-threatening condition that is characterised by low blood pressure despite adequate fluid replacement, and organ dysfunction or failure. Sepsis is an important cause of death in people of all ages. Both a UK Parliamentary and Health Service Ombudsman enquiry (2013) and UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD, 2015) have recently highlighted sepsis as being a leading cause of avoidable death that kills more people than breast, bowel and prostate cancer combined. Clinicians and healthcare professionals of all kinds, at all levels of seniority and in all clinical settings often find sepsis difficult to diagnose with certainty. Although people with sepsis may have a history of infection, fever is not present in all cases. The signs and symptoms of sepsis are usually very non-specific and can be missed if clinicians do not think "could this be sepsis?". In the same way that healthcare professionals consider "could this pain be cardiac in origin?" when presented with someone of any age with chest pain, this guideline aims to make "could this be sepsis?" the first consideration for anyone presenting with a possible infection. Detailed guidelines exist for the management of sepsis in adult and paediatric intensive care units, and by intensive care clinicians called to other settings. To reduce avoidable deaths, people with sepsis need to be recognised early and treatment initiated. This guideline aims to ensure healthcare systems in all clinical settings consider sepsis as an immediate life-threatening condition that should be recognised and treated as an emergency. The guideline outlines the immediate actions required for those with suspicion of sepsis and who are at highest risk of morbidity and mortality from sepsis. It provides a framework for risk assessment, treatment and follow-up or "safety-netting" of people not requiring immediate resuscitation.

3.52 Harris, A. M., et al. (2016). "Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention." Ann Intern Med 164(6): 425-434.

BACKGROUND: Acute respiratory tract infection (ARTI) is the most common reason for antibiotic prescription in adults. Antibiotics are often inappropriately prescribed for patients with ARTI. This article presents best practices for antibiotic use in healthy adults (those without chronic lung disease or immunocompromising conditions) presenting with ARTI. METHODS: A narrative literature review of evidence about appropriate antibiotic use for ARTI in adults was conducted. The most recent clinical guidelines from professional societies were complemented by meta-analyses, systematic reviews, and randomized clinical trials. To identify evidence-based articles, the Cochrane Library, PubMed, MEDLINE, and EMBASE were searched through September 2015 using the following Medical Subject Headings terms: "acute bronchitis," "respiratory tract infection," "pharyngitis," "rhinosinusitis," and "the common cold." HIGH-VALUE CARE ADVICE 1: Clinicians should not perform testing or initiate antibiotic therapy in patients with bronchitis unless pneumonia is suspected. HIGH-VALUE CARE ADVICE 2: Clinicians should test patients with symptoms suggestive of group A streptococcal pharyngitis (for example, persistent fevers, anterior cervical adenitis, and tonsillopharyngeal exudates or other appropriate combination of symptoms) by rapid antigen detection test and/or culture for group A Streptococcus. Clinicians should treat patients with antibiotics only if they have confirmed streptococcal pharyngitis. HIGH-VALUE CARE ADVICE 3: Clinicians should reserve antibiotic treatment for acute rhinosinusitis for patients with persistent symptoms for more than 10 days, onset of severe symptoms or signs of high fever (>39 degrees C) and purulent nasal discharge or facial pain lasting for at least 3 consecutive days,

or onset of worsening symptoms following a typical viral illness that lasted 5 days that was initially improving (double sickening). HIGH-VALUE CARE ADVICE 4: Clinicians should not prescribe antibiotics for patients with the common cold.