

ECCMID 2017

SY150 Year in Infectious Diseases

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Speakers:

1 Susanna Esposito, Milan, Italy

2 Guy Thwaites, Ho Chi Minh City, Viet Nam

3 BJ Kullberg, Nijmegen, Netherlands

References

Maternal immunization

1.1 Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. Winter K, Nickell S, Powell M, Harriman K. Clin Infect Dis. 2017 Jan 1;64(1):3-8.

BACKGROUND: Most severe and fatal cases of pertussis occur in infants <8 weeks of age, before initiation of the primary pertussis vaccine series. Women are recommended to receive tetanus, diphtheria, and acellular pertussis (Tdap) vaccine at the start of the third trimester of each pregnancy to optimize transplacental transfer of antibodies to the fetus. This recommendation was made by the Advisory Committee for Immunization Practices based on immunogenicity data, and no studies in the United States have yet evaluated the effectiveness of this strategy in reducing pertussis incidence in infants.

METHODS: We evaluated a cohort of mothers with documented Tdap vaccination histories in the California Immunization Registry to determine whether infants whose mothers received Tdap vaccine at 27-36 weeks gestation had a lower risk of pertussis at <8 weeks of age than infants born to women who received Tdap vaccine within 14 days post partum.

RESULTS: Tdap vaccination received at 27-36 weeks gestation was found to be 85% (95% confidence interval, 33%-98%) more effective than postpartum Tdap vaccination at preventing pertussis in infants <8 weeks of age. Vaccination at 27-36 weeks gestation was more effective at preventing pertussis in infant than vaccination during the second trimester.

CONCLUSIONS: Tdap vaccination at 27-36 weeks gestation was 85% more effective than postpartum vaccination at preventing pertussis in infants <8 weeks of age. Efforts should be made by prenatal care providers to provide Tdap vaccine to pregnant women during routine prenatal visits at the earliest opportunity between 27 and 36 weeks gestation.

1.2 Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial. Madhi SA, Cutland CL, Jose L, Koen A, Govender N, Wittke F, Olugbosi M, Meulen AS, Baker S, Dull PM, Narasimhan V, Slobod K. Lancet Infect Dis. 2016 Aug;16(8):923-34.

BACKGROUND: Maternal group B streptococcus (GBS) serotype-specific capsular antibody concentrations are correlated with susceptibility to neonatal GBS invasive disease. Maternal immunisation against GBS during pregnancy might protect infants across the period of susceptibility to invasive disease, but no licensed vaccine exists. This study assessed the safety and immunogenicity of a CRM197-conjugated trivalent GBS vaccine in non-pregnant and pregnant women, and antibody transfer to their infants.

METHODS: We did a phase 1b/2, randomised, observer-blind single-centre study of an investigational trivalent GBS vaccine in healthy non-pregnant women (cohort 1), and a dose-ranging study in healthy

pregnant women (cohort 2). The study was done at the Chris Hani Baragwanath Academic Hospital in Soweto, South Africa. Participants were healthy non-pregnant or pregnant (28-35 weeks' gestation) women aged 18-40 years. In cohort 1, non-pregnant women were randomly assigned (2:1) to receive the investigational vaccine (two injections, 1 month apart, of a 20 µg dose [of each serotype] of aluminium hydroxide-adjuvanted investigational vaccine) or placebo. In cohort 2, pregnant women were randomly assigned (1:1:1:1) to receive one injection at 28-35 weeks' gestation of 0.5 µg, 2.5 µg, or 5.0 µg of the non-adjuvanted investigational vaccine (for each serotype), or placebo. All study participants and study staff not involved with vaccine preparation were masked to the randomisation group. The vaccine contained an equal dose (0.5 µg, 2.5 µg, 5.0 µg, or 20 µg) of each of three glycoconjugates (serotypes Ia, Ib and III). Reactogenicity was monitored to day 7 and unsolicited adverse events (adverse events) and infant safety were recorded throughout the study. The primary outcomes were tolerability and GBS-specific antibody response (measured as geometric mean concentrations [GMCs] in µg/mL) following the two injections for cohort 1, and selection of one vaccine dose based on analysis of serotype-specific antibody responses at delivery (+72 h) for use in subsequent studies. These outcomes were assessed in participants or infants of participants who correctly received the study vaccine with no major protocol deviations, and provided evaluable serum samples at day 1 and the scheduled timepoints throughout the study. This study is registered with ClinicalTrials.gov, NCT01193920.

FINDINGS: Between Oct 5, 2010, and Sept 21, 2011, we screened 75 non-pregnant and 417 pregnant healthy South African women. Of these, 60 non-pregnant women were enrolled in cohort 1 (40 randomly assigned to the GBS 20 µg group and 40 randomly assigned to the placebo group) and 320 pregnant women were enrolled in cohort 2 (80 in each of the four groups). Among the randomised groups of pregnant women, 33-40% experienced at least one local and 54-71% one systemic solicited adverse event, less than 4% of which were severe, and the rate did not differ by study group. Also, 2% of the pregnancies resulted in stillbirth and 3.5% of the liveborn babies died by 12 months age, none of these deaths were attributed to vaccination. There was one death in a GBS-vaccine recipient, which too was unrelated to vaccination. For cohort 1, serotype-specific antibody concentrations were significantly higher, as evident by no overlap of the 95% CIs of GMCs against all three serotypes in the vaccinated group than the placebo group. For cohort 2, pregnant women in all vaccine groups had significantly higher GMCs than did those in the placebo group at delivery (eg, GMCs against serotype Ia were 11 µg/mL [95% CI 7.0-18] for the GBS vaccine 0.5 µg group, 18 µg/mL [11-29] for the GBS vaccine 2.5 µg group, 22 µg/mL [13-35] for the GBS vaccine 5.0 µg group, and 0.64 µg/mL [0.42-0.98] for the placebo group) and at all measured timepoints. GMCs did not differ significantly between the vaccine doses at any of the measured timepoints ($p > 0.05$).

INTERPRETATION: The vaccine was well tolerated and induced capsular-specific antibody responses, in non-pregnant and pregnant women. Maternal vaccination led to higher GBS serotype-specific antibody concentrations in infants than did placebo, with both interventions resulting in similar safety profiles.

FUNDING: Novartis Vaccines and Diagnostics division, now part of the GlaxoSmithKline group of companies.

Meningitis prevention

1.3 Meningococcal serogroup B strain coverage of the multicomponent 4CMenB vaccine with corresponding regional distribution and clinical characteristics in England, Wales, and Northern Ireland, 2007-08 and 2014-15: a qualitative and quantitative assessment. Parikh SR, Newbold L, Slater S, Stella M, Moschioni M, Lucidarme J, De Paola R, Giuliani M, Serino L, Gray SJ, Clark SA, Findlow J, Pizza M, Ramsay ME, Ladhani SN, Borrow R. *Lancet Infect Dis*. 2017 Mar 30. pii: S1473-3099(17)30170-6.

BACKGROUND: The UK introduced 4CMenB-a multicomponent vaccine against serogroup B meningococcal disease-into the national infant immunisation programme in September, 2015. The Meningococcal Antigen Typing System (MATS) was used to estimate coverage by 4CMenB of invasive meningococcal group B isolates obtained during 2007-08 in England and Wales (MATS coverage). We aimed to repeat the MATS survey for invasive meningococcal group B isolates obtained during 2014-15, before 4CMenB introduction; compare strain coverage between 2007-08 and 2014-15; and investigate associations between MATS coverage, age, region, and disease outcomes.

METHODS: Invasive serogroup B meningococcal isolates from cases in England, Wales, and Northern Ireland during 2014-15 were assayed using MATS and compared with 2007-08 data. MATS coverage was assessed by geographical region and age group. Clinical characteristics, risk factors, and outcomes were assessed according to MATS coverage for 2014-15 English cases.

FINDINGS: In 2014-15, 165 of 251 (66%; 95% CI 52-80) meningococcal group B isolates were estimated

by MATS to be covered by 4CMenB, compared with 391 of 535 (73%; 95% CI 57-87) in 2007-08. The proportion of MATS-positive isolates with one vaccine antigen increased from 23% (122 of 535) in 2007-08 to 31% (78 of 251) in 2014-15, whereas the proportion with more than one antigen fell from 50% (269 of 535) to 35% (87 of 251). This effect reflected changes in circulating strains, particularly ST-269 clonal complex strains. MATS coverage increased with age, varied by geographical region, and was associated with more severe disease.

INTERPRETATION: In 2014-15, two-thirds of meningococcal group B isolates were predicted to be covered by 4CMenB. Temporal changes in MATS coverage underscore the need for continued monitoring of antigen expression and diversity, particularly in countries with 4CMenB programmes.

FUNDING: Public Health England, GlaxoSmithKline.

1.4 Persistence of bactericidal antibodies following booster vaccination with 4CMenB at 12, 18 or 24 months and immunogenicity of a fifth dose administered at 4 years of age – a phase 3 extension to a randomised controlled trial. Iro MA, Snape MD, Voysey M, Jawad S, Finn A, Heath PT, Bona G, Esposito S, Diez-Domingo J, Prymula R, Oduyungbo A, Toneatto D, Dull P, Pollard AJ; European Men B Vaccine Study Group. *Vaccine*. 2017 Jan 5;35(2):395-402.

BACKGROUND: 4CMenB is immunogenic in infants and toddlers. We assessed persistence of human complement serum bactericidal activity (hSBA) following a fourth dose administered at 12, 18 or 24 months and characterised the antibody response to a fifth dose administered at 4 years of age.

METHODS: A phase 3, open label, multi-centre extension to a randomised controlled trial conducted in four countries (number of centres): Czech Republic (nineteen), Italy (four), Spain (four) and the United Kingdom (four). Four-year-old children who were either 4CMenB-naïve or had previously received a variety of 3-dose infant priming schedules and a booster vaccine as toddlers (follow-on group) were recruited. Venous blood samples were obtained to determine hSBA against four reference strains; acting as targets to assess immunity to each of the vaccine antigens, NadA (5/99), fHbp (H44/76), PorA (NZ98/254), and NHBA (M10713) at baseline (prior to vaccination, all participants) and one month following a dose of 4CMenB for all vaccine-naïve and follow-on participants primed with the 2, 3, 4 schedule, and a third of follow-on participants primed with a 2, 4, 6 month schedule.

RESULTS: At baseline (prior to vaccination), the proportion of participants (n=468) with hSBA titers ≥ 5 was similar across all follow-on groups: 89-100% against 5/99; 12-35% for H44/76; 8-12% for NZ98/254 and 53-80% for M10713 compared with 5%, 0%, 0%; and 60% respectively, for the vaccine-naïve controls (n=206). Following a dose of 4CMenB at 4 years of age, this increased to 100% (5/99), 97-100% (H44/76), 80-95% (NZ98/254) and 84-100% (M10713) (n=210), compared with 89%, 70%, 24%, and 76% respectively for vaccine-naïve controls (n=192).

CONCLUSION: Waning of protective antibodies occurred 12-36 months after toddler booster regardless of age at boost. This was least marked against target strains 5/99 and M10713. A robust memory response occurred after a booster dose given at 4 years of age.

Biomarkers in paediatric infectious diseases

1.5 A host-protein based assay to differentiate between bacterial and viral infections in preschool children (OPPORTUNITY): a double-blind, multicentre, validation study. van Houten CB, de Groot JA, Klein A, Srugo I, Chistyakov I, de Waal W, Meijssen CB, Avis W, Wolfs TF, Shachor-Meyouhas Y, Stein M, Sanders EA, Bont LJ. *Lancet Infect Dis*. 2017 Apr;17(4):431-440.

BACKGROUND: A physician is frequently unable to distinguish bacterial from viral infections. ImmunoXpert is a novel assay combining three proteins: tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), interferon gamma induced protein-10 (IP-10), and C-reactive protein (CRP). We aimed to externally validate the diagnostic accuracy of this assay in differentiating between bacterial and viral infections and to compare this test with commonly used biomarkers.

METHODS: In this prospective, double-blind, international, multicentre study, we recruited children aged 2-60 months with lower respiratory tract infection or clinical presentation of fever without source at four hospitals in the Netherlands and two hospitals in Israel. A panel of three experienced paediatricians adjudicated a reference standard diagnosis for all patients (ie, bacterial or viral infection) using all available clinical and laboratory information, including a 28-day follow-up assessment. The panel was masked to the assay results. We identified majority diagnosis when two of three panel members agreed on a diagnosis and unanimous diagnosis when all three panel members agreed on the diagnosis. We

calculated the diagnostic performance (ie, sensitivity, specificity, positive predictive value, and negative predictive value) of the index test in differentiating between bacterial (index test positive) and viral (index test negative) infection by comparing the test classification with the reference standard outcome.

FINDINGS: Between Oct 16, 2013 and March 1, 2015, we recruited 777 children, of whom 577 (mean age 21 months, 56% male) were assessed. The majority of the panel diagnosed 71 cases as bacterial infections and 435 as viral infections. In another 71 patients there was an inconclusive panel diagnosis. The assay distinguished bacterial from viral infections with a sensitivity of 86.7% (95% CI 75.8-93.1), a specificity of 91.1% (87.9-93.6), a positive predictive value of 60.5% (49.9-70.1), and a negative predictive value of 97.8% (95.6-98.9). In the more clear cases with unanimous panel diagnosis (n=354), sensitivity was 87.8% (74.5-94.7), specificity 93.0% (89.6-95.3), positive predictive value 62.1% (49.2-73.4), and negative predictive value 98.3% (96.1-99.3).

INTERPRETATION: This external validation study shows the diagnostic value of a three-host protein-based assay to differentiate between bacterial and viral infections in children with lower respiratory tract infection or fever without source. This diagnostic based on CRP, TRAIL, and IP-10 has the potential to reduce antibiotic misuse in young children.

1.6 Sensitivity and Specificity of Soluble Triggering Receptor Expressed on Myeloid Cells-1, Midregional Proatrial Natriuretic Peptide and Midregional Proadrenomedullin for Distinguishing Etiology and to Assess Severity in Community-Acquired Pneumonia. Esposito S, Di Gangi M, Cardinale F, Baraldi E, Corsini I, Da Dalt L, Tovo PA, Correra A, Villani A, Sacco O, Tenero L, Dones P, Gambino M, Zampiero A, Principi N; Ita-CAP Study Group. *PLoS One*. 2016 Nov 15;11(11):e0163262.

STUDY DESIGN: This study aimed to evaluate the diagnostic accuracy of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), midregional proatrial natriuretic peptide (MR-proANP) and midregional proadrenomedullin (MR-proADM) to distinguish bacterial from viral community-acquired pneumonia (CAP) and to identify severe cases in children hospitalized for radiologically confirmed CAP. Index test results were compared with those derived from routine diagnostic tests, i.e., white blood cell (WBC) counts, neutrophil percentages, and serum C-reactive protein (CRP) and procalcitonin (PCT) levels.

METHODS: This prospective, multicenter study was carried out in the most important children's hospitals (n = 11) in Italy and 433 otherwise healthy children hospitalized for radiologically confirmed CAP were enrolled. Among cases for whom etiology could be determined, CAP was ascribed to bacteria in 235 (54.3%) children and to one or more viruses in 111 (25.6%) children. A total of 312 (72.2%) children had severe disease.

RESULTS: CRP and PCT had the best performances for both bacterial and viral CAP identification. The cut-off values with the highest combined sensitivity and specificity for the identification of bacterial and viral infections using CRP were ≥ 7.98 mg/L and ≤ 7.5 mg/L, respectively. When PCT was considered, the cut-off values with the highest combined sensitivity and specificity were ≥ 0.188 ng/mL for bacterial CAP and ≤ 0.07 ng/mL for viral CAP. For the identification of severe cases, the best results were obtained with evaluations of PCT and MR-proANP. However, in both cases, the biomarker cut-off with the highest combined sensitivity and specificity (≥ 0.093 ng/mL for PCT and ≥ 33.8 pmol/L for proANP) had a relatively good sensitivity (higher than 70%) but a limited specificity (of approximately 55%).

CONCLUSIONS: This study indicates that in children with CAP, sTREM-1, MR-proANP, and MR-proADM blood levels have poor abilities to differentiate bacterial from viral diseases or to identify severe cases, highlighting that PCT maintains the main role at this regard.

FUNDING: MeMed Diagnostics.

Infection & inflammation

1.7 Thymosin $\alpha 1$ represents a potential potent single-molecule-based therapy for cystic fibrosis. Romani L, Oikonomou V, Moretti S, Iannitti RG, D'Adamo MC, Villella VR, Pariano M, Sforza L, Borghi M, Bellet MM, Fallarino F, Pallotta MT, Servillo G, Ferrari E, Puccetti P, Kroemer G, Pessia M, Maiuri L, Goldstein AL, Garaci E. *Nat Med*. 2017 Apr 10. doi: 10.1038/nm.4305

Cystic fibrosis (CF) is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) that compromise its chloride channel activity. The most common mutation, p.Phe508del, results in the production of a misfolded CFTR protein, which has residual channel activity but is prematurely degraded. Because of the inherent complexity of the pathogenetic mechanisms

involved in CF, which include impaired chloride permeability and persistent lung inflammation, a multidrug approach is required for efficacious CF therapy. To date, no individual drug with pleiotropic beneficial effects is available for CF. Here we report on the ability of thymosin alpha 1 ($T\alpha 1$)-a naturally occurring polypeptide with an excellent safety profile in the clinic when used as an adjuvant or an immunotherapeutic agent-to rectify the multiple tissue defects in mice with CF as well as in cells from subjects with the p.Phe508del mutation. $T\alpha 1$ displayed two combined properties that favorably opposed CF symptomatology: it reduced inflammation and increased CFTR maturation, stability and activity. By virtue of this two-pronged action, $T\alpha 1$ has strong potential to be an efficacious single-molecule-based therapeutic agent for CF.

1.8 IL-1 receptor antagonist ameliorates inflammasome-dependent inflammation in murine and human cystic fibrosis. Iannitti RG, Napolioni V, Oikonomou V, De Luca A, Galosi C, Pariano M, Massi-Benedetti C, Borghi M, Puccetti M, Lucidi V, Colombo C, Fiscarelli E, Lass-Flörl C, Majo F, Cariani L, Russo M, Porcaro L, Ricciotti G, Ellemunter H, Ratclif L, De Benedictis FM, Talesa VN, Dinarello CA, van de Veerdonk FL, Romani L. *Nat Commun.* 2016 Mar 14;7:10791. doi: 10.1038/ncomms10791.

Dysregulated inflammasome activation contributes to respiratory infections and pathologic airway inflammation. Through basic and translational approaches involving murine models and human genetic epidemiology, we show here the importance of the different inflammasomes in regulating inflammatory responses in mice and humans with cystic fibrosis (CF), a life-threatening disorder of the lungs and digestive system. While both contributing to pathogen clearance, NLRP3 more than NLRC4 contributes to deleterious inflammatory responses in CF and correlates with defective NLRC4-dependent IL-1Ra production. Disease susceptibility in mice and microbial colonization in humans occurs in conditions of genetic deficiency of NLRC4 or IL-1Ra and can be rescued by administration of the recombinant IL-1Ra, anakinra. These results indicate that pathogenic NLRP3 activity in CF could be negatively regulated by IL-1Ra and provide a proof-of-concept evidence that inflammasomes are potential targets to limit the pathological consequences of microbial colonization in CF.

Viral hepatitis

2.1 The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet*. 2016 Sep 10;388(10049):1081-8.

BACKGROUND: With recent improvements in vaccines and treatments against viral hepatitis, an improved understanding of the burden of viral hepatitis is needed to inform global intervention strategies. We used data from the Global Burden of Disease (GBD) Study to estimate morbidity and mortality for acute viral hepatitis, and for cirrhosis and liver cancer caused by viral hepatitis, by age, sex, and country from 1990 to 2013.

METHODS: We estimated mortality using natural history models for acute hepatitis infections and GBD's cause-of-death ensemble model for cirrhosis and liver cancer. We used meta-regression to estimate total cirrhosis and total liver cancer prevalence, as well as the proportion of cirrhosis and liver cancer attributable to each cause. We then estimated cause-specific prevalence as the product of the total prevalence and the proportion attributable to a specific cause. Disability-adjusted life-years (DALYs) were calculated as the sum of years of life lost (YLLs) and years lived with disability (YLDs).

FINDINGS: Between 1990 and 2013, global viral hepatitis deaths increased from 0.89 million (95% uncertainty interval [UI] 0.86-0.94) to 1.45 million (1.38-1.54); YLLs from 31.0 million (29.6-32.6) to 41.6 million (39.1-44.7); YLDs from 0.65 million (0.45-0.89) to 0.87 million (0.61-1.18); and DALYs from 31.7 million (30.2-33.3) to 42.5 million (39.9-45.6). In 2013, viral hepatitis was the seventh (95% UI seventh to eighth) leading cause of death worldwide, compared with tenth (tenth to 12th) in 1990.

INTERPRETATION: Viral hepatitis is a leading cause of death and disability worldwide. Unlike most communicable diseases, the absolute burden and relative rank of viral hepatitis increased between 1990 and 2013. The enormous health loss attributable to viral hepatitis, and the availability of effective vaccines and treatments, suggests an important opportunity to improve public health.

FUNDING: Bill & Melinda Gates Foundation.

2.2 Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. *N Engl J Med*. 2016 Jun 16;374(24):2324-34.

BACKGROUND: Few data are available regarding the use of tenofovir disoproxil fumarate (TDF) during pregnancy for the prevention of mother-to-child transmission of hepatitis B virus (HBV).

METHODS: In this trial, we included 200 mothers who were positive for hepatitis B e antigen (HBeAg) and who had an HBV DNA level higher than 200,000 IU per milliliter. Participants were randomly assigned, in a 1:1 ratio, to receive usual care without antiviral therapy or to receive TDF (at an oral dose of 300 mg per day) from 30 to 32 weeks of gestation until postpartum week 4; the participants were followed until postpartum week 28. All the infants received immunoprophylaxis. The primary outcomes were the rates of mother-to-child transmission and birth defects. The secondary outcomes were the safety of TDF, the percentage of mothers with an HBV DNA level of less than 200,000 IU per milliliter at delivery, and loss or seroconversion of HBeAg or hepatitis B surface antigen at postpartum week 28.

RESULTS: At delivery, 68% of the mothers in the TDF group (66 of 97 women), as compared with 2% in the control group (2 of 100), had an HBV DNA level of less than 200,000 IU per milliliter ($P < 0.001$). At postpartum week 28, the rate of mother-to-child transmission was significantly lower in the TDF group than in the control group, both in the intention-to-treat analysis (with transmission of virus to 5% of the infants [5 of 97] vs. 18% [18 of 100], $P = 0.007$) and the per-protocol analysis (with transmission of virus to 0 vs. 7% [6 of 88], $P = 0.01$). The maternal and infant safety profiles were similar in the TDF group and the control group, including birth-defect rates (2% [2 of 95 infants] and 1% [1 of 88], respectively; $P = 1.00$), although more mothers in the TDF group had an increase in the creatine kinase level. After the discontinuation of TDF, alanine aminotransferase elevations above the normal range occurred more frequently in mothers in the TDF group than in those in the control group (45% [44 of 97 women] vs. 30% [30 of 100], $P = 0.03$). The maternal HBV serologic outcomes did not differ significantly between the groups.

CONCLUSIONS: In a cohort of HBeAg-positive mothers with an HBV DNA level of more than 200,000 IU per milliliter during the third trimester, the rate of mother-to-child transmission was lower among those who received TDF therapy than among those who received usual care without antiviral therapy. (Funded by Gilead Sciences; ClinicalTrials.gov number, NCT01488526.)

Malaria

2.3 Antimalarial Activity of KAF156 in Falciparum and Vivax Malaria. *N Engl J Med.* 2016 Sep 22;375(12):1152-60

Background KAF156 belongs to a new class of antimalarial agents (imidazolopiperazines), with activity against asexual and sexual blood stages and the preerythrocytic liver stages of malarial parasites. **Methods** We conducted a phase 2, open-label, two-part study at five centers in Thailand and Vietnam to assess the antimalarial efficacy, safety, and pharmacokinetic profile of KAF156 in adults with acute *Plasmodium vivax* or *P. falciparum* malaria. Assessment of parasite clearance rates in cohorts of patients with vivax or falciparum malaria who were treated with multiple doses (400 mg once daily for 3 days) was followed by assessment of the cure rate at 28 days in a separate cohort of patients with falciparum malaria who received a single dose (800 mg). **Results** Median parasite clearance times were 45 hours (interquartile range, 42 to 48) in 10 patients with falciparum malaria and 24 hours (interquartile range, 20 to 30) in 10 patients with vivax malaria after treatment with the multiple-dose regimen and 49 hours (interquartile range, 42 to 54) in 21 patients with falciparum malaria after treatment with the single dose. Among the 21 patients who received the single dose and were followed for 28 days, 1 had reinfection and 7 had recrudescence infections (cure rate, 67%; 95% credible interval, 46 to 84). The mean (\pm SD) KAF156 terminal elimination half-life was 44.1 \pm 8.9 hours. There were no serious adverse events in this small study. The most common adverse events included sinus bradycardia, thrombocytopenia, hypokalemia, anemia, and hyperbilirubinemia. Vomiting of grade 2 or higher occurred in 2 patients, 1 of whom discontinued treatment because of repeated vomiting after receiving the single 800-mg dose. More adverse events were reported in the single-dose cohort, which had longer follow-up, than in the multiple-dose cohorts. **Conclusions** KAF156 showed antimalarial activity without evident safety concerns in a small number of adults with uncomplicated *P. vivax* or *P. falciparum* malaria. (Funded by Novartis and others; ClinicalTrials.gov number, NCT01753323 .).

2.4 The spread of artemisinin-resistant *Plasmodium falciparum* in the Greater Mekong Subregion: a molecular epidemiology observational study. *Lancet Infect Dis.* 2017 Feb 1. pii: S1473-3099(17)30048-8.

BACKGROUND: Evidence suggests that the PfKelch13 mutations that confer artemisinin resistance in falciparum malaria have multiple independent origins across the Greater Mekong subregion, which has motivated a regional malaria elimination agenda. We aimed to use molecular genotyping to assess antimalarial drug resistance selection and spread in the Greater Mekong subregion.

METHODS: In this observational study, we tested *Plasmodium falciparum* isolates from Myanmar, northeastern Thailand, southern Laos, and western Cambodia for PfKelch13 mutations and for Pfplasmepsin2 gene amplification (indicating piperaquine resistance). We collected blood spots from patients with microscopy or rapid test confirmed uncomplicated falciparum malaria. We used microsatellite genotyping to assess genetic relatedness.

FINDINGS: As part of studies on the epidemiology of artemisinin-resistant malaria between Jan 1, 2008, and Dec 31, 2015, we collected 434 isolates. In 2014-15, a single long PfKelch13 C580Y haplotype (-50 to +31.5 kb) lineage, which emerged in western Cambodia in 2008, was detected in 65 of 88 isolates from northeastern Thailand, 86 of 111 isolates from southern Laos, and 14 of 14 isolates from western Cambodia, signifying a hard transnational selective sweep. Pfplasmepsin2 amplification occurred only within this lineage, and by 2015 these closely related parasites were found in ten of the 14 isolates from Cambodia and 15 of 15 isolates from northeastern Thailand. C580Y mutated parasites from Myanmar had a different genetic origin.

INTERPRETATION: Our results suggest that the dominant artemisinin-resistant *P. falciparum* C580Y lineage probably arose in western Cambodia and then spread to Thailand and Laos, outcompeting other parasites and acquiring piperaquine resistance. The emergence and spread of fit artemisinin-resistant *P. falciparum* parasite lineages, which then acquire partner drug resistance across the Greater Mekong subregion, threatens regional malaria control and elimination goals. Elimination of falciparum malaria from this region should be accelerated while available antimalarial drugs still remain effective.

FUNDING: The Wellcome Trust and the Bill and Melinda Gates Foundation.

Tuberculosis

2.5 Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. *Lancet*. 2016 Mar 19;387(10024):1187-97.

BACKGROUND: HIV-associated tuberculosis is difficult to diagnose and results in high mortality. Frequent extra-pulmonary presentation, inability to obtain sputum, and paucibacillary samples limits the usefulness of nucleic-acid amplification tests and smear microscopy. We therefore assessed a urine-based, lateral flow, point-of-care, lipoarabinomannan assay (LAM) and the effect of a LAM-guided anti-tuberculosis treatment initiation strategy on mortality.

METHODS: We did a pragmatic, randomised, parallel-group, multicentre trial in ten hospitals in Africa--four in South Africa, two in Tanzania, two in Zambia, and two in Zimbabwe. Eligible patients were HIV-positive adults aged at least 18 years with at least one of the following symptoms of tuberculosis (fever, cough, night sweats, or self-reported weightloss) and illness severity necessitating admission to hospital. Exclusion criteria included receipt of any anti-tuberculosis medicine in the 60 days before enrolment. We randomly assigned patients (1:1) to either LAM plus routine diagnostic tests for tuberculosis (smear microscopy, Xpert-MTB/RIF, and culture; LAM group) or routine diagnostic tests alone (no LAM group) using computer-generated allocation lists in blocks of ten. All patients were asked to provide a urine sample of at least 30 mL at enrolment, and trained research nurses did the LAM test in patients allocated to this group using the Alere Determine tuberculosis LAM Ag lateral flow strip test (Alere, USA) at the bedside on enrolment. On the basis of a positive test result, the nurses made a recommendation for initiating anti-tuberculosis treatment. The attending physician made an independent decision about whether to start treatment or not. Neither patients nor health-care workers were masked to group allocation and test results. The primary endpoint was 8-week all-cause mortality assessed in the modified intention-to-treat population (those who received their allocated intervention). This trial is registered with ClinicalTrials.gov, number NCT01770730.

FINDINGS: Between Jan 1, 2013, and Oct 2, 2014, we screened 8728 patients and randomly assigned 2659 to treatment (1336 to LAM, 1323 to no LAM). 108 patients did not receive their allocated treatment, mainly because they did not meet the inclusion criteria, and 23 were excluded from analysis, leaving 2528 in the final modified intention-to-treat analysis (1257 in the LAM group, 1271 in the no LAM group).

Overall all-cause 8-week mortality occurred in 578 (23%) patients, 261 (21%) in LAM and 317 (25%) in no LAM, an absolute reduction of 4% (95% CI 1-7). The risk ratio adjusted for country was 0.83 (95% CI 0.73-0.96), $p=0.012$, with a relative risk reduction of 17% (95% CI 4-28). With the time-to-event analysis, there were 159 deaths per 100 person-years in LAM and 196 per 100 person-years in no LAM (hazard ratio adjusted for country 0.82 [95% CI 0.70-0.96], $p=0.015$). No adverse events were associated with LAM testing.

INTERPRETATION: Bedside LAM-guided initiation of anti-tuberculosis treatment in HIV-positive hospital inpatients with suspected tuberculosis was associated with reduced 8-week mortality. The implementation of LAM testing is likely to offer the greatest benefit in hospitals where diagnostic resources are most scarce and where patients present with severe illness, advanced immunosuppression, and an inability to self-expectorate sputum.

FUNDING: European Developing Clinical Trials Partnership, the South African Medical Research Council, and the South African National Research Foundation.

2.6 Transmission of Extensively Drug-Resistant Tuberculosis in South Africa. *N Engl J Med*. 2017 Jan 19;376(3):243-253.

Background Drug-resistant tuberculosis threatens recent gains in the treatment of tuberculosis and human immunodeficiency virus (HIV) infection worldwide. A widespread epidemic of extensively drug-resistant (XDR) tuberculosis is occurring in South Africa, where cases have increased substantially since 2002. The factors driving this rapid increase have not been fully elucidated, but such knowledge is needed to guide public health interventions. **Methods** We conducted a prospective study involving 404 participants in KwaZulu-Natal Province, South Africa, with a diagnosis of XDR tuberculosis between 2011 and 2014. Interviews and medical-record reviews were used to elicit information on the participants' history of tuberculosis and HIV infection, hospitalizations, and social networks. *Mycobacterium tuberculosis* isolates underwent insertion sequence (IS)6110 restriction-fragment-length polymorphism analysis, targeted gene sequencing, and whole-genome sequencing. We used clinical and genotypic case definitions to calculate the proportion of cases of XDR tuberculosis that were due to inadequate treatment of multidrug-resistant (MDR) tuberculosis (i.e., acquired resistance) versus those that were due

to transmission (i.e., transmitted resistance). We used social-network analysis to identify community and hospital locations of transmission. Results Of the 404 participants, 311 (77%) had HIV infection; the median CD4+ count was 340 cells per cubic millimeter (interquartile range, 117 to 431). A total of 280 participants (69%) had never received treatment for MDR tuberculosis. Genotypic analysis in 386 participants revealed that 323 (84%) belonged to 1 of 31 clusters. Clusters ranged from 2 to 14 participants, except for 1 large cluster of 212 participants (55%) with a LAM4/KZN strain. Person-to-person or hospital-based epidemiologic links were identified in 123 of 404 participants (30%).

Conclusions The majority of cases of XDR tuberculosis in KwaZulu-Natal, South Africa, an area with a high tuberculosis burden, were probably due to transmission rather than to inadequate treatment of MDR tuberculosis. These data suggest that control of the epidemic of drug-resistant tuberculosis requires an increased focus on interrupting transmission. (Funded by the National Institute of Allergy and Infectious Diseases and others.).

Enteric fever

2.7 Gatifloxacin versus ceftriaxone for uncomplicated enteric fever in Nepal: an open-label, two-centre, randomised controlled trial. *Lancet Infect Dis.* 2016 May;16(5):535-45.

BACKGROUND: Because treatment with third-generation cephalosporins is associated with slow clinical improvement and high relapse burden for enteric fever, whereas the fluoroquinolone gatifloxacin is associated with rapid fever clearance and low relapse burden, we postulated that gatifloxacin would be superior to the cephalosporin ceftriaxone in treating enteric fever.

METHODS: We did an open-label, randomised, controlled, superiority trial at two hospitals in the Kathmandu valley, Nepal. Eligible participants were children (aged 2-13 years) and adult (aged 14-45 years) with criteria for suspected enteric fever (body temperature $\geq 38.0^{\circ}\text{C}$ for ≥ 4 days without a focus of infection). We randomly assigned eligible patients (1:1) without stratification to 7 days of either oral gatifloxacin (10 mg/kg per day) or intravenous ceftriaxone (60 mg/kg up to 2 g per day for patients aged 2-13 years, or 2 g per day for patients aged ≥ 14 years). The randomisation list was computer-generated using blocks of four and six. The primary outcome was a composite of treatment failure, defined as the occurrence of at least one of the following: fever clearance time of more than 7 days after treatment initiation; the need for rescue treatment on day 8; microbiological failure (ie, blood cultures positive for *Salmonella enterica* serotype Typhi, or Paratyphi A, B, or C) on day 8; or relapse or disease-related complications within 28 days of treatment initiation. We did the analyses in the modified intention-to-treat population, and subpopulations with either confirmed blood-culture positivity, or blood-culture negativity. The trial was powered to detect an increase of 20% in the risk of failure. This trial was registered at ClinicalTrials.gov, number NCT01421693, and is now closed.

FINDINGS: Between Sept 18, 2011, and July 14, 2014, we screened 725 patients for eligibility. On July 14, 2014, the trial was stopped early by the data safety and monitoring board because S Typhi strains with high-level resistance to ciprofloxacin and gatifloxacin had emerged. At this point, 239 were in the modified intention-to-treat population (120 assigned to gatifloxacin, 119 to ceftriaxone). 18 (15%) patients who received gatifloxacin had treatment failure, compared with 19 (16%) who received ceftriaxone (hazard ratio [HR] 1.04 [95% CI 0.55-1.98]; $p=0.91$). In the culture-confirmed population, 16 (26%) of 62 patients who received gatifloxacin failed treatment, compared with four (7%) of 54 who received ceftriaxone (HR 0.24 [95% CI 0.08-0.73]; $p=0.01$). Treatment failure was associated with the emergence of S Typhi exhibiting resistance against fluoroquinolones, requiring the trial to be stopped. By contrast, in patients with a negative blood culture, only two (3%) of 58 who received gatifloxacin failed treatment versus 15 (23%) of 65 who received ceftriaxone (HR 7.50 [95% CI 1.71-32.80]; $p=0.01$). A similar number of non-serious adverse events occurred in each treatment group, and no serious events were reported.

INTERPRETATION: Our results suggest that fluoroquinolones should no longer be used for treatment of enteric fever in Nepal. Additionally, under our study conditions, ceftriaxone was suboptimum in a high proportion of patients with culture-negative enteric fever. Since antimicrobials, specifically fluoroquinolones, are one of the only routinely used control measures for enteric fever, the assessment of novel diagnostics, new treatment options, and use of existing vaccines and development of next-generation vaccines are now a high priority.

FUNDING: Wellcome Trust and Li Ka Shing Foundation.

2.8 A novel ciprofloxacin-resistant subclade of H58 Salmonella Typhi is associated with fluoroquinolone treatment failure. *Elife*. 2016 Mar 11;5:e14003

The interplay between bacterial antimicrobial susceptibility, phylogenetics and patient outcome is poorly understood. During a typhoid clinical treatment trial in Nepal, we observed several treatment failures and isolated highly fluoroquinolone-resistant Salmonella Typhi (S. Typhi). Seventy-eight S. Typhi isolates were genome sequenced and clinical observations, treatment failures and fever clearance times (FCTs) were stratified by lineage. Most fluoroquinolone-resistant S. Typhi belonged to a specific H58 subclade. Treatment failure with S. Typhi-H58 was significantly less frequent with ceftriaxone (3/31; 9.7%) than gatifloxacin (15/34; 44.1%)(Hazard Ratio 0.19, $p=0.002$). Further, for gatifloxacin-treated patients, those infected with fluoroquinolone-resistant organisms had significantly higher median FCTs (8.2 days) than those infected with susceptible (2.96) or intermediately resistant organisms (4.01)(p S. Typhi clade internationally, but there are no data regarding disease outcome with this organism. We report an emergent new subclade of S. Typhi-H58 that is associated with fluoroquinolone treatment failure.

Antimicrobial Stewardship

3.1 Interventions to improve antibiotic prescribing practices for hospital inpatients.

Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2017. p. CD003543

BACKGROUND: Antibiotic resistance is a major public health problem. Infections caused by multidrug-resistant bacteria are associated with prolonged hospital stay and death compared with infections caused by susceptible bacteria. Appropriate antibiotic use in hospitals should ensure effective treatment of patients with infection and reduce unnecessary prescriptions. We updated this systematic review to evaluate the impact of interventions to improve antibiotic prescribing to hospital inpatients.

OBJECTIVES: To estimate the effectiveness and safety of interventions to improve antibiotic prescribing to hospital inpatients and to investigate the effect of two intervention functions: restriction and enablement.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library), MEDLINE, and Embase. We searched for additional studies using the bibliographies of included articles and personal files. The last search from which records were evaluated and any studies identified incorporated into the review was January 2015.

SELECTION CRITERIA: We included randomised controlled trials (RCTs) and non-randomised studies (NRS). We included three non-randomised study designs to measure behavioural and clinical outcomes and analyse variation in the effects: non-randomised trials (NRT), controlled before-after (CBA) studies and interrupted time series (ITS) studies. For this update we also included three additional NRS designs (case control, cohort, and qualitative studies) to identify unintended consequences. Interventions included any professional or structural interventions as defined by the Cochrane Effective Practice and Organisation of Care Group. We defined restriction as 'using rules to reduce the opportunity to engage in the target behaviour (or increase the target behaviour by reducing the opportunity to engage in competing behaviours)'. We defined enablement as 'increasing means/reducing barriers to increase capability or opportunity'. The main comparison was between intervention and no intervention.

DATA COLLECTION AND ANALYSIS: Two review authors extracted data and assessed study risk of bias. We performed meta-analysis and meta-regression of RCTs and meta-regression of ITS studies. We classified behaviour change functions for all interventions in the review, including those studies in the previously published versions. We analysed dichotomous data with a risk difference (RD). We assessed certainty of evidence with GRADE criteria.

MAIN RESULTS: This review includes 221 studies (58 RCTs, and 163 NRS). Most studies were from North America (96) or Europe (87). The remaining studies were from Asia (19), South America (8), Australia (8), and the East Asia (3). Although 62% of RCTs were at a high risk of bias, the results for the main review outcomes were similar when we restricted the analysis to studies at low risk of bias. More hospital inpatients were treated according to antibiotic prescribing policy with the intervention compared with no intervention based on 29 RCTs of predominantly enablement interventions (RD 15%, 95% confidence interval (CI) 14% to 16%; 23,394 participants; high-certainty evidence). This represents an increase from 43% to 58%. There were high levels of heterogeneity of effect size but the direction consistently favoured intervention. The duration of antibiotic treatment decreased by 1.95 days (95% CI 2.22 to 1.67; 14 RCTs; 3318 participants; high-certainty evidence) from 11.0 days. Information from non-randomised studies showed interventions to be associated with improvement in prescribing according to antibiotic policy in routine clinical practice, with 70% of interventions being hospital-wide compared with 31% for RCTs. The risk of death was similar between intervention and control groups (11% in both arms), indicating that antibiotic use can likely be reduced without adversely affecting mortality (RD 0%, 95% CI -1% to 0%; 28 RCTs; 15,827 participants; moderate-certainty evidence). Antibiotic stewardship interventions probably reduce length of stay by 1.12 days (95% CI 0.7 to 1.54 days; 15 RCTs; 3834 participants; moderate-certainty evidence). One RCT and six NRS raised concerns that restrictive interventions may lead to delay in treatment and negative professional culture because of breakdown in communication and trust between infection specialists and clinical teams (low-certainty evidence). Both enablement and restriction were independently associated with increased compliance with antibiotic policies, and enablement enhanced the effect of restrictive interventions (high-certainty evidence). Enabling interventions that included feedback were probably more effective than those that did not (moderate-certainty evidence). There was very low-certainty evidence about the effect of the interventions on reducing *Clostridium difficile* infections (median -48.6%, interquartile range -80.7% to -19.2%; 7 studies). This was also the case for resistant gram-negative bacteria (median -12.9%, interquartile range -

35.3% to 25.2%; 11 studies) and resistant gram-positive bacteria (median -19.3%, interquartile range -50.1% to +23.1%; 9 studies). There was too much variance in microbial outcomes to reliably assess the effect of change in antibiotic use. Heterogeneity of intervention effect on prescribing outcomes. We analysed effect modifiers in 29 RCTs and 91 ITS studies. Enablement and restriction were independently associated with a larger effect size (high-certainty evidence). Feedback was included in 4 (17%) of 23 RCTs and 20 (47%) of 43 ITS studies of enabling interventions and was associated with greater intervention effect. Enablement was included in 13 (45%) of 29 ITS studies with restrictive interventions and enhanced intervention effect.

AUTHORS' CONCLUSIONS: We found high-certainty evidence that interventions are effective in increasing compliance with antibiotic policy and reducing duration of antibiotic treatment. Lower use of antibiotics probably does not increase mortality and likely reduces length of stay. Additional trials comparing antibiotic stewardship with no intervention are unlikely to change our conclusions. Enablement consistently increased the effect of interventions, including those with a restrictive component. Although feedback further increased intervention effect, it was used in only a minority of enabling interventions. Interventions were successful in safely reducing unnecessary antibiotic use in hospitals, despite the fact that the majority did not use the most effective behaviour change techniques. Consequently, effective dissemination of our findings could have considerable health service and policy impact. Future research should instead focus on targeting treatment and assessing other measures of patient safety, assess different stewardship interventions, and explore the barriers and facilitators to implementation. More research is required on unintended consequences of restrictive interventions.

3.2 Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial. *Lancet Infect Dis.* 2016 Feb 29;16(7):819–27.

BACKGROUND: In critically ill patients, antibiotic therapy is of great importance but long duration of treatment is associated with the development of antimicrobial resistance. Procalcitonin is a marker used to guide antibacterial therapy and reduce its duration, but data about safety of this reduction are scarce. We assessed the efficacy and safety of procalcitonin-guided antibiotic treatment in patients in intensive care units (ICUs) in a health-care system with a comparatively low use of antibiotics.

METHODS: We did a prospective, multicentre, randomised, controlled, open-label intervention trial in 15 hospitals in the Netherlands. Critically ill patients aged at least 18 years, admitted to the ICU, and who received their first dose of antibiotics no longer than 24 h before inclusion in the study for an assumed or proven infection were eligible to participate. Patients who received antibiotics for presumed infection were randomly assigned (1:1), using a computer-generated list, and stratified (according to treatment centre, whether infection was acquired before or during ICU stay, and dependent on severity of infection [ie, sepsis, severe sepsis, or septic shock]) to receive either procalcitonin-guided or standard-of-care antibiotic discontinuation. Both patients and investigators were aware of group assignment. In the procalcitonin-guided group, a non-binding advice to discontinue antibiotics was provided if procalcitonin concentration had decreased by 80% or more of its peak value or to 0.5 µg/L or lower. In the standard-of-care group, patients were treated according to local antibiotic protocols. Primary endpoints were antibiotic daily defined doses and duration of antibiotic treatment. All analyses were done by intention to treat. Mortality analyses were completed for all patients (intention to treat) and for patients in whom antibiotics were stopped while being on the ICU (per-protocol analysis). Safety endpoints were reinstitution of antibiotics and recurrent inflammation measured by C-reactive protein concentrations and they were measured in the population adhering to the stopping rules (per-protocol analysis). The study is registered with ClinicalTrials.gov, number NCT01139489, and was completed in August, 2014.

FINDINGS: Between Sept 18, 2009, and July 1, 2013, 1575 of the 4507 patients assessed for eligibility were randomly assigned to the procalcitonin-guided group (761) or to standard-of-care (785). In 538 patients (71%) in the procalcitonin-guided group antibiotics were discontinued in the ICU. Median consumption of antibiotics was 7.5 daily defined doses (IQR 4.0–12.7) in the procalcitonin-guided group versus 9.3 daily defined doses (5.0–16.6) in the standard-of-care group (between-group absolute difference 2.69, 95% CI 1.26–4.12, $p < 0.0001$). Median duration of treatment was 5 days (3–9) in the procalcitonin-guided group and 7 days (4–11) in the standard-of-care group (between-group absolute difference 1.22, 0.65–1.78, $p < 0.0001$). Mortality at 28 days was 149 (20%) of 761 patients in the procalcitonin-guided group and 196 (25%) of 785 patients in the standard-of-care group (between-group absolute difference 5.4%, 95% CI 1.2–9.5, $p = 0.0122$) according to the intention-to-treat analysis, and 107 (20%) of 538 patients in the procalcitonin-guided group versus 121 (27%) of 457 patients in the standard-of-care group (between-group absolute difference 6.6%, 1.3–11.9, $p = 0.0154$) in the per-protocol analysis. 1-year mortality in the per-protocol analysis was 191 (36%) of 538 patients in the procalcitonin-guided

and 196 (43%) of 457 patients in the standard-of-care groups (between-group absolute difference 7.4, 1.3-13.8, $p=0.0188$).

INTERPRETATION: Procalcitonin guidance stimulates reduction of duration of treatment and daily defined doses in critically ill patients with a presumed bacterial infection. This reduction was associated with a significant decrease in mortality. Procalcitonin concentrations might help physicians in deciding whether or not the presumed infection is truly bacterial, leading to more adequate diagnosis and treatment, the cornerstones of antibiotic stewardship.

FUNDING: Thermo Fisher Scientific.

3.3 Impact of Infectious Diseases Consultation on Mortality of Cryptococcal infection in Patients without HIV. *Clin Infect Dis*; 2016 Dec 7;80(5):ciw786.

BACKGROUND: An infectious disease (ID) consultation is often obtained to treat patients with cryptococcosis due to the complex nature of the disease, but has never been demonstrated to impact outcomes.

METHODS: We assembled a retrospective cohort of 147 consecutive cases of cryptococcosis in patients without HIV. Patients who were diagnosed less than 24 hours prior to death were excluded. Survival analysis was performed with Cox regression with survival censored past 90 days.

RESULTS: The patients with an ID consult had a higher fungal burden but a lower 90-day mortality compared to patients without ID involvement (27% vs 45%, $p<0.001$), with an adjusted hazard ratio of not receiving an ID consult of 4.1 (95% CI: 2.2, 7.6). The ID consult group was more likely to receive an indicated lumbar puncture (86% vs 32%, $p<0.001$), and more likely to be treated with amphotericin B (AmB) (87% vs 24%, $p<0.001$) and flucytosine (5-FC) (57% vs 16%, $p<0.001$) when indicated. The duration of therapy with AmB (14 vs 11 days, $p=0.05$) and 5-FC (7.5 vs 1 days, $p<0.001$) was longer in the ID consult group.

DISCUSSION: Patients that received an ID consult were significantly less likely to die in the 90 days following diagnosis. Patients seen by ID physicians were more likely to be managed according to evidence based practice established by randomized controlled trials and published in IDSA guidelines. These data suggest that an ID consult should be an integral part of clinical care of patients with cryptococcosis.

Fungal Infections

3.4 Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. *N Engl J Med*. 2016 Feb 11;374(6):542–54.

BACKGROUND: Cryptococcal meningitis associated with human immunodeficiency virus (HIV) infection causes more than 600,000 deaths each year worldwide. Treatment has changed little in 20 years, and there are no imminent new anticytotoxic agents. The use of adjuvant glucocorticoids reduces mortality among patients with other forms of meningitis in some populations, but their use is untested in patients with cryptococcal meningitis.

METHODS: In this double-blind, randomized, placebo-controlled trial, we recruited adult patients with HIV-associated cryptococcal meningitis in Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi. All the patients received either dexamethasone or placebo for 6 weeks, along with combination antifungal therapy with amphotericin B and fluconazole.

RESULTS: The trial was stopped for safety reasons after the enrollment of 451 patients. Mortality was 47% in the dexamethasone group and 41% in the placebo group by 10 weeks (hazard ratio in the dexamethasone group, 1.11; 95% confidence interval [CI], 0.84 to 1.47; $P=0.45$) and 57% and 49%, respectively, by 6 months (hazard ratio, 1.18; 95% CI, 0.91 to 1.53; $P=0.20$). The percentage of patients with disability at 10 weeks was higher in the dexamethasone group than in the placebo group, with 13% versus 25% having a prespecified good outcome (odds ratio, 0.42; 95% CI, 0.25 to 0.69; $P<0.001$).

Clinical adverse events were more common in the dexamethasone group than in the placebo group (667 vs. 494 events, $P=0.01$), with more patients in the dexamethasone group having grade 3 or 4 infection (48 vs. 25 patients, $P=0.003$), renal events (22 vs. 7, $P=0.004$), and cardiac events (8 vs. 0, $P=0.004$). Fungal clearance in cerebrospinal fluid was slower in the dexamethasone group. Results were consistent across Asian and African sites.

CONCLUSIONS: Dexamethasone did not reduce mortality among patients with HIV-associated cryptococcal meningitis and was associated with more adverse events and disability than was placebo. (Funded by the United Kingdom Department for International Development and others through the Joint Global Health Trials program; Current Controlled Trials number, ISRCTN59144167.).

3.5 Increased incidence of co-infection in critically ill patients with influenza. *Intensive Care Med*; 2017 Jan 5;43(1):48–58.

BACKGROUND: Co-infection is frequently seen in critically ill patients with influenza, although the exact rate is unknown. We determined the rate of co-infection, the risk factors and the outcomes associated with co-infection in critically ill patients with influenza over a 7-year period in 148 Spanish intensive care units (ICUs).

METHODS: This was a prospective, observational, multicentre study. Influenza was diagnosed using the polymerase chain reaction. Co-infection had to be confirmed using standard bacteriological tests. The primary endpoint of this analysis was the presence of community-acquired co-infection, with secondary endpoints including ICU, 28-day and hospital mortality.

RESULTS: Of 2901 ICU patients diagnosed with influenza, 482 (16.6 %) had a co-infection. The proportion of cases of co-infection increased from 11.4 % (110/968) in 2009 to 23.4 % (80/342) in 2015 ($P < 0.001$). Compared with patients without co-infection, patients with co-infection were older [adjusted odds ratio (aOR) 1.1, 95 % confidence interval 1.1-1.2; $P < 0.001$] and were more frequently immunosuppressed due to existing HIV infection (aOR 2.6 [1.5-4.5]; $P < 0.001$) or preceding medication (aOR 1.4 [1.1-1.9]; $P = 0.03$). Co-infection was an independent risk factor for ICU mortality (aOR 1.4 [1.1-1.8]; $P < 0.02$), 28-day mortality (aOR 1.3 [1.1-1.7]; $P = 0.04$) and hospital mortality (aOR 1.9 [1.5-2.5]; $P < 0.001$).

CONCLUSIONS: Co-infection in critically ill patients with influenza has increased in recent years. In this Spanish cohort, age and immunosuppression were risk factors for co-infection, and co-infection was an independent risk factor for ICU, 28-day and hospital mortality.

3.6 Influenza-Associated Aspergillosis in Critically Ill Patients. *Am J Respir Crit Care Med*. 2017 Apr 7;rccm.201612-2540LE.

Currently no abstract available

3.7 Emergence of Multidrug-Resistant *Candida auris* on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses. *Clin Infect Dis*. 2017 Jan 15;64(2):134–40.

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.
