Infectious Diseases Research Review™

Making Education Easy

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## In this issue:



**Abbreviations used in this issue:**

**ACG** = American College of Gastroenterology; **CI** = confidence interval; **FMT** = faecal microbiota transplantation; **HBV** = hepatitis B virus; **ICU** = intensive care unit; **ITT** = intention-to-treat; **IVIG** = intravenous immunoglobulin; **WHO** = World Health Organisation.



# Welcome to the eleventh issue of Infectious Diseases Research Review.

First up we take a look at a study investigating the 7-year efficacy of the malaria candidate vaccine RTS,S/AS01 in young African children and discover an estimated rate of malaria averted of only 32%. The trial did, however, only evaluate a three-dose regimen, rather than the four-dose regimen recommended by the WHO. Next we review another vaccine study, this time a meningococcal B vaccine (4CmenB) used pre-licence at a US university experiencing an outbreak of *Neisseria meningitidis* B and discover that only 66% of participants receiving two doses of the vaccine exhibited protective human serum bactericidal antibody (hSBA) titres against the meningococcal B outbreak strain. Also in this issue we investigate a novel microbiome therapeutic for *Clostridium difficile* infection, procalcitonin guidance and antibiotic treatment in the critically ill, laninamivir octanoate post-exposure prophylaxis for influenza, isavuconazole for rare invasive fungal diseases, the incidence of herpes zoster over a 60-year period in Olmsted County, Minnesota, fosfomycin trometamol for gonococcal urethritis, hepatitis B virus core antibody transmission via immunoglobulin products and the American College of Gastroenterology clinical guidelines for acute diarrhoeal infections.

We hope you find our selection for Infectious Diseases Research Review stimulating reading and we welcome your feedback. Furthermore, if you have discovered or been involved with what you think is significant global research, please let us know and we will consider it for inclusion next time.

Kind Regards,

**Dr Tony Korman**

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## Seven-year efficacy of RTS,S/AS01 malaria vaccine among young African children

**Authors:** Olotu A et al.

**Summary:** This follow-up study looked at the incidence of clinical malaria (primary endpoint; temperature of ≥37.5°C and infection with *Plasmodium falciparum* of >2500 parasites per cubic millimetre) in African children 7 years after they had received three doses of either the RTS,S/AS01 candidate malaria vaccine (n = 223) or a rabies vaccine (control group; n = 224) at 5 to 17 months of age. The malaria exposure of each participant was estimated with the use of prevalence data of malaria among residents within a 1 km radius of the child's home. A total of 1002 episodes of clinical malaria occurred in RTS,S/AS01 recipients and 992 episodes in the control group over the 7-year follow-up period. In an ITT analysis, the vaccine efficacy was 4.4% (95% CI -17.0 to 21.9: p = 0.66), while in the per-protocol analysis it was 7.0% (95% CI -14.5 to 24.6: p = 0.52). The vaccine efficacy was found to significantly (p = 0.006) wane over time, including negative efficacy during the fifth year among children with higher-than-average exposure to malaria parasites (ITT: -43.5%; 95% CI -100.3 to -2.8 [p = 0.03]; per-protocol analysis: -56.8%; 95% CI -118.7 to -12.3 [p = 0.008]).

**Comment:** RTS,S/AS01 is a recombinant malaria vaccine against the pre-erythrocytic stage of the parasite in which regions of *P. falciparum* circumsporozoite protein are fused to hepatitis B surface antigen. A phase 2, randomised, double-blind trial of a three-dose regimen originally reported that 65 cases of malaria were averted by vaccination per 100 vaccinated children. This extended follow-up analysis during years 5-7 of surveillance estimated only 32 cases averted per 100 vaccinated children, including an excess of approximately 14 cases per 100 vaccinated children in the high exposure cohort. However, the trial evaluated only a three-dose regimen (rather than the four-dose regimen recommended by the WHO). Also, this site had lower rates of malaria transmission than many other sites and there was a high attrition of the original cohort over time. Reports of extended surveillance analysis from other study sites are awaited.

***Reference: N Engl J Med. 2016;374(26):2519-29***

Abstract

## Immunogenicity of a meningococcal B vaccine during a university outbreak

**Authors:** Basta NE et al.

**Summary:** These researchers quantified immune responses induced by 4CMenB, a multicomponent meningococcal serogroup B vaccine, used prior to licensure on the basis of special consideration by the FDA to respond to an outbreak of *Neisseria meningitidis* B at a US university in 2013. A seroprevalence survey among students was undertaken in order to assess vaccination status and collect serum specimens to quantify titres of serum bactericidal antibodies (SBA) with an assay that included human complement (hSBA). Seropositivity (defined as an hSBA titre of four or higher) for the outbreak strain was identified in 66.1% (95% CI 61.8-70.3) of 499 participants who received two doses of 4CMenB vaccine 10 weeks apart; however, the geometric mean titre was low at 7.6 (95% CI 6.7 to 8.5). Analysis of a random subgroup of 61 vaccinees who did not have a detectable protective response to the outbreak strain revealed 86.9% (95% CI 75.8-94.2) seropositive for the 44/76-SL strain; geometric mean titre of 17.4 (95% CI 13.0-23.2). Seropositivity to the 5/99 strain was seen in all vaccinees (100%; 95% CI 94.1-100) and the geometric mean titre was higher (256.3; 95% CI 187.3-350.7). There was a moderate correlation between the outbreak strain and the response to the 44/76-SL strain (Pearson's correlation 0.64; $p < 0.001$) but this was not seen with the response to the 5/99 strain (Pearson's correlation -0.06; $p = 0.43$). No cases of meningococcal disease caused by *N. meningitidis* B were reported among vaccinated students.

**Comment:** Quadrivalent meningococcal vaccines against serogroups A, C, Y and W-135 are now available. However, vaccine development against meningococcus serogroup B has been challenging. Studies of 4CMenB suggested that the vaccine is immunogenic against vaccine reference strains after two doses in young adults. There was no previous assessment of the breadth of 4CMenB vaccine-induced immunity against diverse meningococcal B strains. The 4CMenB vaccine was used at a university experiencing a sustained outbreak. Only 66% of participants who received two doses of the 4CMenB vaccine had protective hSBA titres against a meningococcal B outbreak strain. Further evaluation of 4CMenB efficacy is needed because of the limitations in drawing inferences about protection from immunogenicity data alone. These findings raise the question of whether a third dose of 4CMenB vaccine might increase the proportion of seropositive responses against strains that were not perfectly matched to the vaccine.

***Reference: N Engl J Med. 2016;375(3):220-8***
Abstract

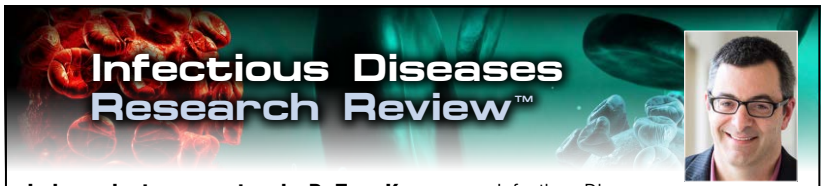
## A novel microbiome therapeutic increases gut microbial diversity and prevents recurrent *Clostridium difficile* infection

**Authors:** Khanna S et al.

**Summary:** This study investigated the safety and efficacy of bacterial spores for preventing recurrent *Clostridium difficile* infection (CDI). Spores from healthy donor stool specimens treated with ethanol to eliminate pathogens were fractionated and encapsulated for oral delivery as SER-109. Thirty patients (mean age 65 years; 67% female) who had responded to standard-of-care antibiotics received either SER-109 on two consecutive days (geometric mean dose $1.7 \times 10^9$ spores) or treatment on one day (geometric mean dose $1.1 \times 10^8$ spores). Twenty-six (86.7%) patients met the primary efficacy end point of absence of *C. difficile*-positive diarrhoea during an 8-week follow-up period. A further three patients with early, self-limiting *C. difficile*-positive diarrhoea did not require antibiotics and tested negative for *C. difficile* at 8 weeks; therefore, 96.7% (29 of 30) achieved clinical resolution. SER-109 exhibited a favorable safety profile.

**Comment:** CDI is associated with antibiotic-induced dysbiosis and repair of the microbiome via faecal microbiota transplantation (FMT) is an effective treatment of recurrent CDI. SER-109 is composed of approximately 50 species of Firmicute (gram-positive organisms, including Bacilli and Clostridia) spores derived from stool specimens from healthy donors. Efficacy of SER-109 has been demonstrated in rodent CDI models. In this open-label, single-arm, descending-dose study of oral SER-109, 29 of 30 patients with recurrent CDI achieved clinical resolution with a favorable safety profile. Clinical improvement occurred in parallel with restoration of a healthy diverse gut microbiome in recipients of SER-109. A larger placebo-controlled trial is underway that will better define the efficacy and safety profile of SER-109. Novel biologic agents such as oral SER-109 and nontoxigenic *C. difficile* strains may be highly efficacious options to restore the gut microbiome for treatment of CDI and may be safer and more practical than FMT.

***Reference: J Infect Dis. 2016;214(2):173-81***
Abstract




**Independent commentary by Dr Tony Korman**, an Infectious Diseases Physician and Clinical Microbiologist. He is Director, Monash Infectious Diseases, and Director, Microbiology at Monash Health, Victoria's largest healthcare network and theme leader, Infectious Diseases, Centre for Inflammatory Diseases, School of Clinical Sciences, Monash University.

## Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

**Authors:** de Jong E et al.

**Summary:** This unblinded, prospective, multicentre, randomised, controlled, open-label intervention trial in 15 ICUs in the Netherlands (a health-care system with a comparatively low use of antibiotics) assessed the efficacy and safety of procalcitonin-guided antibiotic therapy in critically ill patients >18 years of age who had received their first dose of antibiotics < 24 h prior to study inclusion for an assumed or proven infection between Sept 2009 and July 2013. Patients were randomised to receive either procalcitonin-guided (n = 761) or standard-of-care (n = 785) antibiotic discontinuation. Non-binding advice to discontinue antibiotics was provided to the procalcitonin-guided group if their procalcitonin concentration had decreased by 80% or more of its peak value or to ≤0·5 µg/L. Those in the standard-of-care group were treated according to local antibiotic protocols. Overall, 538 patients (71%) in the procalcitonin-guided group discontinued antibiotics in the ICU. The median consumption and duration of treatment was 7·5 daily defined doses (IQR 4·0-12·7) and 5 days (3-9) in the procalcitonin-guided group versus 9·3 daily defined doses (5·0-16·6) and 7 days (4-11) in the standard-of-care group; between-group absolute differences 2·69 (95% CI 1·26-4·12; p < 0·0001) and 1·22 (95% CI 0·65-1·78; p < 0·0001), respectively. According to ITT analysis, the 28-day mortality rate was 20% in the procalcitonin-guided group versus 25% in the standard-of-care group (between-group absolute difference 5·4% [95% CI 1·2-9·5; p = 0·0122]), while per-protocol analysis revealed rates of 20% and 27%, respectively (between-group absolute difference 6·6% [95% CI 1·3-11·9; p = 0·0154]). The 1-year mortality according to per-protocol analysis was 36% in the procalcitonin-guided group versus 43% in the standard-of-care group; between-group absolute difference 7·4% [95% CI 1·3-13·8; p = 0·0188]).

**Comment:** Procalcitonin has been advocated as a biomarker which could be used to assist the decision to discontinue antibiotics in critically ill patients. The previous PRORATA trial showed a significant reduction in antibiotic treatment duration, but a non-significant increased 60-day mortality in the procalcitonin arm raised safety concerns. The Stop Antibiotics on Procalcitonin guidance Study (SAPS) was conceived as a pragmatic trial with fewer exclusion criteria than previous trials (although immunosuppressed patients were not included), with mortality used as a safety endpoint. Procalcitonin monitoring coupled with a non-binding advice to consider stopping using antibiotics reduced duration of antibiotic treatment (7 to 5 days), even though physicians did not adhere to the stopping advice in more than half of the patients. The procalcitonin-guided group had a lower mortality than the standard-of-care group. Procalcitonin guidance can safely reduce antibiotic duration in critically ill patients, and analysis of cost-effectiveness of this approach is needed.

***Reference: Lancet Infect Dis. 2016;16(7):819-27***
Abstract

## Long-acting neuraminidase inhibitor laninamivir octanoate as post-exposure prophylaxis for influenza

**Authors:** Kashiwagi S et al.

**Summary:** This double-blind, multicentre, randomised, placebo-controlled study tested a single administration of inhaled laninamivir octanoate 40 mg or laninamivir octanoate 20 mg once daily for 2 days versus placebo for influenza post-exposure prophylaxis (n = 801). Clinical influenza occurred in 12.1% (32/265) of placebo, 4.5% (12/267) of laninamivir octanoate 40 mg (p = 0.001), and 4.5% (13/269) of laninamivir octanoate 20 mg recipients. Relative risk reductions were 62.8% and 63.1%. Adverse event incidences were similar across treatment groups.

**Comment:** A single dose of inhaled laninamivir octanoate, a long-acting neuraminidase inhibitor, has been demonstrated to be an effective treatment for influenza. Laninamivir octanoate administered daily for 2 or 3 days was also effective in post-exposure prophylaxis of influenza in household contacts. In this study, a single inhalation of 40 mg of laninamivir octanoate was effective for preventing the development of influenza in household contacts. However, the vast majority of the index patients were infected with influenza A(H3N2), with few patients with influenza A(H1N1) or influenza B virus. The randomisation and study analysis were all done on an individual basis, not for the whole family, and children aged <10 years were excluded. Also, viral resistance to laninamivir octanoate was not assessed. A single inhalation of laninamivir octanoate may have great advantages over drugs that require daily administration (e.g. oseltamivir). Further studies in high-risk populations, such as nursing home residents are awaited.

***Reference: Clin Infect Dis. 2016;63(3):330-7***
Abstract

## Isavuconazole treatment of cryptococcosis and dimorphic mycoses

**Authors:** Thompson GR 3rd et al.

**Summary:** The open-label, nonrandomised, phase III VITAL study (n = 38) examined the efficacy and safety of a novel, broad-spectrum, triazole antifungal agent, oral or intravenous isavuconazole 200 mg 3 times per day for 2 days then 200 mg once-daily for a median of 180 days, in the treatment of rare invasive fungal diseases (Cryptococcus spp. [n = 9], Paracoccidioides spp. [n = 10], Coccidioides spp. [n = 9], Histoplasma spp. [n = 7], Blastomyces spp. [n = 3]). At end of treatment, 24 (63%) patients had an overall response, and eight (21%) had stable invasive fungal disease without progression. Progressive invasive fungal disease occurred in six (16%) patients despite the antifungal therapy. Adverse events occurred in 33 (87%) patients.

**Comment:** Isavuconazole is a new triazole with a broad spectrum of antifungal activity, approved for use in the treatment of aspergillosis and mucormycosis following the completion of phase III trials. Isavuconazole has potential advantages over other azoles, including no demonstrable food effect, minimal interpatient pharmacokinetic differences and a favourable safety profile. In the open-label nonrandomised phase III VITAL study, isavuconazole was effective as primary and salvage therapy in patients with cryptococcosis and endemic dimorphic fungal infections. The small nonrandomised study design limits the ability to compare the efficacy and safety of isavuconazole directly to other azoles for treatment of these fungal infections. However, the response rate observed in this study is similar to those previously reported for azoles. Isavuconazole is a long awaited welcome addition to the limited antifungal armamentarium for clinicians dealing with these difficult fungal infections.

***Reference: Clin Infect Dis. 2016;63(3):356-62***
Abstract

## Increasing incidence of herpes zoster over a 60-year period from a population-based study

**Authors:** Kawai K et al.

**Summary:** Data from a population-based cohort study conducted in Olmsted County, Minnesota, between 1945-1960 and 1980-2007 was interrogated to determine long-term trends for herpes zoster incidence. In total, 8017 herpes zoster patients were identified; 58.7% female, 6.6% immunocompromised. Age- and sex-adjusted incidence rates increased >4-fold between 1945-1949 and 2000-2007, from 0.76 (95% CI 0.63-0.89) to 3.15 (95% CI 3.04-3.26) per 1000 person-years. The rate of increase was 2.5% per year (adjusted incidence rate ratio 1.025 [95% CI 1.023-1.026]; p < 0.001). Herpes zoster incidence increased across all age groups and sexes. There was no change in the rate of increase before versus after varicella vaccination was introduced.

**Comment:** The incidence of herpes zoster increased >4-fold from 1945-1960 to 1980–2007 in this population-based cohort study. The incidence of herpes zoster steadily increased among all age groups and both sexes. The cause of the increase of herpes zoster remains unknown. There was no change in the rate of increase before versus after the introduction of varicella vaccination. Furthermore, the increase of herpes zoster was unlikely to be due to increased patient healthcare-seeking related to the availability of antiviral therapies, as a similar rate of increase was observed before and after their introduction in the mid-1980s. Major strengths of the study include medical records validation of herpes zoster cases and complete case ascertainment through a well established medical records linkage system. The increasing public health burden of herpes zoster is concerning and this study emphasises the importance of preventing herpes zoster and its complications through vaccination in older adults.

***Reference: Clin Infect Dis. 2016;63(2):221-6***
Abstract

## Randomized controlled clinical trial on the efficacy of fosfomycin trometamol for uncomplicated gonococcal urethritis in men

**Authors:** Yuan Z et al.

**Summary:** A single centre, open, randomised controlled trial tested oral fosfomycin trometamol 3 g (days 1, 3, 5; n = 62) versus a single administration of intramuscular ceftriaxone 250 mg plus oral azithromycin 1 g (n = 64) for the treatment of uncomplicated gonococcal urethritis in 152 men. After 7 days, 121 participants had complete clinical resolution of signs and symptoms. However, five patients (two fosfomycin trometamol and three control recipients) discontinued the intervention after unsuccessful treatment (urethral purulent discharge) and were switched to other treatment regimens. Per-protocol analysis suggested that both clinical and microbiological cure occurred in 96.8% (60/62) of fosfomycin trometamol recipients and 95.3% (61/64) of control recipients. Bacterial smears and cultures from urethral or urine specimens were negative on a test-of-cure visit at day 14 and no recurrences occurred.

**Comment:** Multidrug-resistant *Neisseria gonorrhoeae* is a major global health threat. Due to emerging reduced susceptibility to cephalosporins, alternatives for treating *N. gonorrhoeae* infections are urgently needed. In vitro studies have demonstrated that fosfomycin has good activity against ceftriaxone-resistant *N. gonorrhoeae*. Previous clinical investigations evaluating fosfomycin for the treatment of *N. gonorrhoeae* infections have been confounded by methodological limitations. In this randomised controlled trial, there was an excellent rate of clinical and microbiologic cure (97%), equivalent to the control group treated with ceftriaxone. There were no recurrences at the day 14 test-of-cure visit, and no serious adverse effects. Further studies could confirm fosfomycin as a useful option for treatment of *N. gonorrhoeae* infections. With increasing use of fosfomycin for treatment of multidrug resistant urinary tract infections, ongoing surveillance for fosfomycin resistance in *N. gonorrhoeae* will be required.

***Reference: Clin Microbiol Infect. 2016;22(6):507-12***
Abstract

## Transmission of hepatitis B core antibody and galactomannan enzyme immunoassay positivity via immunoglobulin products: A comprehensive analysis

**Authors:** Ramsay I et al.

**Summary:** This analysis examined hepatitis B virus (HBV) serology and galactomannan enzyme immunoassay (GM-EIA) positivity in a cross-sectional analysis of 80 patients receiving immunoglobulin therapy (>6 months), a prospective analysis in 16 patients commencing intravenous immunoglobulin (IVIG) therapy, and pre- and post-infusion analysis in 37 patients receiving IVIG. Prior to IVIG, of the 80 patients, nine were positive for HBV surface antibodies and one was equivocal for HBV core antibody. After IVIG, 79 were positive for surface antibody, 37 were positive for core antibody, and 10 were equivocal for core antibody. Among those receiving products that appear to transmit core antibody, negative results were correlated with lower surface antibody titres and greater time since infusion, indicating a simple concentration effect. The proportion of patients testing positive for HBV core antibody increased progressively with each infusion in those newly commencing IVIG. Some IVIG products were positive for GM-EIA and index values rose in corresponding patient samples pre- to post-infusion. Overall, five of 37 pre-infusion samples and 15 of 37 post-infusion samples were positive for GM-EIA.

**Comment:** Immunoglobulin products including IVIG are derived from the pooled plasma of donors. These products may contain clinically important antibodies that the recipient did not previously produce. After 6 months of immunoglobulin therapy, 46% of patients in this study had false-positive HBV core antibody and 41% had false-positive galactomannan results. Patients with false-positive HBV cAb results from receiving IVIG might therefore receive unnecessary antiviral prophylaxis and monitoring. False-positive galactomannan results may also lead to unnecessary investigations and treatment (with potential adverse effects). Baseline measurement of HBV cAb is recommended, and subsequent positive tests should be interpreted based on the development of clinical hepatitis or risk factors for HBV. Baseline measurement of serum galactomannan is also recommended, and testing the IVIG product directly could assist with interpretation of galactomannan post-infusion results. Further analysis to determine the cause of the galactomannan positivity is in progress.

***Reference: Clin Infect Dis. 2016;63(1):57-63***
Abstract

## ACG clinical guideline: Diagnosis, treatment, and prevention of acute diarrheal infections in adults

**Authors:** Riddle MS et al.

**Summary/Comment:** The American College of Gastroenterology present an evidence-based approach to prevention, diagnosis and therapy for acute diarrhoeal infection. Recommendations include:

**Diagnosis:**

- Stool diagnostic studies for dysentery, moderate–severe disease, and symptoms lasting >7 days to clarify the aetiology of the illness and enable specific directed therapy
- Traditional diagnostic methods (including bacterial culture) do not reveal aetiology in the majority of cases. Culture-independent methods (e.g. PCR) can be recommended as an adjunct to traditional methods
- It is not recommended to undertake antibiotic sensitivity testing.

**Treatment:**

- The use of balanced electrolyte rehydration is recommended over other oral rehydration options in the elderly with severe diarrhoea or any traveller with cholera-like watery diarrhoea. Most individuals can keep up with fluids and salt by consumption of water, juices, sports drinks, soups and saltine crackers
- Use of probiotics or prebiotics is not recommended except in cases of post-antibiotic-associated illness
- Bismuth subsalicylates can be administered to control rates of stool passage and may help travellers function better during bouts of mild-to-moderate illness
- In patients receiving antibiotics for traveller's diarrhoea, adjunctive loperamide therapy should be administered to decrease the duration of diarrhoea and increase chance for a cure
- Evidence does not support empiric antimicrobial therapy, except in cases of traveller's diarrhoea where the likelihood of bacterial pathogens justifies the potential side effects of antibiotics
- Antibiotic use for community-acquired diarrhoea is discouraged, as most community-acquired diarrhoea is viral (norovirus, rotavirus, adenovirus) and not susceptible to antibiotics.

***Reference: Am J Gastroenterol. 2016;111(5):602-22***
Abstract



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