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INSIDE

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Viruses Across the World

SPECIAL FEATURE

By Stan Deresinski, MD, FACP

Source: The ProMED listserv and other sources are efflorescent with reports of outbreaks of viral infections around the world, some of which I have summarized here.

Chikungunya in Italy[1]

BETWEEN JULY 4TH AND AUGUST 28TH 2007, MORE THAN 100 residents of Castiglione di Cervia and Castiglione di Ravenna, adjacent villages separated by the River Savio, suffered acute febrile illnesses with myalgias, arthralgis, and frequently, skin rash.[1] Further cases occurred and, as of September 13th, 2007, a total of 254 have been identified in the Emilia Romagna Region. Laboratory investigation identified chikungunya virus as the etiologic agent, with evidence of *Aedes albopictus* having served as the vector. This was the first time that this mosquito has been involved in an outbreak of human illness in Europe.

The epidemic of chikungunya infections actually began in Kenya in 2004 and the Comoros Islands in 2005, with subsequent spread to other islands in the Indian Ocean.[2,3] Of the 770,000 residents of Reunion, 265,000 became ill, and syndromes not formerly associated with chikungunya, such as meningoencephalitis, were observed, albeit rarely. The mortality rate was approximately 1%. Travelers to Indian Ocean sites also began presenting to clinicians in Europe with chikungunya fever. Subsequent spread to India, where the number of cases is likely to be in the millions, guaranteed that additional cases would be detected in travelers from countries other than those in Europe, and I and my colleagues have seen a number of cases in Indian residents of Silicon Valley who had returned from visits back home. In some cases, the febrile illness had already resolved by the time they presented, but they were left with severe, often disabling arthral-

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gias that lasted months. (I wonder how many have had futile "million" rheumatologic evaluations?)

The vectors of chikungunya are *Aedes aegypti* in Africa and *Aedes albopictus* in the Indian Ocean islands. Since the latter is present in tropical and temperate regions in many areas of the world, it was predicted to only be a matter of time until the virus took hold in one or more of these areas, with establishment of local patterns of transmission,[3] an event which has now happened in Italy.

Dengue in Texas[4]

Between 1980-1999, 64 cases of autochthonously-transmitted dengue fever were identified on the Texas side of the border with Mexico. A cross-sectional serosurvey in Brownsville, Texas, and Matamoros, Tamaulipas, Mexico, performed in the autumn of 2004, has now demonstrated that this is a vast underestimate of the cases of dengue occurring in that area. In Brownsville, 40% of residents had serological evidence of past dengue infection, while this was true of 40% of those across the Rio Grande in Matoros. Mosquito larvae (*Aedes aegypti*, *Aedes albopictus*, *Culex quinquefasciatus*) were detected in 30% of households in each municipality, and there was serological evidence of recent dengue infection in 2% on the Texas side and 7.3% on the Mexican side. Neutralization studies indicated that the circulating dengue viruses were of serotypes 1 and 2.

Marburg in Uganda[5]

Although a small outbreak of Marburg virus infection at an underground gold mine in Uganda was declared ended in August 2007, a new case has now been reported. The first identified case died on July 14th, with a small number of cases subsequently observed; the mine was closed. The new case, however, occurred in a man who was guarding the closed mine, but nonetheless elected to enter it, presumably to find some gold for himself.

Marburg, like the agent of Ebola hemorrhagic fever, is a filovirus. Marburg was first identified at the Marburg Virus Institute in Germany, in monkeys that had been imported from Uganda. Recent serological data suggest that Marburg, like Ebola, is carried by bats,[6] which were abundant in and around the Ugandan goldmine. A much larger outbreak of Marburg hemorrhagic fever than that discussed here occurred in the Democratic Republic of Congo, which borders Uganda, in goldminers in 1998. That outbreak terminated contemporaneously with the flooding of the mine. An outbreak in Angola in 2004-2005 was associated with 150 deaths. Finally, 6 people have died of Marburg in Congo since April 2007.

Ebola in the Democratic Republic of Congo (DRC)[5]

The health ministry of the DRC announced on October 2, 2007, that a 25th case of Ebola virus infection had been confirmed as part of an outbreak centered in the Kambugu zone, approximately 150 km from the capital city of Kinshasa. There have been 10 deaths, with the current case fatality rate estimated at 40%. An additional 49 cases are under investigation.

Ross River virus in Australia[5]

Ninety-three people have been reported to be infected with Ross River virus in the southern Brisbane area of Queensland in recent weeks, an approximate 300% increase from the number reported during the same period in each of the 5 previous years. This mosquito-borne alphavirus (Family: Togaviridae) can cause prolonged disability because of the frequent occurrence of long-persisting arthralgias. In the past, the joint involvement, which led to the description of epidemics of "benign polyarthritis" in the 1920s, has previously led to the misdiagnoses of acute rheumatic fever or gonococcal arthritis.

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Rift Valley fever in Kenya[5]

On September 20th, it was announced that the deaths of 2 women in the Nakuru district, an area frequented by tourists, was due to Rift Valley fever. These cases raised concern about the potential resurgence of this infection in East Africa, where outbreaks had occurred earlier in the year. A total of 684 cases, with 155 deaths, had occurred in Kenya from November 2006 to March 2007, and in Tanzania, there had been 264 cases, including 109 deaths, which had been recorded between January 13th and May 3rd. Additional cases of infection with this bunyavirus have occurred in Somalia in the Horn of Africa.

Japanese encephalitis virus (JEV) in India[5]

Twelve deaths reported September 29, 2007, brought the total number of childhood deaths due to JEV in eastern Uttar Pradesh, since January, to 227. This outbreak, which is a yearly occurrence, is somewhat larger than that in 2006, an unfortunate occurrence for an infection that is vaccine-preventable.

Zika in Yap[6]

This outbreak, discussed in the September 2007 issue of *Infectious Disease Alert*, judging from the lack of additional reporting, has apparently resolved. ■

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Micafungin for Invasive Candidiasis

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Micafungin at doses of both 100 mg and 150 mg daily was non-inferior to caspofungin in the treatment of invasive candidiasis and there was no significant difference in outcomes when the two doses of micafungin were compared.*

Source: Pappas PG, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis*. 2007;45:883-893.

Patients with invasive candidiasis were randomized to blinded treatment with either caspofungin (70 mg on day one, followed by 50 mg daily), or one of 2 doses of micafungin (100 mg or 150 mg daily). Approximately 85% of the 595 randomized patients had candidemia. Patients in each treatment arm received a median of 14 days of therapy, including 4-7.5 days of oral fluconazole in 15.1%-21.9% in each arm, as allowed by protocol. Almost three-fourths of infections were due to *Candida albicans*, followed in frequency by *C. tropicalis* (16.6%), *C. glabrata* (16.4%), and *C. parapsilosis* (15.9%). Neutropenia was present at baseline in 8.4% of patients.

The size of the population randomized was chosen in order to have a > 90% power to determine non-inferiority of micafungin at a lower bound of the difference between treatment arms of -15%. Treatment success, defined as investigator-determined clinical and mycological success at the end of blinded intravenous therapy in the modified intent-to-treat population, was the primary efficacy end point, and was achieved in 76.4%, 71.4%, and 72.3% of patients assigned micafungin 100 mg, micafungin 150 mg, and caspofungin, respectively. Both micafungin regimens were noninferior to treatment with caspofungin. This remained true at subsequent evaluations, with the last occurring 6 weeks after the end of all antifungal therapy. There was no significant difference between treatment arms in the treatment of infections due to *C. albicans* or the non-albicans species. The median time to blood culture negativity was 2 days in the micafungin 100 mg group, as well

as in the caspofungin group; it was 3 days in the group given micafungin 150 mg.

Approximately one-fourth of patients in each group did not have their intravenous catheters removed, a feature associated with poorer overall response, regardless of assigned treatment. Thus, treatment success was achieved in 77.9% of 384 patients whose IV catheter was removed or replaced, while only 63.2% of 144 patients whose catheter remained in place were successfully treated (P = .001). The overall mortality was 29.6%, and did not differ significantly among the treatment groups.

COMMENTARY

This is the latest in the past several years in a series of randomized, therapeutic trials evaluating newer antifungal agents in the treatment of invasive candidiasis, and the first to compare 2 echinocandins. Previously, caspofungin therapy was comparable to the use of amphotericin B deoxycholate in a primary analysis and superior in a clinically evaluable population.[1] Anidulafungin was found to be superior to fluconazole,[2] while voriconazole was non-inferior to amphotericin B deoxycholate,[3] and micafungin was non-inferior to liposomal amphotericin B.[4] Thus, we have a variety of trials that provide us with data to assist us in deciding on optimal anti-candidal therapy, but strangely, the answer remains somewhat muddy. It seems to me that it would be generally preferred to use an agent other than an amphotericin B preparation, given the complexities of administration and toxicity of these products. Fluconazole is active against most, but not all Candida isolates, so that it probably should not be used as empiric therapy in patients with severe, potentially life-threatening infections. Voriconazole is active against some fluconazole-resistant Candida. The echinocandins seem to be emerging as the preferred initial empiric therapy of many clinicians, but the choice among the 3 available echinocandins is more difficult and is not made easier by the study reviewed here.

Some comparisons indicated a non-significant trend toward superior outcomes in patients receiving 100 mg of micafungin daily compared to those receiving a higher dose. If correct, this finding would be consistent with a paradoxical effect, in which higher concentrations are less effective at inhibiting growth of the microorganism than are some lower doses.

Another interesting observation was that only 11 of 595 (1.8%) had chorioretinits at baseline, a figure much lower than has been reported in the past with candidemia, but consistent with the results in some other clinical trials. This suggests that earlier observational studies, which reported an incidence as high as 30%, were either grossly inaccurate or the patients had suffered from prolonged candidemia before it was recognized and treated. ■

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The Impact of Prescribing Antibiotics to Children

ABSTRACT & COMMENTARY

By Hal B. Jenson, MD

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Dr. Jenson is on the speaker's bureau for Merck.

Synopsis: *Prescribing β-lactam antibiotics for children with upper respiratory tract infections is associated with in a 3-fold increase in the MIC for ampicillin and 2-fold increase of the ICEHin1056 resistance gene of oropharyngeal Haemophilus isolates. The effect in individuals is transient (less than 12 weeks) but is sustained in the population.*

Source: Chung A, et al: Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: Prospective cohort study. *BMJ*. 2007;335:429.

An observational cohort study in the United Kingdom of 119 children 6 months to 12 years of age with upper respiratory tract infections (either otitis media or presumed viral infections) compared

antibiotic resistance of oropharyngeal Haemophilus isolates among 71 children who received a β-lactam antibiotic (amoxicillin, 70; cephradine, 1) and 48 who did not receive any antibiotic. Throat swabs were obtained at 0, 2, and 12 weeks, and plated onto 2 Haemophilus selective media plates. Antibiotic resistance was measured by 1) the geometric mean minimum inhibitory concentration (MIC) for ampicillin; and 2) the presence of the integrative and conjugate element ICEHin1056, which encodes β-lactamase among nasopharyngeal Haemophilus species.

The antibiotic and no antibiotic groups were similar in mean age (each 5.4 years), mean number of children in the household (1.16 vs 1.13), and previous exposure to antibiotics at any time (87% vs 85%), or within 3 months (13% vs 20%). Daycare or school attendance was more common among children who received an antibiotic (96% vs 85%, $P = 0.05$). The initial MIC for ampicillin was 2.4 μ/mL in the antibiotic group and 4.1 μ/mL in the no antibiotic group ($P = 0.24$), and the proportion of children initially with ICEHin1056 was 32% vs 38%, respectively ($P = 0.52$). The presence of ICEHin1056 was high even among children who had never received an antibiotic (8 of 15, 53%).

At 2 and 12 weeks, the MIC for ampicillin in the no antibiotic group was 2.7 μg/mL at each visit, which was not significantly different from the baseline of 4.1 μg/mL. Among children who had received an antibiotic, the MIC increased to 9.2 μg/mL at 2 weeks ($P = 0.005$), 3.5 times higher than for the no antibiotic group, and at 12 weeks, the MIC fell to 5.7 μg/mL ($P = 0.06$).

There was no significant difference in the prevalence of ICEHin1056 homologues at 2 and 12 weeks in the no antibiotic group, which was 36% and 37% compared to 38% at baseline. In the antibiotic group, the prevalence doubled to 67% at 2 weeks ($P = 0.002$) and fell at 12 weeks to 36%, close to the baseline of 32%. However, ICEHin1056 was identified in Haemophilus isolates from most children of both groups (83%, 95% confidence interval, 76-89%) on at least one occasion.

COMMENTARY

This community study confirms that the short-term impact of prescribing antibiotics to children includes a 3-fold increase in the MIC for ampicillin among oropharyngeal Haemophilus species and a 2-fold increase, to 67%, in the prevalence of the ICEHin1056 resistance element. These changes are transient, and the prevalence of resistant Haemophilus returns to baseline within 12 weeks. These changes indicate that a β-lactamase resistant antibiotic, such as amoxicillin-clavulanate, should be prescribed if antibiotic therapy is indicated for a child who has received a β-lactam antibiotic within 12 weeks.

The greater concern is the high equilibrium of resistant Haemophilus species in the community, which in this study was at a baseline of 32-37%. Significantly, resistant Haemophilus species were recovered from 83% of all children at some time. It appears that although the adverse impact of antibiotics on an individual child is transitory, there is sufficient pressure to sustain a high level of antibiotic resistance in the population. Two potential counter responses include developing guidelines for prescribing shorter courses of antibiotics, and more importantly, not prescribing antibiotics for children with presumed viral upper respiratory tract infections. ■

Culture-Negative Prosthetic Joint Infection

ABSTRACT & COMMENTARY

Dean L. Winslow, MD, FACP, FIDSA
Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center; Clinical Professor of Medicine, Stanford University School of Medicine
Dr. Winslow serves as a consultant to Siemens Diagnostics, and is on the speaker's bureau for Boehringer-Ingelheim and GSK.

Synopsis: *A retrospective cohort study of culture-negative (CN) prosthetic joint infection (PJI) was performed on patients who underwent total hip or total knee arthroplasty at Mayo Clinic from 1990-1999. Of the 897 episodes of PJI during this period, 60 episodes of CN PJI were identified. Of these, 53% of patients had received prior antimicrobial therapy. Outcomes following treatment with either 2-stage exchange or with debridement and retention were comparable to that seen in patients with culture-positive PJI.*

Source: Berbari EF, et al. Culture-negative prosthetic joint infection. *Clin Infect Dis*. 2007;45:1113-1119.

This retrospective cohort study from the section of Orthopedic Infectious Diseases at Mayo Clinic presents their experience with CN PJI cases seen between 1990 and 1999. Only first episode CN PJI were included in the study. Berbari and colleagues

employed a strict case definition which included the presence of purulence surrounding the prosthesis (as determined by the surgeon), histopathologic findings of acute inflammation of periprosthetic tissue samples consistent with infection, or a cutaneous sinus tract communicating with the prosthesis, in addition to there having been negative aerobic and anaerobic culture attempts. Standard culture techniques were employed, and either synovial fluid or homogenized tissue samples were used to inoculate both solid media and broth cultures. In addition to standard aerobic and anaerobic cultures, fungal and AFB cultures were set up in many cases.

Demographic characteristics of the patients were consistent with the larger group of 897 patients seen during the same time period with culture-positive PJI. The median duration from prosthesis implantation to diagnosis of CN PJI was quite long, 1269 days, and the median duration of symptoms prior to diagnosis was 103 days. Use of antimicrobial therapy during the 3 months prior to diagnosis of CN PJI was present in 32 (53%) of 60 episodes. Interestingly, outcome of therapy for the patients with CN PJI was similar to the larger group of all patients with PJI treated during the same time period. Five-year survival free of treatment failure was 82% across the 60 episodes. Looking at specific surgical therapy, the 5-year survival figures were 94% in the 34 patients who underwent 2-stage replacement and 71% for the 12 patients who underwent debridement and retention. The 8 patients who underwent resection arthroplasty were followed for only 3 years, and their survival free of treatment failure was 50% during this period.

Among the 10 total episodes where treatment failure occurred, 5 again "relapsed" with CN PJI, 2 relapses were due to *S. aureus*, one due to coagulase-negative staph, and one due to group B streptococcus.

COMMENTARY

It is clear that patients with CN PJI are heterogeneous with respect to etiology. The use of antibiotics within 3 months of diagnosis was probably the major factor in the causation of negative cultures in patients who clearly had PJI using the study's case definition. However, in other cases, it is likely that sampling error, or more likely sequestration of bacteria in biofilms, may have played a role. Supporting the hypothesis that organism sequestration in biofilm may play a role in false negative cultures seen in PJI is supported by an interesting paper recently published from this same group which showed that sonication of removed hip and knee prostheses was more sensitive for microbiologic diagnosis of PJI than standard methods of processing tissue for culture.[1] However, this technique may be associated with increased risk of specimen contamination.[2]

As to treatment, it appeared that the outcome in patients treated with 2-stage replacement was superior to that seen in patients treated with debridement and retention of the prosthesis, although this conclusion must be tempered by the caveat of potential selection bias. It is of interest, that in this series, the outcome of patients treated with a first-generation cephalosporin was no worse than those treated with antimicrobials with activity against methicillin-resistant organisms or drug-resistant gram-negative rods. ■

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Cholera Cases: Past, Present, and Future

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

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Dr. Scully reports no financial relationship relevant to this field of study.

This article originally appeared in the October 2007 issue of Travel Medicine Advisor. It was edited by Frank Bia, MD, MPH. Dr. Bia is Professor of Medicine and Laboratory Medicine, Yale University School of Medicine He is a consultant for Pfizer and Sanofi Pasteur, and receives funds from Johnson & Johnson.

Synopsis: *Although imported cholera cases in developed countries, such as France, may continue to decline, the global number of cholera cases continues to rise at an alarming rate. Orally administered cholera vaccine may hold promise in controlling cholera epidemics.*

Source: Tarantola A, et al. Retrospective analysis of the cholera cases imported to France from 1973 to 2005. *J Travel Med* 2007; 14:209-214.

THIS RETROSPECTIVE ANALYSIS REVIEWS DETAILS OF the 129 proven cholera cases imported to

France between January 1, 1973 and December 31, 2005. All strains were identified as *Vibrio cholerae* serogroup 01. The peak years of activity were 1980-1989, when most patients acquired their illness while visiting Morocco and Algeria, likely as a result of immigrants returning to these countries to visit friends and relatives. This trend disappeared, resulting in no further cases from Morocco or Algeria after the year 2000, as these countries essentially became cholera free. Since 1996, the geographic sources of imported cholera acquisition in France have been travel to Africa, mostly West Africa, or Asia.

The mean age of patients was 35 years, but during 1980-1999, there was a relatively higher proportion of imported cases in the younger ages (0-15) and older patients (over 66). The majority of patients (82%, n = 57) required hospitalization, and a total of 2 deaths occurred. There was a significant seasonality, with 82% of cases being reported between May and September. Cholera cases were reported from a wide variety of regions in France, and not just the larger cities with significant immigrant populations, such as Paris, Lyon, or Marseilles. In addition, the diagnosis of imported cholera was increasingly made in the nonteaching hospitals of France.

COMMENTARY

The historical trend of imported cholera cases in French travelers, initially after travel to Morocco and Algeria, but more recently after travel to other areas of Africa and Asia, is consistent with the pattern for global cases reported to the World Health Organization (WHO). The number of imported cholera cases is small relative to the impressive numbers reported from endemic areas. In 2006, the number of cholera cases reported to the WHO soared to 236,896, up from 131,943 cases in 2005 (overall increase of 79%).[1] The majority of cases were from Africa (234,349 cases), followed by Asia (2,472), with India reporting most of the Asian cases (1,939 cases). A total of 33 countries in Africa reported cholera cases, but the African countries with the greatest burden of disease were Angola, Ethiopia, Sudan, and Democratic Republic of the Congo. Together, these 4 countries alone reported 186,928 cases, with 4,988 deaths. The United Republic of Tanzania had an almost 5-fold increase in cases compared to 2005, with 14,297 cases. Malawi, Mozambique, Zambia, and Zimbabwe all reported increased numbers of cholera cases in 2006.

Despite these impressive numbers, the WHO estimates that cholera cases remain underreported. One reason is that not all countries consistently report cholera cases to the WHO. For example, several cholera outbreaks in 2004 on the Indian continent and Southeast Asia (Bangladesh, Myanmar, and Pakistan) occurred, yet they were not reported to the WHO.[2] Another reason for underestimation of cholera is that milder cases may not seek medical care, and a stool specimen may not be obtained. Lastly, the fear that negative publicity regarding a cholera outbreak will adversely affect the tourism industry in a developing country may also contribute to underreporting.

Orally administered cholera vaccine (OCV) offers some promise in controlling cholera epidemics. A mass immunization program using an oral, inactivated, whole cell, recombinant vaccine cholera toxin B subunit (WC-rBS)) for 19,550 non-pregnant individuals in Beira, Mozambique, was associated with 78% protection.[3] The WHO has now prequalified this vaccine (Dukoral™) for use in the setting of cholera outbreaks. Two doses (3 doses for children ages 2-6) are given at least one week apart. Booster doses are given after 2 years for children older than 6 years and adults, but children 2-6 years are given a booster after 6 months. This vaccine is also licensed for short-term protection (< 3 months) against diarrhea caused by ETEC (enterotoxigenic *Escherichia coli*). The vaccine is available in the United Kingdom, Canada, and many other countries such as Peru, Thailand, and Sweden, but is not yet available in the United States.

Countries without access to safe water and basics of adequate sanitation will remain at risk for epidemic cholera disease. The latest country to be added to the list is Iraq, with 3,182 cases of watery diarrhea, suspected as cholera, 9 deaths, and 283 stool isolates of *Vibrio cholera* reported by health officials from just 5 out of 11 districts of Sulaymaniyah Governate as of September 6, 2007.[4,5] The outbreaks are occurring in the Kurdish province of Sulaimaniyah and Kirkuk. Health officials in Iraq suspect the source of the outbreak is cracked water pipes that have allowed contamination by sewage. Unfortunately, the political instability of this war-torn country, the disruption of the existing infrastructure, the dwindling number of health care providers, and the lack of safe drinking water are perfect ingredients for epidemic cholera disease. ■

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Quadrivalent HPV Vaccine as a Travel Vaccine

ABSTRACT & COMMENTARY

By Michele Barry, MD, FACP
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Dr. Barry receives no funding from any issue related to this commentary. She is a consultant for Ford Foundation and had received funding from Johnson and Johnson and Sanofi-Pasteur.

Synopsis: *In June, 2006, the FDA licensed the first human papillomavirus vaccine (HPV) to prevent cervical cancer and other HPV-associated cancers: vaginal, urethral, and oral tumors. Is this yet another travel vaccine for our patients?*

Source: Markowitz LE, et al. Quadrivalent human papillomavirus vaccine: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2007;56:1-24.

HPV IS THE MOST COMMON SEXUALLY TRANSMITTED infection in the United States; an estimated 6.2 million persons are newly infected every year. Although over 100 HPV types have been identified, the quadrivalent vaccine Gardasil®, made by Merck, protects against 4 HPV types (6, 11, 16, 18); types 16 and 18 are responsible for 70% of cervical cancers, and types 6 and 11 are associated with 90% of all genital warts. This prophylactic vaccine made from non-infectious, HPV-derived particles is recommended for females ages 9-26 years. Ideally, the vaccine should be administered before onset of sexual activity. Administration of the Merck vaccine, which has no thimerosal, an organomercury preservative, requires 2 booster doses (0.5 mL intramuscularly) at 2 and 4 months. Duration of efficacy, thus far, has only been demonstrated for 5 years — future booster doses may be needed. The vaccine is available in a single dose vial or a prefilled syringe. Storage is at 2°-8° C (36°-46° F), and it should not be frozen. Vaccination can be administered for women with abnormal pap smears who are HPV positive to protect against other HPV infections, but it will not help or change the medical course of these abnormal pap smears. The private sector list price of the vaccine is $119.75 per dose — $360 for the full 3 vaccine doses.

COMMENTARY

During these times of globalization, college and high school students are traveling the world and are inundating travel health clinics. Experiencing freedom while being away from home and school leads to increased sexual activity, sometimes called "situational disinhibition."[1] The travel clinic visit presents the perfect time to offer the HPV vaccine, as trips often coincide with increased sexual activity with new partners or travel companions. Unfortunately, the students' traveling schedules often do not allow enough time for full immunization, but certainly a first dose, and educational materials about the benefits of full vaccination, can be offered. Such educational materials can instruct the traveler that, in addition to cervical cancer, HPV infection is also associated with anogenital cancers such as cancer of the vulva, vagina, penis, and anus. Studies support a role for HPV also causing a subset of oral cavity and pharyngeal cancers. HPVs are non-enveloped, double-stranded DNA viruses that are classified as "types," designated on the basis of nucleotide sequences, with numbers assigned in order of their discovery.

Genital HPV infection is primarily transmitted soon after an individual's sexual activity begins. One study has shown that 14.3% of women aged 18-25 with one lifetime sex partner, 22.3% with 2 lifetime partners, and 31% with more than 3 lifetime partners had HPV infection.[2] A 2002 National Survey in the United States revealed that 40% of females in the United States were sexually active by age 16; 70% by age 18.[3] The majority of HPV infections are transient and asymptomatic and cause no clinical problems; 70% of new HPV infection clears within one year. Persistent infection with high-risk, cancer-inducing types is one consequence of infection that vaccination may prevent.

The longest follow-up of the phase II trial of women vaccinated has been 5 years, and it reveals that antibody titers plateau by about 24 months, but there is no evidence of waning efficacy in preventing cervical cancers at this point, ie, 95.8% efficacy (CI 83.8-99.5%). Follow-up studies by Merck, to determine boosting intervals in the 5,500 women enrolled, will be continued for at least 14 years by following Pap testing results and serologic testing linked to vaccine and cancer registries. Adverse effects to vaccination were mostly local pain, with reporting of fever in less than 5.0%. There were no reports of anaphylaxis. In the future, Cervarix,® a GlaxoSmithKline HPV vaccine submitted to the FDA and pending approval, has a different adjuvant and may require less boosting.

Wynia, at the AMA, has written an interesting article on how public health and public trust were affected by an aggressive stance and lobbying effort by Merck with the release of Gardasil®.[4] His opinion is that a Merck donation of funds to Texas Governor Rick Perry, at the time of his state law mandating vaccination, was inappropriate and self-defeating. He contended that public health decisions should be delegated to the public health community, and public trust relies on a clear separation between those making money on vaccines and those making decisions about which vaccines to require or recommend.

The backlash against the Merck campaign will have seriously held back effective HPV vaccination, should religious conservatives partner with patient advocacy groups and vaccine phobics to question how vaccines are required prior to school entry. Wynia ends by describing the lesson learned from this story: public trust relies upon the public health community making unbiased and fully disclosed decisions without lobbying or market pressures. For this associate editor and commentator, the take-home message from this event is that pharmaceutical companies should not be allowed to influence government in such public health decisions through either funding or lobbying. ■

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CME Questions

4. Which of the following is *TRUE*?
a. Chikungunya virus is tick-borne.
b. Chikungunya and Ross River virus infections are each commomly associated with prolonged joint symptoms.
c. Chikungunya infection has never been locally transmitted in Europe or North America.
d. Chigungunya infection is assocated with a mortality rate in excess of 50%.

5. Which of the following is correct?
a. All cases of dengue virus infection identified in the United States have been imported, not locally acquired.
b. Ross River virus is found in Australia.
c. Japanese B encephalitis causes yearly out breaks in parts of India.
d Marburg and Ebola viruses are tick-borne.

6. Which of the following is correct with regard to the Merck quadrivalent HPV vaccine (Gardasil)?
a. It is a live attenuated viral vaccine.
b. It contains thimerosol.
c. It contains viral-like particles of HPV types associated with both cancer and benign warts.
d. Its admiminstration is associated with reversion of abnormal Pap smears to normal.

Answers: 4. (b); 5.(b); 6. (c)

CME Objectives

The objectives of *Infectious Disease Alert* are to:

• discuss the diagnosis and treatment of infectious diseases;

• present current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;

• present the latest information regarding the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• discuss new information regarding how infectious diseases (eg, AIDS) are transmitted and how such information can lead to the development of new therapy...■

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In Future Issues:

Effects of Antiretroviral Agents on Lipid Panels of HIV-Positive Patients

UPDATES

By Carol A. Kemper, MD, FACP

Quiz: Paresthesias in a soldier stationed in Hawaii

A military serviceman stationed in Hawaii, presented to base with intense pruritus, restlessness, dyspnea, and progressive paresthesias, with burning skin discomfort. His vital signs were stable, he was afebrile, and he denied any nausea, vomiting, or headache. His neurologic examination was intact, although testing with a tuning fork elicited an intense sensation of burning. He was observed overnight for possible respiratory compromise, and given gabapentin with gradual resolution of his symptoms during the next 4 weeks.

What was his diagnosis?

a. Organophosphate insecticide poisoning
b. Guillain-Barre syndrome
c. Saxitoxin toxicity (paralytic shellfish poisoning)
d. Ciguatera poisoning
e. Scombroid
f. Antipersonnel neurobiologic agents

Please see answer on next page.

Flu vaccine Effective in the Elderly

Source: KL Nichols, et al. Effectiveness of Influenza vaccine in the community-dwelling elderly. *N Engl J Med*. 2007;357:1373-1381.

Despite concerns about the immunogenicity and durability of influenza vaccination in the elderly, as well as year-to-year variability in circulating influenza strains and vaccine efficacy, most case control and cohorted data continue to support the benefits of vaccination in the elderly. This large-scale retrospective analysis of pooled data from a large HMO in the United States evaluated the overall effectiveness of influenza vaccination in persons 65 years or older belonging to an HMO. Pool data from 18 cohorts variably dating from 1990 to 2000 were examined for the risk of hospitalization for influenza or pneumonia and death in vaccinated vs unvaccinated persons. Elderly persons residing in nursing homes or long-term care facilities were not included in this assessment.

There were a total of 713,872 person-seasons spanning the 10 consecutive flu seasons. Subgroup analyses were conducted as defined by age, gender, co-existing medical conditions, prior hospitalization, and number of recent outpatient care visits. Various confounders were also examined. Baseline characteristics of the 2 groups were similar with regard to age, although (not surprisingly) the vaccinated group had a greater prevalence of one or more pre-existing medical conditions, and number of hospitalization and outpatient visits.

During the 10 influenza seasons, there were 4599 hospitalizations for pneumonia and influenza, and 8796 deaths occurred. Raw data for hospitalization were, on average, 0.6% and 0.7% for vaccinated vs unvaccinated persons. Death rates were, on average, 1% and 1.6% per season (!). Increasing age and pre-existing medical conditions were the strongest predictor of hospitalization and death.

On average, after adjustment for important co-variates, influenza vaccination was associated with a 27% reduction in the risk of hospitalization (adjusted OR .73) and a 48% reduction in the risk of death (adjusted OR .52). This figures varied from year to year, in large part determined by whether the vaccine was a good match for circulating strains of influenza virus that season. During the 2 years where there was a poorer match, vaccine effectiveness dropped to 37% lower death rates. In seasons with a better match, vaccine effectiveness improved to 52% lower death rates. Thus, even in years with a poorer match, influenza vaccination was associated with a significant reduction in the risk of hospitalization and death, though the benefit was not quite as great as during flu seasons with a better match. Although the risks may not be immediately tangible, the data confirm that vaccination of the elderly should remain a high priority in this country.

PEP for Sex

Source: Landovitz RJ, et al. Preventing HIV infection after a potential sexual exposure. *Infect Med*. 2007;24:239-246.

Post-sexual exposure prophylaxis with antiretroviral treatment (ART), what is euphemistically called "PEP for sex," has now become the standard of care for persons with possible high-risk sexual exposure to HIV. However, there is still uncertainty on the part of many practitioners about "who, what, and how long."

PEP for sex can and should be administered by those on the front lines of patient care — ER and urgent care physicians and primary care practitioners — in concert with the advice of an infectious disease or HIV specialist as needed, and there is plenty of information online, including the 2005 CDC Guidelines to assist them. The following is a brief synopsis of those recommendations.

Why? In order to provide appropriate treatment recommendations and counseling, practitioners should understand the risks of HIV transmission associated with various sexual activities, which are generally quite low. The presence of certain factors, such a traumatic mucosal skin breaks, genital ulcer disease, cervical ectopy and inflammation (or certain subtypes of HIV not common in the United States) can increase that risk. In health

care workers, the use of AZT monotherapy is believed to reduce the risk of transmission of HIV associated with high-risk percutaneous needles sticks by about 81%. This, and animal data, support the use of PEP for high-risk sexual exposure, although patients should be counseled that 100% efficacy is unlikely, and breakthrough infections have been documented, even when appropriate ART has been administered in a timely fashion.

Timing and duration of therapy? Following transmission, there is a window period of about 3 to 5 days before HIV infection is established. Therefore, PEP must be administered < 72 hours after exposure (the sooner, the better) and continued for 28 days. Breakthrough infections have been documented when treatment was initiated later than 72 hours, or the duration of treatment was 3 or 10 days (in animal models).

Who? PEP should be administered to any person with insertive or receptive anal, vaginal, or oral contact, regardless of whether ejaculation occurred (eg, the condom slipped or broke). Mucous membrane or non-intact skin contact with any potentially infected body fluids (eg, ejaculate, genital secretions) is also an indication for PEP. The case must be known HIV-negative, unknown HIV status, or have a preliminarily positive rapid HIV test pending confirmation; a positive rapid test is not a basis for refusing PEP. The contact should be known HIV positive, or someone considered at reasonably high risk of being positive based on sexual behavior, drug use, or local epidemiology. Administering PEP for random sexual encounters where the risk of HIV transmission is believed to be reasonably low should be avoided. However, it is reasonable to err on the conservative side of this equation, especially when dealing with a patient who is distraught or adamant about receiving PEP. In other words, PEP should never be refused to someone who truly believes it is necessary, even if you do not. There is adequate time for reassurance and further consideration of the risks in the days following.

Which agents? Two nucleoside analogs are considered standard PEP prophylaxis (eg, combivir, or various combinations of stavudine, lamivudine or emtricitabine, and tenofovir). A third drug should be added if there is a > 15% prevalence of nucleoside resistance in your area, or the contact person is believed to be receiving ART and may have HIV resistance. In such circumstances, individualization of therapy may be necessary, and an HIV or ID specialist can be consulted. Third agents include protease inhibitors (kaletra, atazanavir, fosamprenavir, crixivan, nelfinavir), a non-nucleoside reverse transcriptase inhibitor (Sustiva, but not nelfinavir), or tenofovir.

What tests to order? At baseline, routine HIV antibody testing should be performed, along with hepatitis B and C, RPR, and other STD tests. Follow-up HIV testing should be done no sooner than 4 weeks, and is probably best done at 2 to 3 month post-exposure. Plasma HIV testing using PCR is not recommended, as the frequency of false-positives is too high. Follow-up testing for hepatitis B and C and RPR is recommended. Routine labs (cell counts, liver panel, serum creatinine) may be done at baseline, at 2 weeks, and at 4 to 6 weeks, but some argue that it is reasonable to defer such testing unless the person experiences symptoms or toxicity.

Answer to Quiz

The key was in the history: The soldier had eaten healthy portions of fish for both lunch and dinner. Although ciguatera toxin is present in Hawaii, especially in Amberjack or Kahala, in an ironic twist, the man had purchased frozen fish from a local grocer. The fish was packaged in Fiji, and identified as a *Cephalopholis miniata*, or coral cod, and contained high amounts of ciguatera toxin, especially the head.

Ciguatera toxin exposure is a risk for military personnel stationed anywhere where ciguatera toxin is present in the environment, including Hawaii, the South Pacific, the Gulf Coast, the Caribbean, and the parts of Asia. In these areas, military personnel should be cautioned about the potential risks of eating certain fish (especially reef fishes, such as amberjack in Hawaii and the South Pacific, and barracuda in Florida and the Gulf), limiting portion size to less than 50 grams, and avoiding eating the head, viscera and roe.

There is no antitoxin or known treatment for the symptoms, which can last weeks. Studies suggest that some of the symptoms may be improved with gabapentin, but mannitol is no longer recommended. For reasons which are not clear, nuts, nut oils, sesame oil, and alcohol may make the symptoms worse, and should be avoided for 3 months after exposure.

Military health care providers should be able to distinguish ciguatera toxicity from other illnesses, toxins, and biologic and chemical agents. Ciguatera toxicity is commonly associated with acute-onset nausea, vomiting, abdominal pain, and progressive paresthesias, and can occasionally result in bradycardia and hypotension, but not muscular paralysis. In contrast, saxitoxin (paralytic shell fish poisoning) or tetrodotoxin, which is produced by dinoflagellates, and becomes concentrated in shellfish, is one of the more potent toxins. Similar to ciguatera toxicity, patients present with abdominal pain, nausea and vomiting, and paresthesias, or burning sensation of lips, face, tongue, and fingertips, progressing to the extremities, but then develop muscle weakness, progressing to respiratory failure. Botulinum toxin would present with similar symptoms of nausea, vomiting, with descending muscular weakness, beginning with the smaller muscles of the eye, throat (diplopia, dysphagia, dysarthria), with bradycardia and hypotension in more severe cases. On the other hand, *Clostridium perfringens* toxin, a common cause of food poisoning, results in acute upper gastrointestinal symptoms and abdominal crampy discomfort but quickly resolves within 1 to 2 days. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Are Thiazolidinediones (TZDs) Safe?

In this issue: *Are thiazolidinediones safe? New study shows Zometa reduces risk of hip fractures and improves survival; Merck HIV vaccine proven ineffective in clinical trials; no causal association found between exposure to mercury from thimerosal; and FDA approvals.*

There's no hotter topic in medicine right now than the safety of the thiazolidinediones (TZDs) rosiglitazone (Avandia) and pioglitazone (Actos). Several meta-analysis have pooled data from multiple clinical trials and come to different conclusions regarding the safety of the drugs. The September 12 issue of *JAMA* contained two papers, both meta-analysis, the of first which suggests that pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. An increase in heart failure was noted, although no increase in mortality (*JAMA* 2007; 298:1180-1188).

The second paper looked at rosiglitazone and noted that in patients with impaired glucose tolerance or type 2 diabetes, use of rosiglitazone for at least 12 months was associated with a significantly increased risk of myocardial infarction and heart failure, again without a significant increase risk of cardiovascular mortality (*JAMA* 2007; 298:1189-1195). This followed on conflicting meta-analysis regarding the risk of rosiglitazone published in the *New England Journal of Medicine* in June and July, the first of which suggested the rosiglitazone was associated with an increase risk of myocardial infarction and increased risk of death from cardiovascular causes (*NEJM* 2007; 356:2457-2471), while the second showed an increased risk of heart failure but no increased risk of myocardial infarction or death from cardiovascular causes (*NEJM* 2007;357:28-38). The studies led to congressional hearings, multiple editorials in medical journals and eventually led the FDA to recommend black box warnings regarding the risk of heart failure for both drugs in July. But despite cries from consumer groups suggesting that this was the Cox-2 debacle redux, the FDA stopped short of taking rosiglitazone off the market. The most recent entry into the fray is a new meta-analysis from the Lahey Clinic in Boston. This review analyzed over 3000 studies of which 7 were used for the analysis—all randomized double-blind clinical trials of drug-related congestive heart failure in prediabetic or diabetic patients given either rosiglitazone or pioglitazone. In over 20,000 patients, 360 had congestive heart failure, 214 on TZDs and 146 on comparators. As with other studies there was an increase risk of heart failure associated with both drugs (relative risk 1.72, 95% CI 1.21-2.24, P= 0.002), but again no increase in cardiovascular death was noted with either drug (RR 0.93). The authors suggest that TZDs cause worsening heart failure, but are not associated with progressive systolic or diastolic dysfunction of the left ventricle that leads to death. They also suggest that more studies are needed (*Lancet* 2007;370:1129-1136). The take home message from all the studies is to use caution in TZDs in patients with diabetes and heart failure (NYHA I and II), and to carefully monitor patients for worsening signs and symptoms including weight gain and edema. Initiation of these drugs in patients with established NYHA Class III or IV heart failure is contraindicated.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5413. E-mail: iris.young@ahcmedia.com.

Zometa and hip fractures

A single 5 mg infusion of zoledronic acid (Zometa) within 90 days of a hip fracture reduced the risk of new fractures and improved survival according to new study. Zoledronic acid is a long acting bisphosphonate that is approved for once yearly treatment of postmenopausal osteoporosis. The drug is effective at reducing vertebral, hip, and non-vertebral fractures in women with osteoporosis. In this current study, 1065 men and women with hip fractures were assigned to receive yearly intravenous zoledronic acid 5 mg IV or placebo, the infusions were administered within 90 days of surgical repair of a hip fracture. All patients received vitamin D and calcium. Mean age was 74.5 years, with approximately 75% women. The rate of new clinical fracture was 8.6% in the zoledronic acid group and 13.9% in the placebo group (35% risk reduction, $P = 0.001$). The respective rates of new clinical vertebral fractures were 1.7% vs 3.8% ($P = 0.02$) and for non-vertebral fractures 7.6% vs 10.7% ($P = 0.03$). The death rate was 28% less in the zoledronic acid group (101 of 1054 [9.6%] vs 141 of 1057 [13.3%], $P= 0.01$). No cases of osteonecrosis of the jaw were reported and no adverse effects of healing fractures were noted. The authors conclude that an annual infusion of zoledronic acid within 90 days of a low trauma hip fracture was associated with reduced rate of new fractures and improved survival (published early at www.NEJM.org September 17, 2007).

Merck HIV Vaccine Ineffective in Clinical Trial

After years of development and clinical trials Merck has announced that their HIV vaccine is ineffective in a large clinical trial, and the company has halted further test vaccinations. Other HIV vaccines have also failed but many had hoped that the Merck vaccine, which worked by stimulating T cells, might be more effective. The trial, which was begun in 2004 vaccinated 3000 uninfected volunteers in the US and Latin America. Among 741 patients who received a least one dose of the vaccine, 24 new HIV infections were identified, compared to 21 infections in 762 patients who received placebo. Work continues on other HIV vaccines, currently 30 worldwide are in clinical trials, but the failure of the Merck vaccine is seen is a major setback for HIV researchers.

Thimerosal and Mercury Exposure

Thimerosal has been the subject of intense scrutiny for years regarding its potential link to various neuropsychological deficits in children. Thimerosal has been used as a preservative in vaccines and gamma globulin for decades, although it is rarely used now because it is metabolized to mercury and thiosalicylate, potentially leading to high mercury levels in children. In a new study from the CDC and several large HMOs, 1047 children between ages of seven and 10 years were enrolled and tested for 42 neuropsychological outcomes, then the medical records were examined for history of exposure to mercury from thimerosal. Prenatal mercury exposure from thimerosal was associated with better performance on one measure of language and poor performance on one measure of attention and executive functioning. Exposure in infancy up to seven months old was associated with better performance in one measure, fine motor coordination, and on one measure of attention and executive functioning. Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination. The authors conclude that they could not find a causal association between early exposure to mercury from thimerosal and deficits in neuropsychological functioning at age 7 to 10 years (*NEJM* 2007; 357: 1281-1292).

FDA Actions

Eli Lilly has received approval from the FDA to market raloxifene (Evista) for the indication of reducing the risk of breast cancer in postmenopausal women with osteoporosis and postmenopausal women who are at high risk for invasive breast cancer. Raloxifene is a selective estrogen receptor modulator (SERM) that is already approved for prevention and treatment of osteoporosis in postmenopausal women. The drug was recently required to add labeling regarding an increased risk of fatal strokes in women taking the drug. It also carries a black box warning regarding risk of thromboembolism in women who are at high risk (those with an active or past history or thromboembolism).

Just in time for the winter flu season, the FDA has approved nasal influenza vaccine (FluMist) for use in children between the ages of 2 and 5. Previously the vaccine was only approved for children 5 years old and older and adults up to age 49. The CDC is recommending all children between the ages of 6 months to 59 months receive a flu vaccine. Children ages 2-8 who have never received a flu vaccine will initially require two doses of fluMist at least one month apart.

The FDA has approved a new oral granules form of terbinafine for the treatment of tinea capitis (ringworm) in children. The preparation may be sprinkled on food, allowing easier administration to children who may not otherwise take medicine over the two weeks required to treat tinea. Terbinafine granules are indicated for the treatment of tinea capitis in children age 4 years and older. It is marketed by Novartis AG as Lamisil Oral Granules. ■