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# Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

## ABSTRACT & COMMENTARY

# Global Health: Infections Still Matter

*Infectious diseases responsible for nearly half of child and maternal mortality*

*By Philip R. Fischer, MD, DTM&H*

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**Dr. Fischer reports no financial relationships in this field of study.**

SOURCE: Bhutta ZA, et al. Global maternal, newborn, and child health – so near and yet so far. *New Engl J Med* 2013;369(23):2226-2235.

At the dawn of this century, world leaders signed a Millennium Declaration with the target of reaching eight specific health-related goals by 2015. There have been great gains toward meeting these goals, but rates of child and maternal mortality (the subjects of the 4th and 5th goals) remain unacceptably high. Significant opportunity for improvement still remains, especially in sub-Saharan Africa (for maternal and child mortality) and in the Indian sub-continent (for neonatal mortality).

What still accounts for the 274,000 annual maternal deaths? Table 1 summarizes reported causes of maternal mortality and shows that infections account for 40% of maternal deaths. Since many of these data come from verbal autopsies and imprecise measures, the details of these diagnostic categories are not always well-defined.

Why are 6,600,000 pre-school-aged children still dying each year? Table 2 shows causes of deaths during the first 28 days (neonatal) and the rest of the first five years.

Bhutta el al make the excellent point that we should not merely consider the causes of death but also the "causes of the causes" — the

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underlying social determinants that still allow women and children to die of these more direct causes. Poverty, undernutrition, poor sanitation, and inadequate medical services underlie the tangible infectious and non-infectious causes of death. In fact, undernutrition contributes to 45% of the childhood deaths. Sadly, more than a third of maternal and childhood deaths occur in countries where there is active armed conflict.

Application of existing evidence-based interventions could markedly reduce the current rates of maternal and child mortality. Only about half of women in the "Countdown Countries" (the 75 countries that account for 95% of maternal and child deaths) receive desired family planning, at least four antenatal visits, the presence of a skilled attendant at birth, and postnatal care. In these countries, only 40% of babies benefit from exclusive breastfeeding in the initial months of life; 80% get basic vaccines; less than 40% get antibiotics when they have pneumonia. Clearly, health care system changes will be needed to improve the world's currently unacceptable child and maternal mortality rates.

**Table 2. Causes of Childhood Death**

| Age Group | Cause | % of Deaths |
|---|---|---|
| Neonatal | | |
| | Sepsis/Meningitis | 5 |
| | Pneumonia | 4 |
| | Diarrhea | 1 |
| | Tetanus | 1 |
| | Prematurity | 14 |
| | Intra-Partum Event | 9 |
| | Congenital Anomaly | 4 |
| | "Other" | 2 |
| 1-60 months | | |
| | Pneumonia | 14 |
| | Diarrhea | 10 |
| | Malaria | 7 |
| | Measles | 2 |
| | Meningitis | 2 |
| | HIV/AIDS | 2 |
| | Injury | 5 |
| | "Other" | 18 |

**Table 1. Causes of Maternal Death**

| Cause | Percent of Maternal Deaths |
|---|---|
| | |
| Sepsis | 9 |
| Hepatitis | 13 |
| Syphilis | 6 |
| "Other Infections" | 12 |
| Hemorrhage | 23 |
| Hypertension | 19 |
| Obstructed Labor | 4 |
| Other | 14 |

## ■ COMMENTARY

As the world's population has grown from 4.5 billion in 1990 to 7 billion now, annual deaths of pre-school aged children have dropped from 12.6 to 6.6 million. Several countries are on target to meet the Millennium Development Goals for child and maternal mortality, but there is still significant potential for ongoing progress — particularly in the half of countries that account for 95% of the deaths.

As death rates have dropped around the world, efforts have shifted from simple survival to improved health. Injuries and non-communicable diseases are appropriately receiving more attention. Nonetheless, as capably reviewed by Bhutta et al, infectious diseases are still responsible for nearly half of child and maternal mortality. Improvements in health care systems will be needed to decrease the risk of infectious disease deaths in women and children. ■

# Bird Flu – On the Move?

*By Stan Deresinski, MD, FACP, FIDSA*

Clinical Professor of Medicine, Stanford University, Editor of Infectious Disease Alert

In the last 11 months of 2013, there was a total of 144 confirmed cases of H7N9 infection in China, with 46 deaths. This case total was almost duplicated during one month — January of this year — during which 127 cases were reported. No evidence of sustained person-to-person spread of H7N9 has been found, though some evidence points to limited person-to-person spread in rare circumstances. No cases of H7N9 outside of China have been reported. The new H7N9 virus has not been detected in people or birds in the United States

Human cases of influenza due to the avian virus, H7N9, were first detected in February 2013 in China. During spring of that year, the World Health Organization (WHO) reported 132 human H7N9 infections, with 44 deaths, with most cases having illness onset during the month of April. The following month, however, the number of cases plummeted, likely as a result of both a change in seasons (like seasonal influenza, avian viruses circulate at higher levels in cold compared to warm weather) and control measures, including the closure of live bird markets. This respite was short-lived, with cases once again appearing in October and in January alone there was a total of 127 cases, with 44 deaths. These 127 cases were just 17 fewer than reported in all of 2013.

Contact with infected poultry accounts for almost all cases of infection, which can be asymptomatic. Serosurvey data from outbreak areas found no instances of seropositivity among 1129 general population subjects, while >6% of 396 poultry workers had a hemagglutination inhibition titer of ≥ 80.[1]

Human-to-human transmission has occurred and an example is illustrated by a report of 15 cases from China received on February 7 and 9 of 2013. Thirteen had been exposed to live poultry. Of the 14 people who have survived their infections at the time of the report, 8 were hospitalized in critical condition, 5 were in severe condition, and one, a 5-year-old boy, had a mild illness. The boy who was a close contact with a 41-year old woman with infection. Of note is that this family is from Guangxi province, which borders Vietnam. Fortunately, sustained human-to-human transmission has not been observed.

H7N9 is resistant to adamantanes but, with some exceptions, is susceptible to neuraminidase inhibitors. An amino acid change in the viral neuraminidase associated with drug resistance, NA-R292K (N2 numbering), has been found in some H7N9 clinical isolates.[2] These isolates are highly resistant to both oseltamivir and peramivir and have reduced susceptibility to zanamivir. Unfortunately, this mutation does not impair viral fitness since H7N9 reassortants with and without the resistance mutation demonstrate comparable replication within human respiratory epithelial cells, as well as similar virulence in mice and transmissibility in guinea pigs.

Travelers to countries with known outbreaks of avian influenza should avoid poultry farms, contact with animals in live bird markets, entering areas where poultry may be slaughtered, or contact with any surfaces that appear to be contaminated with faeces from poultry or other animals. Frequent hand washing should be performed, as well as maintenance of food safety and hygiene. WHO does not advise special screening at points of entry with regard to this event, nor does it currently recommend any travel or trade restrictions.

**References**

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2. Hai R, et al. Influenza A(H7N9) virus gains neuraminidase inhibitor resistance without loss of in vivo virulence or transmissibility. *Nature Comm* 2013; Dec 10;4:2854. doi: 10.1038/ncomms3854. ■

ABSTRACT & COMMENTARY

# The Concept of Healthcare-Associated Pneumonia Is Not Accurate for Predicting Antibiotic Resistant Pathogens

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**Dr. Watkins reports no financial relationships in this field of study**

SYNOPSIS: A systematic review and meta-analysis found that the healthcare-associated pneumonia concept was based on low-quality evidence confounded by publication bias and does not accurately identify antibiotic resistant pathogens.

SOURCE: Chalmers JD, et al. Healthcare-Associated Pneumonia Does Not Accurately Identify Potentially Resistant Pathogens: A Systematic Review and Meta-Analysis. *Clin Infect Dis* 2014; 58:330-339.

The term healthcare-associated pneumonia (HCAP) was first proposed in the 2005 guidelines from the American Thoracic Society and the Infectious Diseases Society of America.[1] It was defined as pneumonia occurring in nursing-home residents, patients hospitalized for 2 or more days in the preceding 3 months, patients receiving home infusion therapy or wound care, and patients attending a hemodialysis center in the preceding 30 days. The concept of HCAP was based on the reasoning that patients with frequent healthcare contacts would initially require broad-spectrum antibiotic therapy because they would be at higher risk for resistant pathogens (and consequently higher mortality) compared to patients without such contacts. However, HCAP has been controversial with some experts questioning the quality of the studies while others have suggested the HCAP concept varies geographically. Therefore, because of these uncertainties Chalmers and colleagues sought to determine how accurately HCAP identifies patients with resistant pathogens, to evaluate the quality of the HCAP studies and their potential for bias, and to validate or refute the HCAP concept.

The study was a systematic review and meta-analysis of papers published between January 1980 to January 2013. Of the 16,520 publications initially identified, 24 studies that included 22,456 patients were evaluated in the meta-analysis. The entry criteria were: (1) original publications that included a cohort of patients with HCAP compared with a CAP cohort; and (2) reporting of one of the study outcomes (microbiology or clinical). The primary outcome measured was the frequency of potentially resistant organisms in the HCAP group compared to the CAP group. Potentially resistant organisms included methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeroginosa*, and Gram-negative Enterobactereriaceae. The secondary outcomes were the frequency of the organisms individually, and the frequency of typical and atypical CAP pathogens. The denominator for the frequency of the pathogens in each group was the total number of patients with HCAP or CAP. Finally, the clinical outcomes measured were intensive care unit admission and mortality.

Of the 24 studies included in the meta-analysis, 4 were rated to be low risk for bias, while 10 were judged to be at high risk. Only 5 used the ATS/IDSA guidelines definition for HCAP while the others used modified versions such as including immunocompromised patients. There were statistically significant differences in the frequency of pathogens isolated in the HCAP group compared to the CAP group; *Streptococcus pneumoniae* and the atypical

pathogens were less common (P <.05) while *S. aureus*, MRSA, Enterobacteriaceae and *P. aeruginosa* were more common (P <.0001). A positive likelihood ratio (PLR)>10 or a negative likelihood ratio (NLR) < 0.1 was used to identify a clinically meaningful test along with an area under the receiver operator characteristic curve (AUC) > 0.75. None of the pathogens identified had a PLR > 10 or a NLR < 0.1 nor did HCAP reach the AUC threshold of 0.75 in any of the analyses. Thus, HCAP was not a clinically useful parameter by these statistical criteria. Moreover, limiting the analysis to only prospective studies found no increased risk for ICU admission (n = 4 studies; odds ratio (OR), 0.99; 95% CI, 0.45-2.17; P = .98). The rate of HCAP did vary by region, which was increased in studies from North America (OR, 1.55; 95% CI, 1.35-1.78; P <.0001) but not in Europe (OR, 1.06; 95% CI, 0.56-2.01; P = .90) or Asia (OR, 1.47; 95% CI, 0.92-2.36; P = .10). In the 4 studies that provided adjusted ORs based on age and comorbid illnesses, no significant increase in mortality was associated with HCAP (OR, 1.20; 95% CI, 0.85-1.70; P = .30). Subanalysis found that HCAP performed poorly in European studies (sensitivity 40.0; specificity 75.0), prospective studies (sensitivity 56.3; specificity 70.3), and high-quality studies (sensitivity 51.5; specificity 74.5), none of which reached the AUC threshold of 0.75.

## ■ COMMENTARY

The results from this study do not support HCAP being a useful clinical concept. The HCAP definition was poor at discriminating between patients who needed antibiotic coverage for MDR pathogens and those who did not. It is therefore logical to conclude that treating all HCAP cases the same will lead to over treatment in areas of low MDR organism prevalence and under treatment in areas of high prevalence. The authors found a publication bias for small studies which had unusually high frequencies of MDR pathogens. This likely distorts the literature by exaggerating the risks associated with HCAP. Indeed, the excess mortality in HCAP is more likely caused by advanced age and co-morbidities than MDR organisms. Given the risks of broad-spectrum antibiotics (e.g. *Clostridium difficile* infection, promoting antibiotic resistance) and the lack of high-quality evidence that such therapy improves outcomes in HCAP, a re-examination of this practice seems warranted.

There are some limitations to the study that need to be mentioned. As with all meta-analyses, the conclusions reached are only as valid as the quality of the source studies. Overall the general quality of the studies included in the analysis was poor. Only a few applied strict criteria for classification of the isolates as true pathogens and the higher-quality ones reported lower frequencies of such pathogens. Another limitation was that Enterobacteriaceae were rarely subdivided into extended-spectrum β-lactamase (ESBL) producing organisms which require different antibiotic therapy (i.e. carbapenems) than non-ESBL producers. Finally, the authors could have selected additional clinical measures such as length of stay and re-admission rates that compared HCAP and CAP.

How do the findings from this meta-analysis potentially impact clinical practice? The data make a strong argument for needing to understand the local prevalence of MDR pathogens and creating appropriate treatment algorithms in regions where such prevalence is high. As noted in an accompanying editorial, we also need to elucidate the risk factors for MDR pathogens in individual patients.[2] One way could be the utilization of MDR pathogen risk scores which help clinicians objectively quantify the risk for these organisms in order to select appropriate antibiotic therapy. The results from this meta-analysis raise important questions about the validity of the current ATS/IDSA guidelines and support the need for a re-evaluation of the HCAP concept.

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1. American Thoracic Society/Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171:388-416.
2. Restrepo MI, et al. Healthcare-associated pneumonia: Where do we go next? *Clin Infect Dis* 2014; 58:340-341. ■

ABSTRACT & COMMENTARY

# Clinical Experience in Critically Ill Patients with MERS-CoV

*By Dean L. Winslow, MD, FACP, FIDSA*

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**Dr. Winslow is a consultant for Siemens Diagnostic**

SYNOPSIS: 12 patients with severe Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) were admitted to 3 ICU's in 2 tertiary care medical centers in Saudi Arabia. All of these patients had severe hypoxemic respiratory failure and most had organ dysfunction involving other organ systems. All patients had pre-existing co-morbid conditions. 5 patients survived hospitalization.

SOURCE: Arabi YM, et al. Clinical Course and Outcomes of Critically Ill Patients With Middle East Respiratory Syndrome Coronavirus Infection. *Ann Int Med* 2014; epub Jan 28.

Between December 2012 and August 2013 114 patients admitted to two hospitals with suspected MERS-CoV infection were shown to be infected with this agent by RT-PCR. 12 patients (including one health care worker who was part of a health care-associated case cluster of 3 HCW's with MERS-CoV infection) required admission to the ICU. All 12 patients had underlying comorbid conditions and presented with acute severe hypoxemic respiratory failure. Median age of patients was 59. The comorbid conditions present in at least 25% of patients included diabetes, hypertension, chronic kidney disease, coronary artery disease, obesity and previous stroke. Patients usually presented to the hospital acutely ill in one day or less following onset of symptoms, which generally consisted of dyspnea, cough and fever. Imaging studies showed findings of lobar/multilobar infiltrates to diffuse airspace disease consistent with ARDS. Most patients (92%) had extrapulmonary manifestations, including shock, acute kidney injury, and thrombocytopenia. All 12 patients required endotracheal intubation and mechanical ventilation, 11 received vasopressors, and 7 required renal replacement therapy. Five (42%) survived the ICU and were alive at day 90. Of the 520 exposed HCWs, only 4 (1%) were positive by RT-PCR for infection with MERS-CoV.

## ■ COMMENTARY

This case series provides a very useful report on the clinical characteristics of patients with severe infection due to MERS-CoV. In contrast to patients with Hantavirus Pulmonary Syndrome and SARS-CoV where severe infection was seen in some previously-healthy individuals, severe disease due to MERS-CoV requiring admission to the ICU was in this series seen only in patients with one or more underlying co-morbid conditions. Despite state-of-the-art critical care management of these 12 patients in the three ICU's in Saudi Arabia, only 5 of 12 patients survived to hospital discharge. In their discussion the authors state that all patients received empiric broad-spectrum antibiotics and many received oseltamivir and various doses of corticosteroids. However, there was no evidence that any of these therapies were helpful. The numbers of secondary cases of MERS-CoV encountered in exposed HCW's was very low with only 4 of 520 exposed HCW's testing positive for the virus by RT-PCR. Of these, 2 were asymptomatic, one had mild disease and was treated symptomatically at home, and one patient (included in the case series) required ICU admission. The relative lack of secondary cases is likely related to the relatively short duration of viral shedding. Only 4 patients had MERS-CoV detected by RT-PCR beyond the first day of admission to the ICU, although one patient shed virus out to day 22. ■

# Dengue in the U.S.

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**Dr. Fischer reports no financial relationships in this field of study.**

SYNOPSIS: In a Boston-based survey of travelers, 19% of individuals who were born in, had lived in, or traveled to dengue-endemic countries showed serologic evidence of previous dengue infection. Even without travel, however, dengue infection occurs in the continental United States. In 2012, a woman from Texas died of dengue-associated hemophagocytic lymphohistiocytosis, the third person to die of locally-acquired dengue in the US during the past ten years.

SOURCES: Sanchez-Vegas C, et al. Prevalence of dengue virus infection in US travelers who have lived in or traveled to dengue-endemic countries. *J Travel Med* 2013;20(6):352-360.

Sharp TM, et al. Fatal hemophagocytic lymphohistiocytosis associated with locally acquired dengue virus infection – New Mexico and Texas, 2012. *MMWR* 2014;63(3):49-54.

Dengue virus is transmitted by Aedes mosquitoes and causes up to 100 million infections, 500,000 hospitalizations, and 22,000 deaths each year. The incidence of dengue has increased 30-fold in the past five decades, and it is expanding to include broader geographic regions.

Travelers are at particular risk of dengue infection. To better understand specific risks, a network of five travel clinics in the Boston area evaluated 600 travelers in 2008-2009. Overall, 19% had serologic evidence of previous dengue infection by ELISA testing. Of the 140 study participants born in dengue-endemic countries, 51% were seropositive; longer residence in the endemic country was associated with a greater likelihood of seropositivity. Of the 30 who had been born in a non-endemic country but who had lived in a dengue-endemic country for more than a year, 40% were seropositive. Of the 421 who had not lived in a dengue-endemic country but who traveled to a dengue-endemic country for two to 52 weeks, 7% were seropositive.

It is generally believed that dengue fever is more severe in individuals who have previously been infected with a dengue virus. Only 3% of the travelers in the Boston study reported a history of having had dengue fever even though 19% had serologic evidence of previous infection. Thus, many people who have spent time in dengue-endemic areas have been infected without knowing it; these individuals are presumably at risk of more severe infection.

As sadly illustrated by the Texas woman reported in *MMWR*, however, severe dengue disease can happen without international travel and without evidence of a previous infection. A 63-year-old on mercaptopurine and mesalamine for inflammatory bowel disease presented for care with fatigue, anorexia, headache, hematuria, and leg pain. The symptoms had started while visiting New Mexico and prompted her return home for care in Texas. She subsequently became febrile, hypotensive, hypoxic, and jaundiced. A liver biopsy showed fulminant hepatitis. The kidneys failed, and hemodialysis was initiated. The patient became encephalopathic and then died one month after her initial presentation. Retrospective review confirmed that she met diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH). A bone marrow aspirate was subsequently tested and found to be positive for dengue virus type 3 RNA. No other etiologic agent was identified that correlated with the disease (despite West Nile Virus testing initially being weakly positive). Inflammatory bowel disease and immunosuppression have been linked to an increased risk of HLH and might have contributed to the fatal outcome in this dengue-infected woman.

## ■ COMMENTARY

While often asymptomatic, dengue can cause symptomatic disease, and the severe pains

with the acute febrile illness have prompted the disease's nickname "breakbone fever." After the initial illness, approximately 1-3% of infected individuals progress to dengue shock syndrome or dengue hemorrhagic fever. These severe forms of dengue carry a 1-5% mortality rate; infants and children in endemic areas are most at risk of poor outcomes.[1] There is no specific treatment available, and management depends on supportive care.

While locally-acquired cases of dengue fever have occurred in Texas, the illness has also re-emerged in Key West, Florida.[2] In Key West, infection among residents was associated with having a bird bath in the yard and with leaving windows open most of the time. Applying insect repellant, using air conditioning, and regular emptying of outdoor water containers were associated with less risk of infection.[2]

Dengue vaccines are under study, and some candidate vaccines are currently being used in clinical trials.[1] For now, however, prevention of dengue infection depends on avoiding mosquito bites during travel and while living in parts of the southern United States (such as Texas and Florida) where dengue is endemic. Protection from dengue-transmitting Aedes mosquitoes must continue inside and during daytime hours. Insect repellants DEET (N,N-diethyl-3-methylbenzamide) and icaridin offer similar protective efficacy against Aedes with topical application.[3]

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3. Lupi E et al. The efficacy of repellents against Aedes, Anopheles, Culex, and Ixodes spp. – a literature review. *Travel Med Infect Dis* 2013;11(6):374-411. ■


# Immunization of Adults – Updates


*By Stan Deresinski, MD, FACP, FIDSA*

*Clinical Professor of Medicine, Stanford University, Editor of Infectious Disease Alert*



SOURCE: Bridges CB, Coyne-Beasley T; Immunization Services Division, National Center for Immunization and Respiratory Diseases, CDC. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older - United States, 2014. *MMWR* 2014; 63:110-2.



SYNOPSIS: Recommendations for immunization of adults have been updated.


Updated standards for immunization of adults were approved by the National Vaccine Advisory Committee (NVAC) in September 2013.[1-3] Some of the changes made are as follows.

• Haemophilus influenzae type B (Hib) vaccine is now recommended for selected adults at increased risk of Hib infection who have not previously received the vaccine. Regardless of previous receipt, adult hematopoietic stem cell transplant recipients should receive 3 doses of Hib vaccine 6-12 months after vaccination. In contrast to previous guidance, it is no longer recommended that HIV-infected individuals be vaccinated against Hib as a result of recognition of their low risk of infection with this organism.

• Recombinant influenza vaccine contains no egg protein and can be administered to individuals 18 through 49 years of age with egg allergy of any severity. Either recombinant or inactivated influenza vaccine (which does contain egg protein) can be given to individual whose only allergic manifestation after egg protein exposure is urticaria.

• A single dose of Tdap vaccine is recommended for previously unvaccinated persons aged 11 years or older, and a Td booster should be administered every 10

years thereafter. Pregnant women continue to be recommended to receive 1 dose of Tdap vaccine during each pregnancy, preferably during 27–36 weeks' gestation, regardless of the interval since prior dose of Tdap or Td vaccine.

• Because the 13-valent conjugated pneumococcal vaccine (PCV13) is recommended to be administered before PPSV23 among persons for whom both vaccines are recommended, the PCV13 footnote now precedes the PPSV23 footnote and includes wording to remind providers of the appropriate order of these vaccines when both are indicated.

• The meningococcal vaccine footnote was edited to clarify which persons need either 1 or 2 doses of vaccine and to provide greater clarity regarding which patients should receive the meningococcal conjugate versus the meningococcal polysaccharide quadrivalent vaccines.

• No changes or minor clarifications were made to the MMR, hepatitis A, or hepatitis B vaccine footnotes; no changes in recommendations were made.

Vaccination levels of adults in the United States are disappointingly low. The NVAC recommends that providers assess vaccination needs for their patients at each visit, recommend needed vaccines, and then, ideally, offer the vaccine or, if the provider does not stock the needed vaccines, refer the patient to a provider who does vaccinate. Vaccination providers should also ensure that patients and their referring health-care providers have documentation of the vaccination.

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Infectious Disease [ALERT]

# Updates

By Carol A. Kemper, MD, FACP

## To gown and glove – or screening surveillance ?

Harris AK, et al. Universal Glove and Gown use and acquisition of antibiotic-resistant bacteria in the ICU; A randomized trial. *JAMA* 2013; 310:1571-1580

A large-scale cluster randomized trial conducted in 20 U.S. intensive care units in 2012 sought to determine whether gowns and gloves for all patient contact significantly reduced acquisition of MRSA and VRE compared with usual precautions. Usual precautions are based on current CDC guidelines recommending contact precautions for patients with recognized infection or colonization with multi-drug resistant organisms. The ICU's were divided into intervention (universal gown/gloving) and usual precautions. The only exclusion criteria was prohibition against active surveillance for MDR.

A total of 92,241 screening swab cultures were collected from 26,180 patients throughout their ICU stay — and the ICU personnel were blinded to the results. The baseline rate of MRSA colonization during a 3 month period before study onset ranged from 3.02% to 16.37%, and the rate of VRE colonization ranged from 3.05% to 24.8%.

In the active intervention group (universal gowning/gloves), acquisition of MRSA and VRE decreased from

2135 events/1000 patient days to 1691 events/1000 patient days, respectively. A similar reduction was observed in the usual care group, with acquisition of MRSA decreasing from 1902 to 1629 events/1000 days. No statistically significant difference was observed between the two groups. Looking at individuals, there were fewer acquisitions of MRSA (-2.98/1000 patient days) within the intervention group compared with the usual care group (p = .042) but no difference was detected for VRE. Universal contact precautions decreased the number of hourly health care entries to the room by about 22% ( p= .02), but it did have a positive effect on hand washing compliance. There was no apparent reduction in health care associated infections such as catheter-associated UTIs, catheter-associated blood stream infections, and ventilator-associated pneumonia.

Many hospitals are moving in the direction of targeted surveillance of certain high-risk groups upon admission, with selective use of contact precautions as appropriate. For one thing, identification of MDR colonization upon admission may facilitate reduction in the rates of "hospital onset" infection – a key goal of most infection control programs nowadays. But the success of this "intervention" likely rests on the frequency of pre-existing colonization with multi-drug resistant organisms. The question is: at what prevalence of colonization is it better to actively screen and isolate vs isolate certain high-risk admissions, vs isolate everyone. Obviously if the rate of MRSA colonization is only 3% in your ICU admissions, you're wasting a lot of effort to gown and glove everyone. But if the rate of colonization in your ICU is 25%, should you attempt to pre-screen and isolate as needed, or just throw everyone into an isolation room, and not waste money and effort on expensive PCR swabs? Someone should be able to model this. ■

## Altered flu presentation in immunosuppression

Memoli MJ et al. *CID* 2014;58(2): 58:214.

Epidemiologic surveys have suggested that immunocompromised patients have greater morbidity and mortality with Influenza. In patients with leukemia/lymphoma, one study found that Influenza resulted in up to 80% incidence of pneumonia and 30% mortality. Similar observations were observed in bone marrow transplant patients. Another study of homologous stem-cell transplant (HSCT) patients undergoing chemotherapy with Influenza were at 30-40% risk for pneumonia, 16-17.5% required ICU care, and 7% died.

From 2008 to 2011, the NIH collected data on 86 patients seen at their facility with Influenza. Of these, 37% were severely immunocompromised (IC), including 59% who had undergone HSCT, 38% with hematologic malignancy; and the rest with solid tumors undergoing immunosupressive chemotherapy. One-fourth of IC patients had received seasonal Influenza vaccine.

The remaining 63% of patients with Influenza were not immunosuppressed, but 81% were overweight, 40% had a variety of other illness, such as diabetes, COPD, etc., and 22% smoked. About 60% of the non-IC patients had received seasonal Influenza vaccine with the previous year.

The non-IC patients presented with typical symptoms of Influenza with dry cough (96%), headache (89%), fever (83%), chills (81%), sweats (77%), body aches (68%); gastrointestinal complaints were not common; and 30% required hospitalization. In contrast, all of the IC patients required hospitalization, and their presentation was often less typical: cough (78%), fever (85%), headache (70%), chills (51%), muscle aches (41%), and GI symptoms were more common. IC patients were more likely to have CXR's performed, and of those who had CXRs performed, IC patients were more likely to have radiographic abnormalities than non-IC subjects (39% vs 23%), p=.015). They required longer stays of admission, more frequent admission to ICU, although only one IC patient died (3%).

IC patients also had significantly longer duration of viral shedding compared with non-IC subjects (19.0 vs 6.4 days) — many were still shedding virus despite resolution of their symptoms. Of the 80 Influenza A strains isolated, 6 (11%) were H1N1, 19.7% were H3N2, and 66.3% were pdm09H1N1 subtype. All 6 of the seasonal H1N1 strains were resistant to oseltamivir and possibly peramivir (carried the H2754 NAI resistance mutation), and all of the H3N2 and pdm09 subtypes were resistant to amantadine. Three of the 6 resistant H1N1 strains were observed at baseline, and 3 developed during treatment.

IC patients, most with hematologic malignancy or HCST, seen at the NIH were at high risk for more severe Influenza, more frequent pulmonary infiltrates (39%), and hospitalization (100%), with longer durations of hospitalization than their non-IC counterparts. Their presentations were often not typical, with a lower incidence of cough and inflammatory-mediated symptoms such as chills and body aches. ■

## Before the Black Death, there was the first Plague

Wagner Dm, et al. Yersinia pestis and the Plague of Justinian 541-543 AD: a genomic analysis. *Lancet* 2014; http://dx.doi.org/10.1016/S1473-3099(13)70323-2.

*Yersinia pestis* was responsible for 3 devastating plagues. The first of these, referred to as the Justinian Plague, began in 541-543 AD, spreading through Asia, Africa, and into the Mediterranean Basin and Europe, and then continued to cycle through these countries every 8 to 12 years for the next 200 years. The death toll was a staggering 15-40%. Subsequent pandemic plagues occurred in the 14-17th c. (the Black Death) and again in the 19th and 20 centuries, even reaching San Francisco by boat in 1900-1904. It was the first time plague had reached the Continental United States. It has long been believed the first plague arose in Africa, travelling to Asia and China by the Silk Road, whereas subsequent plagues arose in China. *Y. pestis* generally arises from rodent reservoirs, and requires an existing healthy rodent reservoir to subsist (although is currently endemic in prairie dogs in the American Southwest).

These investigators sought to determine if ancestral strains of *Y. pestis* from the first pandemic were related to strains responsible for the two subsequent pandemics. DNA was extracted from the teeth of two individuals buried in a medieval cemetery in Bavaria Germany, estimated to be from 525-550 AD, some of which had multiple combined graves suspicious for pandemic victims. Both individuals were radiocarbon dated to have died in approximately 504 AD. Sequences from the core *Y. pestis* genome and three primary plasmids (pPCP1, pMT1, and pCDi) along with genes from 155 other *Y. pestis* strains were compared, creating a Y. pestis phylogeny.

They created a "maximum likelihood tree" of SNPs from all of the strains, using the genome from a strain of Y pseudotuberculosis as the root of the tree (since it is the presumed ancestral source of Y. pestis). Five major branches of the tree evolved, with the 3rd pandemic strain being located within the 5th and final branch. The two Justinian strains were isolated to their own novel branch, distant from the subsequent pandemic strains – meaning this strain was unrelated and dead-ended. The two strains were "interleaved" between two extent groups of Y. pestis recognized for plague foci in Xinjiang, China, where they are still found in rodents and fleas. Thus this data suggests that the Justinian Plague arose in China, similar to other plagues, traveling across Asia to Europe along the Silk Road, but then died out for unclear reasons, either because the population was too sparse and failed to establish newer rodent reservoirs. The two later Plagues were then caused by later strains (distinctly different from the original Plague strain) that were able to establish new rodent reservoirs — spreading back and forth across Asia, Africa and Europe — and eventually reaching the United States. ■

## CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

## CME QUESTIONS

**1. Which of the following sentences is true?**

A. HIV accounts for more childhood deaths than does pneumonia

B. Pneumonia accounts for more childhood deaths than do measles, malaria, meningitis, and HIV combined

C. Millions of women still die each year due to complications of delivery

D. Antibiotics are usually given appropriately to children with pneumonia

**2. Which of the following is correct?**

A. Infection with influenza virus H7N9 is always symptomatic.

B. The mortality rate of patients with symptomatic H7N9 infection is <2%.

C. Most, but not all, H7N9 viruses are susceptible to neuraminidase inhibitors.

D. H7N9 viruses are susceptible to adamantane antivirals.

**3. Which statement about dengue is false?**

A. Dengue is found in southern areas of the United States

B. Evidence of dengue infection is identified in about 19% of returned travelers.

C. In endemic areas, the risk of dengue infection is reduced by clearing standing water from near houses, by closing windows, by using air conditioning, and by using insect repellents.

D. Dengue vaccine is now routinely used for travelers to endemic areas.

## CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latent information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies

## AHC IS GOING DIGITAL

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## [IN FUTURE ISSUES]

Genetic PTX3 deficiency and aspergillosis in stem-cell transplantation

Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1

Long walk to treatment for XDR tuberculosis in South Africa