and cells; has a plasma half-life of approximately 7 hours; shows no significant effect against nACH receptors; and has been shown to be safe and well tolerated in Phase 1 studies [Still JG et al. *Antimicrob Agents Chemother* 2011]. In the recently completed Phase 2 trials, it has shown noninferiority to levofloxacin, with favorable safety and tolerability. Plans are underway for a Phase 3 oral trial and Phase 2 intravenous-oral trial in CABP in 2012.

Kelly Aubart, PhD, GlaxoSmithKline, Collegeville, Pennsylvania, USA, discussed GSK1322322, a novel peptide deformylase inhibitor that is in development for hospitalized CABP, acute bacterial skin, and skin structure infections. The new agent has good activity against gram-positive pathogens, including those that infect the skin and soft tissue, as well as the respiratory tract. It is potent *in vivo* and *in vitro* against a range of pathogens, including MRSA. GSK1322322 was safe and well tolerated in Phase 1 studies. A Phase 2 study in skin and soft tissue infections has recently been completed [NCT01209078].

A Critical Precaution – Immunizations in Reproductive Health

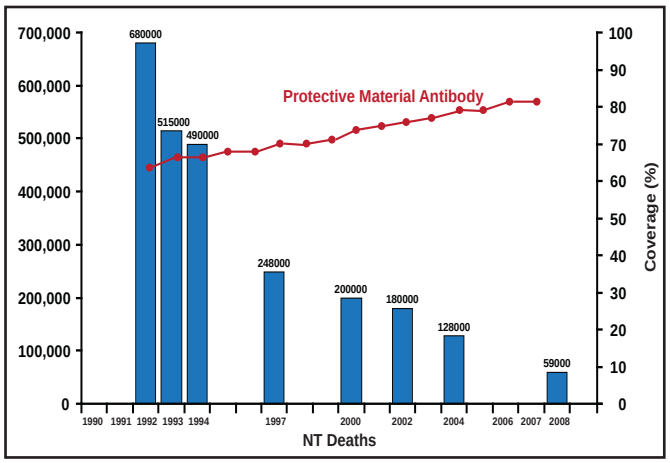
Written by Rita Buckley

Vaccination is one of the most efficient and cost-effective ways to prevent maternal and neonatal morbidity and mortality. For women in their reproductive years, it serves two roles—primary prevention of disease and protection for infants. Linda O. Eckert, MD, University of Washington School of Medicine, Seattle, Washington, USA, discussed vaccines and their recommended use in reproductive-age women.

In the late 1980s, tetanus caused approximately 800,000 neonatal and 30,000 maternal deaths per year. Since the launch of a renewed global maternal-neonatal tetanus elimination program in 2000, there has been a 92% reduction in neonatal tetanus deaths between 1992 and 1998 (Figure 1).

Pertussis cases in the United States (US) jumped from under 10,000 in 2000 to over 25,000 in 2003 [*MMWR* 2004 53:19]. Adults, including grandparent caretakers, were the suspected source of 56% of infant pertussis cases [Bisgard K et al. *Pediatr Infect Dis J* 2004]. The tetanus, diphtheria, pertussis (Tdap) vaccine is now licensed for use in adults aged 65 years and older and is also recommended, rather than tetanus, diphtheria (Td), for use in pregnant women, for those who are health care or child care providers, and in cases of high community incidence or wound prophylaxis [*MMWR* 2011;60(41):1424-1426].

Figure 1. Outcomes From a Global Campaign to Eliminate Neonatal Tetanus.



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The United States Advisory Committee on Immunization Practices (ACIP) currently recommends that women who will be pregnant during the influenza season receive inactivated influenza vaccine to reduce excess maternal mortality during influenza pandemics, offset physiological changes during pregnancy that may increase the morbidity of influenza infections, and reduce the risk of cardiopulmonary hospitalizations during the influenza season.

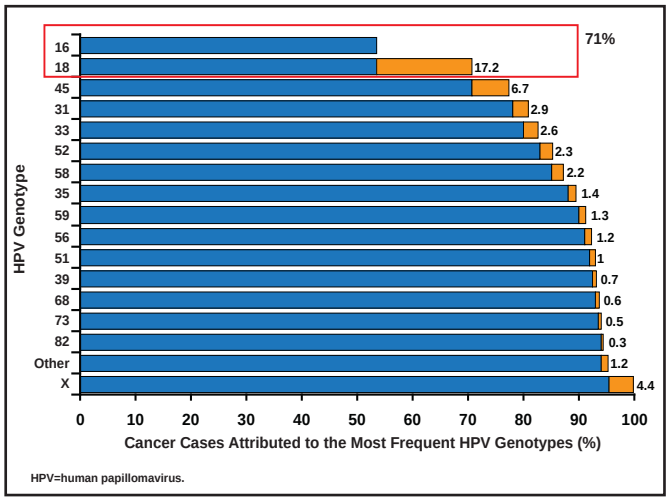
Influenza vaccine that is given to pregnant women is 91.5% effective in preventing hospitalization of their infants for influenza in the first 6 months of life [Benowitz I et al. *Clin Infect Dis* 2010].

Rubella continues to be a significant disease burden. The goal of rubella vaccination is to prevent congenital rubella syndrome (CRS). According to Dr. Eckert, The Americas 2003–2008 campaign to eliminate CRS led to the vaccination of 250,000,000 adolescents and adults in 32 countries and reduced CRS cases by 98%—from 135,947 cases in 1998 to 2998 cases in 2006 [Castillo-Solórzano C et al. *JAMA* 2009].

In the US, 10 women die of cervical cancer every day. However, worldwide, it is the second most common cause of cancer mortality, accounting for 240,000 deaths per year. Most victims are relatively young and poor women, often with dependent children. At least 15 types of human papillomavirus (HPV) have been associated with cervical cancer. Current vaccines confer type-specific immunity to HPV types 16 and 18, which account for 71% of cases of cervical cancer (Figure 2). In contrast, a vaccine that contains the seven most common HPV types would prevent about 87% of cervical cancers [Munoz N et al. *Int J Cancer* 2004]. ACIP recommendations for females aged 9 to 26 years call for immunization with quadrivalent or bivalent vaccine. The former protects against types 6, 11, 16, and 18,

and in Phase 3 trials (n=17,622), it had 100% (95% CI, 75 to 100) efficacy [FUTURE II Study Group. *J Infect Dis* 2007]. The latter protects against types 16 and 18. In a Phase 3 trial (n=16,126), it had 92.9% efficacy (95% CI, 80 to 99) [Paavonen J et al. *Lancet* 2009].

Figure 2. HPV Genotypes in Cervical Cancer.



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Why Can't Microbes Just Get Along?

Written by Noelle Lake, MD

Deborah Hogan, PhD, Department of Microbiology and Immunology, Dartmouth Medical School, Hanover, New Hampshire, USA, has been hard at work exploring the love-hate relationship between two important pulmonary pathogens that are common among patients with cystic fibrosis (CF). She shared the institution's discoveries and discussed the clinical relevance of microbe-microbe interactions in the State-of-the-Art lecture, "*Pseudomonas* and *Candida*: Friends or Foes?"

Today, increasing numbers of patients are experiencing multispecies infections, often bacterial-fungus infections, due to greater use of medical devices, transplantation, and other interventions that allow patients to live longer with chronic diseases. Understanding the interplay between co-infecting organisms and how they affect their hosts may lead to refinements in patient management.

In the environment, *Pseudomonads* have a rather fickle relationship to fungi—sometimes synergistic, as with the colonization and protection of the chanterelle mushroom, and sometimes antagonistic. Dr. Hogan's laboratory is attempting to untangle a similarly convoluted relationship between *Pseudomonas aeruginosa*, a gram-negative bacterium that is common in soil and hospitals, and *Candida albicans*, a ubiquitous fungus that is capable of causing invasive disease. *P. aeruginosa* readily attaches to filamentous *C. albicans*, creating a biofilm, and together they infect catheters, ventilator tubing, and other devices, as well as eyes, wounds, burns, and the lungs of CF patients. Coinfection can negatively affect patients. A 2010 prospective study in *P. aeruginosa*-infected CF patients demonstrated a correlation between the advent of *C. albicans* colonization and an increase in exacerbations [Chotirmall et al. *Chest* 2010].

On a cellular level, this seeming kinship between *P. aeruginosa* and *C. albicans* is actually highly contentious, as it is subject to a kind of interspecies molecular warfare and continual adaptation in the effort to survive. Dr. Hogan highlighted various facets of the relationship, both friendly and antagonistic. *P. aeruginosa* is able to kill filamentous *C. albicans* hyphae by secreting a group of toxic small molecules, called phenazines [Peleg et al. *Nat Rev Microbiol* 2010]. Candida fights back by secreting farnesol, which, in some instances, dismantles *P. aeruginosa*'s phenazine production [Hornby et al. *Appl Environ Microbiol* 2001] but, in other instances increases it by bumping up downstream production [Cugini et al. *Microbiol* 2010]. Farnesol also promotes the conversion of filamentous fungal elements to the more stable yeast morphology, resistant to *P. aeruginosa* attachment and killing [Westwater et al. *Eukaryot Cell* 2005; Deveau et al. *Eukaryot Cell* 2010]. Over time, a chronic co-infection milieu may select for a more synergistically inclined *P. aeruginosa* variant that demonstrates reduced antifungal capacity (due to defective quorum sensing and phenazine production) but improved growth. However, *P. aeruginosa* is also armed with a novel, highly toxic 5-methylphenazine, possibly specifically intended for its *C. albicans* foe, as it is not generally produced by solitary *Pseudomonas* species.

Importantly, microbe-microbe interactions may also impact a host's ability to clear the infection. Recent data show that the presence of *P. aeruginosa* may suppress host immune response to *C. albicans*. In a recent study, single-pathogen infection models with *P. aeruginosa* and *C. albicans* produced the expected immune responses in total cell count and cell differential, with *P. aeruginosa* causing a strong neutrophilic response and *C. albicans* inducing more of a macrophage and eosinophilic response. However, when the two organisms were combined, the immune response more closely resembled that of *P. aeruginosa*, as if *C. albicans* was not present [Allard and Whittaker. *Med Mycol* 2010]. This suggests that coinfection may allow organisms, such as *C. albicans*, to evade immune recognition and set up persistent infections in patients.