For the first time in decades, new TB drugs are available. Dr. Drusano stressed the importance of not risking the emergence of resistance to these agents and questioned the use of a study design in which these drugs are being evaluated against MDR-TB in an optimized background. Lack of knowledge of the detailed susceptibility pattern of the isolate prior to initiation of therapy increases the risk of creating resistant mutants. The question then becomes how to test the drugs in clinical trials.

He suggested starting by examining INH, to which the bug must be resistant, to be called MDR-TB. INH kills rapidly, with multilog decline at standard drug exposures with low minimal inhibitory concentration (MIC) values. Doses as large as 1200 mg cannot completely counter-select resistance amplification as monotherapy. Area under the curve/MIC is the pharmacodynamic-linked variable for cell kill. Because of the fast/slow acetylator divide, different populations will respond somewhat differently to INH. Specifically, fast acetylators will obtain suboptimal results at MIC values >0.25 mg/L. Therefore, noted Dr. Drusano, "wouldn't it be nice to know the MIC distributions in different areas of the world?" Unfortunately, such a database does not exist. In the absence of that information, Dr. Drusano noted that he would test the new drugs in standard patients to learn how to optimize them in combination and to suppress resistance. He stressed the risk of generating and spreading a number of resistant isolates if new drugs are used to treat MDR- and extremely drug-resistent-TB patients as single drugs.

"Combination therapy is the key for successful treatment of TB," he said. He stressed the need to learn to use new agents alone and, more importantly, in combination to optimally kill organisms and suppress resistance. He also suggested a dialog with regulatory officials to get these issues out on the table.

The United States Food and Drug Administration's (FDA) Critical Path Initiative is already transforming the way FDA-regulated products are developed, evaluated, and manufactured. One way is by publishing articles on models and approaches for anti-TB drug testing. "The Global Alliance is taking similar actions," said Dr. Drusano.

New Drugs on the Horizon to Treat MDR Pathogens

Written by Eric Butterman

Aminoglycosides are a well-known class of drugs with proven efficacy; however, they are being used less frequently because of resistance, nephrotoxicity, and ototoxicity. George Zhanel, PhD, University of Manitoba, Winnipeg, Manitoba, Canada, discussed plazomicin (formerly ACHN-490), a new aminoglycoside that is used to treat gram-negative infections, which was evaluated against gentamicin, tobramycin, and amikacin. Dr. Zhanel believes plazomicin is a next-generation aminoglycoside that retains its activity against multidrug-resistant gram-negative and gram-positive bacterial strains that express all clinically relevant aminoglycoside-modifying enzymes. It is not active against organisms that harbor rRNA methyltransferases. Plazomicin is synergistic with daptomycin and ceftobiprole against a variety of MRSA phenotypes and with a variety of β-lactams (eg, cefepime, doripenem, imipenem, and piperacillin-tazobactam) and against *P. aeruginosa* (*in vitro*). At 15 mg/kg IV, plazomicin has a C_{max} of 113 µg/mL, an AUC_{0-24} of 239 h·µg/mL, $t_{1/2}$ of 3.0 hr, and V_{ss} of 0.24 L/kg. Animal and human studies have not reported nephrotoxicity or ototoxicity [Zhanel G et al. *Expert Rev Anti Infect Ther* 2011. Submitted; Zhanel G et al. IDSA 2011]. Plazomicin is currently being investigated in a Phase 2 study to treat complicated urinary tract infections and acute pyelonephritis [NCT01096849].

Prabhavathi Fernandes, PhD, Cempra Pharmaceuticals, Chapel Hill, North Carolina, USA, presented information on macrolides and ketolides with improved antibacterial properties. Dr. Fernandes discussed several investigational programs: a novel series of azetidinyl ketolides that mitigate hepatotoxicity by minimizing hepatic turnover and time-dependent inactivation of CYP3A isoforms in the liver [Magee TV et al. *J Med Chem* 2009]; cethromycin, a ketolide antibiotic that has shown potent activity (similar to telithromycin) against macrolide-resistant bacterial strains but failed to obtain United States Food and Drug Administration approval for community-acquired bacterial pneumonia (CABP) and is now being pursued in superiority trials in simple drug-resistant respiratory infections; and modithromycin, a bridged bicyclic macrolide that is also similar in potency to telithromycin that is active against pneumococcal strains with *erm* and *mef* resistance but has a relatively high (8 µg/mL) MIC_{90} for *H. influenzae* and a very long half-life. Dr. Fernandes concluded her presentation with solithromycin (CEM-101), an oral (Phase 2) and intravenous (Phase 1) fluoroketolide that is being evaluated for the treatment of CABP that has shown activity against *S. pneumoniae,* CA-MRSA, *Enterococci*, and *M. avium* and in animal models of malaria. MICs are similar to azithromycin for gram-negatives, but on average, solithromycin is 8 to 16 times more active for the gram-positive organisms and is active against azithromycin-resistant strains. Solithromycin has 67% oral bioavailability, as compared with 38% for azithromycin; is well distributed into tissues

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

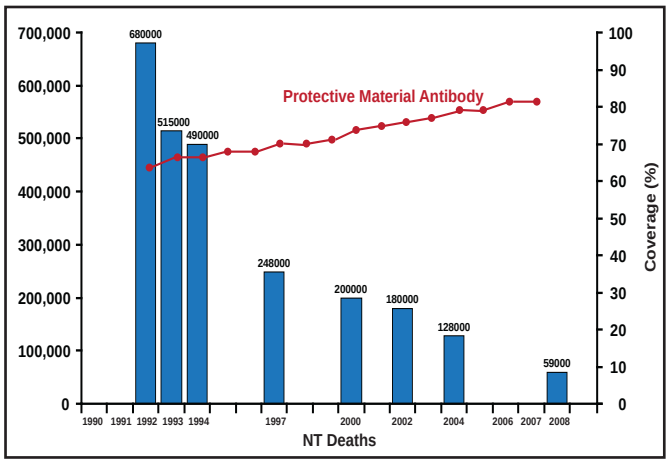
Written by Rita Buckley

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,